



# Comparison Between Administration of Midazolam and Propofol at the End of Anesthesia for Prevention of Emergence Agitation in Children

Masoomah Mahdavi Rad<sup>1</sup>, Mahbobeh Rashidi <sup>1,\*</sup>, Nozar Nassajian <sup>2</sup>, Amir Salari <sup>2</sup>, Ahmad Reza Mohtadi <sup>1</sup>, Saeed Hesam<sup>3</sup> and Ehsan Hedayati <sup>4,\*\*</sup>

<sup>1</sup>Department of Anesthesiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

<sup>2</sup>Department of Anesthesia, Pain Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

<sup>3</sup>Department of Biostatistics and Epidemiology, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

<sup>4</sup>Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

\*Corresponding author: Department of Anesthesiology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Tel: +98-9166168655, Email: m.rashidi8655@gmail.com

\*\*Corresponding author: Department of Medicine, Ahvaz Jundishapur University of Medical Sciences, Esfand St., Golestan, 61357-15794, Ahvaz, Iran. +98-9163406825, Email: hedayate.e@ajums.ac.ir

Received 2019 April 14; Revised 2019 August 03; Accepted 2019 August 09.

## Abstract

**Background:** Comparison of midazolam and propofol has been done hoping to reduce the incidence rates of emergence agitation (EA) after anesthesia. Both drugs however, are still under inspection as for their effect on EA after using Isoflurane for maintenance of anesthesia.

**Objectives:** This study was designed for measuring the effect of either propofol or midazolam near the end of tonsillectomy operation on incidence of EA during the recovery phase.

**Methods:** In this randomized, double-blind study, 90 children, aged 5 to 15, undergoing anesthesia with Isoflurane were randomly assigned to three groups receiving either propofol (group P), midazolam (group M) or saline (group S) near the end of anesthesia. Severity and incidence of EA were then calculated using the pediatric anesthesia emergence delirium (PAED) scale.

**Results:** The mean PAED score in group P was  $(2.87 \pm 2.69)$  and  $(1.90 \pm 2.55)$  in group M. Both were significantly lower than group S  $(7.60 \pm 3.78)$  ( $P < 0.05$ ). However, there was no statistical difference in the duration of post-anesthesia care unit (PACU) stay between groups P  $(42.50 \pm 12.58)$  and M  $(48.33 \pm 24.26)$ , groups P and S  $(52.00 \pm 10.64)$  and between groups M and S ( $P > 0.05$ ). No significant difference was found between all groups for apnea and laryngospasm ( $P > 0.05$ ).

**Conclusions:** Administration of either midazolam or propofol near the end of operation may result in reduction of EA in children undergoing tonsillectomy after Isoflurane anesthesia.

**Keywords:** Midazolam, Propofol, Isoflurane, Emergence Agitation, Anesthesia, PAED

## 1. Background

Isoflurane, with its quick induction, fast emergence and hemodynamic stability has gained widespread acceptance for use on pediatric patients. Nevertheless, Isoflurane has been considered to be connected with EA in pediatrics in early studies. Emergence agitation (EA) in the pediatric patient soon after the end of anesthesia is not uncommon, with occurrence ranging from 10 to 80 percent (1-3). EA is identified by patients' behavior including crying, excitation, irritability, uncooperativeness, disorientation, delirium and thrashing (4-6).

EA is experienced by children undergoing various medical operations. While various factors have been consid-

ered as etiologies of EA, there is no single complete factor that can cause EA. Numerous factors have been recommended, and many factors, such as preschool age, pain, type of surgery, lack of premedication, preoperative anxiety, surgery, awakening in a strange environment, and use of inhalation anesthesia, are recognized to affect EA (1, 4, 7). It has also been recommended that the quick and differential reduction of residual inhalation anesthetics might cause EA in operational patients, however others have shown that quick emergence is not a reason for EA after ending of anesthesia in the pediatric patient (8).

While EA is self-limited and may not lead to any lasting damage, it can result in self-harm and can be a reason for worrying of care providers and parents (9). Various tech-

niques have already been recommended to reduce the occurrence and severity of EA, such as using sedative agents before induction, alteration of the maintenance propofol or injection of sedatives near the end of anesthesia (9, 10). Among these techniques, utilization of sedatives near the end of anesthesia is widely considered as the most convenient and also the most time-appropriate technique in clinical conditions, because it does not depend on the nature of the anesthetic components utilized throughout induction and also maintenance or the duration of anesthesia (11, 12). However, as these studies were performed independently and under different conditions by different evaluation tools, there is no proper comparison between midazolam and propofol available (13). The difference in mechanisms could influence recovery and incidence of complications. Several studies on the effect of Acetaminophen, Ketorolac, and Fentanyl on prevention of EA after sevoflurane anesthesia are done (6, 9, 14, 15). However, so far, no study is conducted on the effects of analgesic compounds on EA induced by Isoflurane.

## 2. Objectives

The present study, for the first time, compares the effects of midazolam and propofol on prevention of EA after maintaining anesthesia using Isoflurane, in children undergoing tonsillectomy.

## 3. Methods

### 3.1. Study Design

This is a clinical randomized double-blinded study, on children undergoing tonsillectomy, hospitalized at surgical unit of a university hospital. The parents consented in writing to participate in the study.

Sample size was calculated using the study by Aouad et al. (12) in which the mean and standard deviation for the pediatric anesthesia emergence delirium (PAED) in propofol group were reported as 8.6 and 3.9, and in normal saline group, 11.5 and 4.5 respectively. The significance level was assumed as below 0.05 level and the power of the study was taken as 0.8. Using the Power and Sample size program, sample size was calculated as 30 per each group. As no study in which there was a significant difference between midazolam and Propofol was known, the sample size could not be calculated this way and therefore it was calculated using propofol and control groups, and the same number was used for the midazolam group.

In this study, a total of ninety-five patients were assessed for eligibility, and ninety children aged 5 to 15, who

met the inclusion criteria and were undergoing tonsillectomy, were randomly divided into three groups according to permuted block randomization, including P group (1.0 mg/kg propofol I.V.), M group (0.05 mg/kg midazolam I.V.), and S group (normal saline I.V.) after obtaining consent from their parents. In addition, the patients and the anesthesiology resident in charge of filling the PAED forms were not made aware of the medication given to each patient.

Inclusion criteria: Children 5 - 15 years of age, planned for tonsillectomy, ASA class I or II, Parents have given consent.

Exclusion criteria: Children with developmental delay, psychological, neurological or behavioral disorders, massive bleeding intra operative that leads to hemodynamic instability or transfusion. Figure 1 shows a flow diagram of this study.

After initial preparation and monitoring and initial serum therapy, following drugs were used for induction in all patients: Atropine 0.02 mg/kg, Fentanyl 2 µg/kg, sodium thiopental (STP) 6 mg/kg, Atracurium: 0.5 mg/kg.

Isoflurane was used in maintenance of anesthesia, as it is more common in use in operating rooms throughout Iran and cheaper compared to other volatile anesthetics, such as sevoflurane. On the other side, other agents, such as Halothane are of restricted access because of known side effects and are not common in use.

The drug was injected immediately after discontinuation of Isoflurane, and we measured the agitation rate at 5, 10, 20, and 30 minutes according to the PAED criteria. The degree of agitation upon awakening was evaluated and recorded at 5, 10, 20 and 30 minutes after emergence, the biggest values were then used for analysis. The incidence and severity of EA was calculated using PAED (16) scale (Table 1).

### 3.2. Data Analysis

In quantitative variables, average and standard deviations were used for data description, and in qualitative variables, frequency and percentage were used. For data analysis chi-square test was used and *t*-test, ANOVA test and regression methods such as logistic regression were used if needed. All analyses were performed using SPSS software version 22.

## 4. Results

### 4.1. Demographic Characteristics

In the present study, all patients who were initially assessed successfully completed the study. No significant difference in gender, age, and weight among the three groups was found (Table 2).

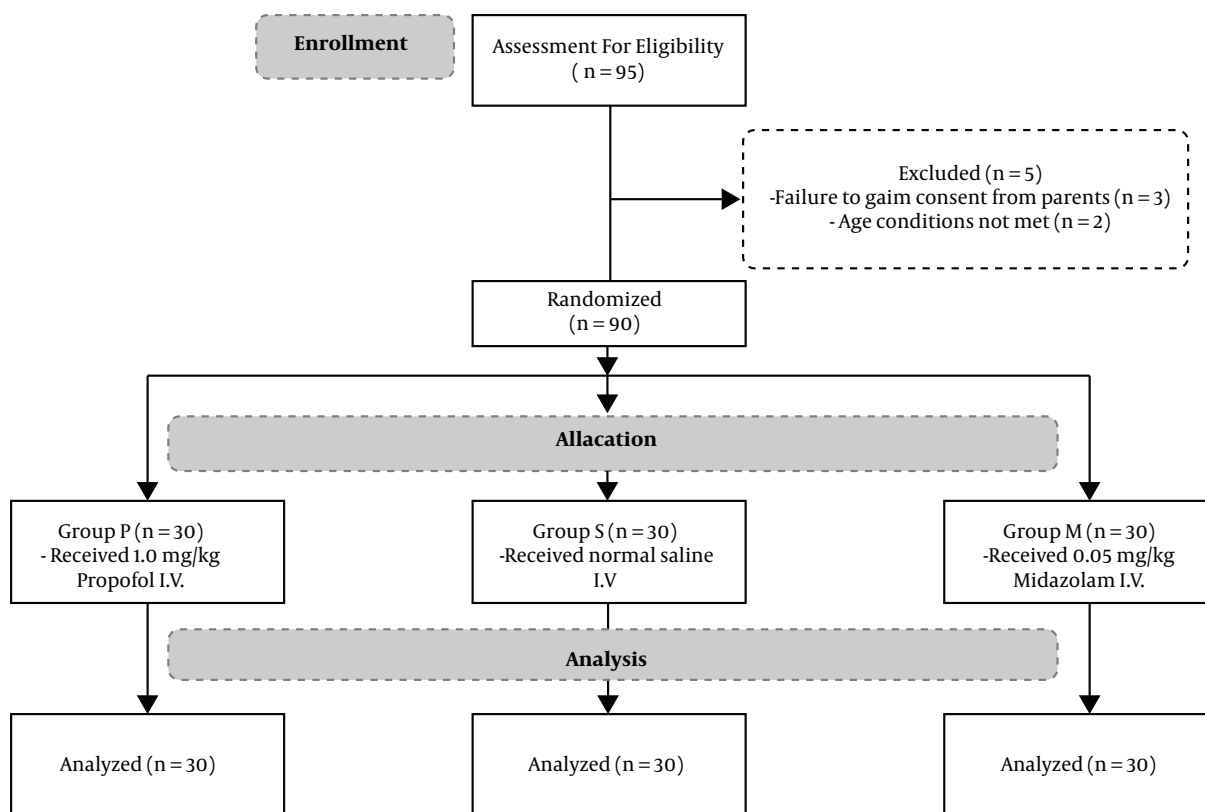


Figure 1. CONSORT flow diagram of the study

Table 1. The Pediatric Anesthesia Emergence Delirium (PAED) Scale (16)

Behaviors	None	A little	Quite a Bit	Very Much	Extremely
Eye contact with the caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of his/her surroundings	4	3	2	1	0
Restlessness	0	1	2	3	4
Inconsolable	0	1	2	3	4

Table 2. Patients' Characteristics

Parameter	Group P	Group M	Group S
Number of Patients	30	30	30
Age	7.60 ± 2.36	8.73 ± 2.64	6.86 ± 2.69
Gender, M/F	20 (66.7)/10 (33.3)	16 (55.3)/14 (46.7)	22 (73.3)/8 (26.7)
Weight	28.70 ± 14.64	36.07 ± 16.71	28.07 ± 31.46

#### 4.2. Incidence of EA

EA was seen 60% (18/30) in group propofol (group P), 20% (6/30) in group midazolam (group M) and 97.6% (29/30) in group S, 5 minutes after being extubated. At 5

minutes, the incidence of EA in both M and P groups was significantly lower than that of group saline (group S) ( $P < 0.001$  and  $P = 0.006$  respectively), results also showed that EA incidence in group M was significantly lower than that

in group P ( $P = 0.002$ ). At other times the incidence of EA in groups M or P was significantly lower than that in group S but there was no significant difference between M and P groups. On the other hand, in all groups, incidence of EA has been higher at 5 minutes after extubation than other times. But the prevalence rate with the increase in its duration significantly decreased in groups P and S, while this difference was not seen in group M (Table 3).

**Table 3.** Incidence of Emergence Agitation in All Groups<sup>a</sup>

Parameter	Group P	Group M	Group S
5 min	18 (60) <sup>b,c</sup>	6 (20) <sup>b,c</sup>	29 (97.6)
10 min	5 (16.7)	3 (10)	24 (80)
20 min	2 (6.7)	3 (10)	14 (46.7) <sup>d</sup>
30 min	1 (3.3) <sup>d</sup>	1 (3.3)	7 (23.3) <sup>d</sup>

Abbreviations: M, midazolam; min, minutes; P, propofol; S, saline.

<sup>a</sup>Values are expressed as No. (%).

<sup>b</sup>Showed a significant difference with group S.

<sup>c</sup>Showed a significant difference between M and P group.

<sup>d</sup>Showed a significant difference within a group at different times compared to 5 minutes after drug injection.

#### 4.3. PAED Score

The mean values of PAED score at 5 minutes after drug injection in group P ( $10.30 \pm 2.84$ ) and group M ( $8.43 \pm 3.65$ ) were significantly lower than the values of group S ( $16.3 \pm 2.61$ ) ( $P < 0.001$ ), but the difference between P and M groups did not reach statistical significance ( $P = 0.081$ ). This means that the severity of agitation in midazolam group was significantly lower than that in S group. On the other hand, in all groups, PAED score was significantly higher at 5 minutes after extubation, the time in which the severity of agitation had somewhat reduced. Also, in different groups, the PAED score at different times showed a significant difference ( $P < 0.05$ ), (Table 4).

**Table 4.** PAED Score of Emergence Agitation in all Groups

Parameter	Group P	Group M	Group S
5 min	$10.30 \pm 2.84^a$	$8.43 \pm 3.65^a$	$16.3 \pm 2.61$
10 min	$7.33 \pm 2.99^a$	$5.20 \pm 3.93^a$	$13.7 \pm 3.93$
20 min	$4.07 \pm 3.00^a$	$3.23 \pm 3.86^a$	$9.80 \pm 3.37$
30 min	$2.87 \pm 2.69^a$	$1.90 \pm 2.55^a$	$7.60 \pm 3.78$

Abbreviations: M, midazolam; min, minutes; P, propofol; S, saline.

<sup>a</sup>Showed a significant different with group S.

#### 4.4. PACU and Other Parameters

The extubation time (the time between the injection of drug and extubation) was prolonged in group P ( $21.9 \pm 8.77$ ) compared to group S ( $14.68 \pm 6.65$ ) ( $P < 0.001$ ).

No significant difference was found in the extubation time between group M ( $20.83 \pm 7.08$ ) with P and S groups. Also there were no significant differences for awakening time (the time between extubation and patient's transfer to post-anesthesia care unit (PACU)) between all groups (Figure 2). No statistical difference was observed between groups P ( $42.50 \pm 12.58$ ) and M ( $48.33 \pm 24.26$ ), groups P and S ( $52.00 \pm 10.64$ ) and between groups M and S in PACU stay duration ( $P < 0.05$ ) (Figure 3). Results showed no significant differences between all groups for apnea and laryngospasm ( $P > 0.05$ ).

## 5. Discussion

In the present study, the effects of propofol and midazolam on EA were assessed in a group of patients who are at high risk for EA regarding to their age and the use of inhaled anesthetics and type of surgery. An EA incidence of 23.3% was observed in the control group. This rate compares to previous studies, which reported incidences between 16 and 34 percent (17, 18). Prophylactic use of i.v. propofol or midazolam reduced the incidence of agitation significantly to 3.3%, without adverse postoperative effects.

Numerous components of the anesthesia process have been inspected with the purpose of decreasing the incidence of EA with variable results (4, 6, 14-16). Propofol had been revealed to have a significant impact on prevention of EA. A study by Uezono et al. (9) suggested a reduction in EA risk by using a continuous propofol infusion while maintaining the anesthesia by using sevoflurane, and a 1 mg/kg dose of propofol administered at the end of operation, after sevoflurane has been discontinued, to decrease the incidence of agitation. Therefore, it is possible that the decreased incidence of EA accounted for the residual effect of propofol (19).

The impact of midazolam on EA remains debatable. Koner et al. found that midazolam premedication had no effect on EA following halothane or sevoflurane anesthesia (10). In another study, midazolam premedication decreased the incidence of EA (6). Chen et al. found that  $0.05 \text{ mg.kg}^{-1}$  midazolam combined with  $0.5 \mu\text{g.kg}^{-1}$  of fentanyl at the end of surgery was effective in reducing the incidence and severity of EA. This result is expected because midazolam has a short duration of action that may not outlast the duration of the surgery (20). Kim et al. also compared propofol and midazolam in strabismus correction surgery. They found that midazolam and propofol reduced the rate of EA by about 40%, resulting in a prophylactic incidence of 40%, still higher than that of Chen (19, 21).

Several researchers have disclosed that midazolam decreases EA by acting on its target effect site  $\text{GABA}_A$ , and also its antagonist, flumazenil reverses this. Nevertheless, the

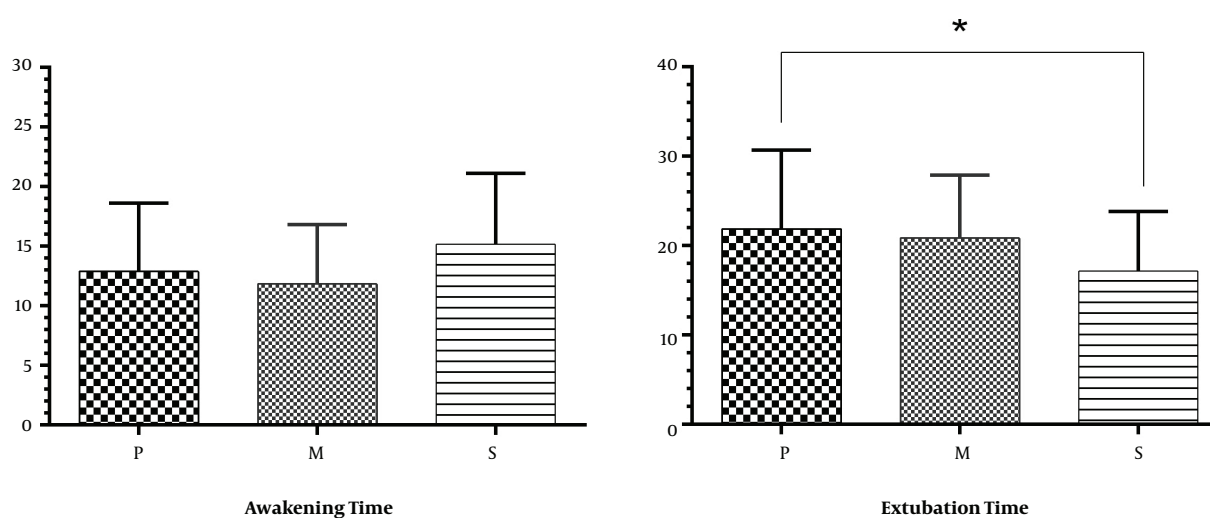


Figure 2. The extubation time and awakening time

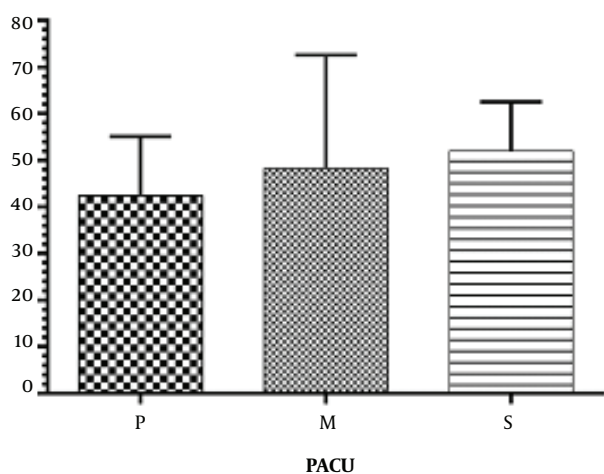


Figure 3. PACU stay duration

exact mechanism remains unknown, in fact it is not recognized whether sevoflurane and midazolam interact at the GABA<sub>A</sub> receptor level (6, 20).

The PAED scale, used for the assessment of EA, is a known tool for evaluating EA, the reliability and validity of which has been previously proved (22-25). While some recent studies (26) propose the use of age-adjusted PAED scores, no such score was used in this study. Using the PAED scale, midazolam and propofol showed comparable effectiveness in preventing EA.

This study faced several limitations. First, we evaluated only children undergoing one specific type of surgery,

namely tonsillectomy. The occurrence of EA is different based on the type of operation, assuming that the efficiency of midazolam and propofol in this study may differ in other operations. Secondly, midazolam and propofol doses utilized in this study are only arbitrary. This, in part is because of the fact that there is no dose of midazolam and propofol similar in potency for elimination of EA induced by Isoflurane. Therefore, a propofol dose of 1 mg/kg was used, similar to the study by Aouad et al. (12) who used this dose for prevention of EA in anesthesia induced by sevoflurane. It had already been demonstrated that in the pediatric patient, sedation with i.v. midazolam (0.05 to 0.1 mg/kg) is safe and effective for invasive or lengthy procedures (19). Therefore, a minimum sedation dose of 0.05 mg/kg for midazolam was used in this study.

### 5.1. Conclusions

In conclusion, administration of either midazolam or propofol near the end of surgical operation may be effective in reducing the severity and incidence of EA in the pediatric patient undergoing tonsillectomy after anesthesia by Isoflurane and neither is significantly more effective than the other.

### Acknowledgments

This study was a part of dissertation by Masoomeh Mahdavi Rad funded by grant number PAIN-9612 by Pain Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.



## Footnotes

**Authors' Contribution:** Study concept and design: Masoomeh Mahdavi Rad, Mahbobeh Rashidi, Ahmad Reza Mohtadi, Amir Salari and Nozar Nassajian. Analysis and interpretation of data: Saeed Hesam and Ehsan Hedayati. Drafting of the manuscript: Masoomeh Mahdavi Rad and Mahbobeh Rashidi. Critical revision of the manuscript for important intellectual content: Masoomeh Mahdavi Rad, Mahbobeh Rashidi, Ahmad Reza Mohtadi, Amir Salari, Nozar Nassajian and Ehsan Hedayati. Statistical analysis: Saeed Hesam.

**Clinical Trial Registration Code:** The study is registered with Iranian Registry of Clinical Trials by Trial ID IRCT20180811040764N1 (irct.ir/trial/33223).

**Conflict of Interests:** The authors declare that no conflict of interest exists.

**Funding/Support:** This study was financially supported by grant PAIN-9612 from the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran.

**Ethical Approval:** This study was approved by the Committee for Ethics in Research of Ahvaz Jundishapur University of Medical Sciences (approval number: IR.AJUMS.REC.1396.948).

**Patient Consent:** The parents consented in writing to participate in the study.

## References

- Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. *Anesth Analg.* 2003;**96**(6):1625-30. table of contents. doi: [10.1213/01.ane.0000062522.21048.61](https://doi.org/10.1213/01.ane.0000062522.21048.61). [PubMed: [12760985](https://pubmed.ncbi.nlm.nih.gov/12760985/)].
- Eckenhoff JE, Kneale DH, Dripps RD. The incidence and etiology of postanesthetic excitement. A clinical survey. *Anesthesiology.* 1961;**22**:667-73. doi: [10.1097/00000542-196109000-00002](https://doi.org/10.1097/00000542-196109000-00002). [PubMed: [13889092](https://pubmed.ncbi.nlm.nih.gov/13889092/)].
- Welborn LG, Hannallah RS, Norden JM, Ruttimann UE, Callan CM. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. *Anesth Analg.* 1996;**83**(5):917-20. doi: [10.1097/00000539-199611000-00005](https://doi.org/10.1097/00000539-199611000-00005). [PubMed: [8895263](https://pubmed.ncbi.nlm.nih.gov/8895263/)].
- Isik B, Arslan M, Tunga AD, Kurtipek O. Dexmedetomidine decreases emergence agitation in pediatric patients after sevoflurane anesthesia without surgery. *Paediatr Anaesth.* 2006;**16**(7):748-53. doi: [10.1111/j.1460-9592.2006.01845.x](https://doi.org/10.1111/j.1460-9592.2006.01845.x). [PubMed: [16879517](https://pubmed.ncbi.nlm.nih.gov/16879517/)].
- Vlajkovic GP, Sindjelic RP. Emergence delirium in children: many questions, few answers. *Anesth Analg.* 2007;**104**(1):84-91. doi: [10.1213/01.ane.0000250914.91881.a8](https://doi.org/10.1213/01.ane.0000250914.91881.a8). [PubMed: [17179249](https://pubmed.ncbi.nlm.nih.gov/17179249/)].
- Ko YP, Huang CJ, Hung YC, Su NY, Tsai PS, Chen CC, et al. Premedication with low-dose oral midazolam reduces the incidence and severity of emergence agitation in pediatric patients following sevoflurane anesthesia. *Acta Anaesthesiol Sin.* 2001;**39**(4):169-77. [PubMed: [11840583](https://pubmed.ncbi.nlm.nih.gov/11840583/)].
- Kanaya A. Emergence agitation in children: risk factors, prevention, and treatment. *J Anesth.* 2016;**30**(2):261-7. doi: [10.1007/s00540-015-2098-5](https://doi.org/10.1007/s00540-015-2098-5). [PubMed: [26601849](https://pubmed.ncbi.nlm.nih.gov/26601849/)].
- Cole JW, Murray DJ, McAllister JD, Hirshberg GE. Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. *Paediatr Anaesth.* 2002;**12**(5):442-7. doi: [10.1046/j.1460-9592.2002.00868.x](https://doi.org/10.1046/j.1460-9592.2002.00868.x). [PubMed: [12060332](https://pubmed.ncbi.nlm.nih.gov/12060332/)].
- Uezono S, Goto T, Terui K, Ichinose F, Ishiguro Y, Nakata Y, et al. Emergence agitation after sevoflurane versus propofol in pediatric patients. *Anesth Analg.* 2000;**91**(3):563-6. doi: [10.1097/00000539-200009000-00012](https://doi.org/10.1097/00000539-200009000-00012). [PubMed: [10960377](https://pubmed.ncbi.nlm.nih.gov/10960377/)].
- Koner O, Ture H, Mercan A, Menda F, Sozubir S. Effects of hydroxyzine-midazolam premedication on sevoflurane-induced paediatric emergence agitation: A prospective randomised clinical trial. *Eur J Anaesthesiol.* 2011;**28**(9):640-5. doi: [10.1097/EJA.0b013e328344db1a](https://doi.org/10.1097/EJA.0b013e328344db1a). [PubMed: [21822077](https://pubmed.ncbi.nlm.nih.gov/21822077/)].
- Abu-Shahwan I, Chowdary K. Ketamine is effective in decreasing the incidence of emergence agitation in children undergoing dental repair under sevoflurane general anesthesia. *Paediatr Anaesth.* 2007;**17**(9):846-50. doi: [10.1111/j.1460-9592.2007.02298.x](https://doi.org/10.1111/j.1460-9592.2007.02298.x). [PubMed: [17683402](https://pubmed.ncbi.nlm.nih.gov/17683402/)].
- Aouad MT, Yazbeck-Karam VG, Nasr VG, El-Khatib MF, Kanazi GE, Bleik JH. A single dose of propofol at the end of surgery for the prevention of emergence agitation in children undergoing strabismus surgery during sevoflurane anesthesia. *Anesthesiology.* 2007;**107**(5):733-8. doi: [10.1097/01.anes.0000287009.46896.a7](https://doi.org/10.1097/01.anes.0000287009.46896.a7). [PubMed: [18073548](https://pubmed.ncbi.nlm.nih.gov/18073548/)].
- Hung WT, Chen CC, Liou CM, Tsai WY. The effects of low-dose fentanyl on emergence agitation and quality of life in patients with moderate developmental disabilities. *J Clin Anesth.* 2005;**17**(7):494-8. doi: [10.1016/j.jclinane.2004.09.014](https://doi.org/10.1016/j.jclinane.2004.09.014). [PubMed: [16297747](https://pubmed.ncbi.nlm.nih.gov/16297747/)].
- Dahmani S, Stany I, Brasher C, Lejeune C, Bruneau B, Wood C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: A meta-analysis of published studies. *Br J Anaesth.* 2010;**104**(2):216-23. doi: [10.1093/bja/aep376](https://doi.org/10.1093/bja/aep376). [PubMed: [20047899](https://pubmed.ncbi.nlm.nih.gov/20047899/)].
- Galinkin JL, Fazi LM, Cuy RM, Chiavacci RM, Kurth CD, Shah UK, et al. Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. *Anesthesiology.* 2000;**93**(6):1378-83. doi: [10.1097/00000542-200012000-00006](https://doi.org/10.1097/00000542-200012000-00006). [PubMed: [11149429](https://pubmed.ncbi.nlm.nih.gov/11149429/)].
- Kim MS, Moon BE, Kim H, Lee JR. Comparison of propofol and fentanyl administered at the end of anaesthesia for prevention of emergence agitation after sevoflurane anaesthesia in children. *Br J Anaesth.* 2013;**110**(2):274-80. doi: [10.1093/bja/aes382](https://doi.org/10.1093/bja/aes382). [PubMed: [23103775](https://pubmed.ncbi.nlm.nih.gov/23103775/)].
- Meyer RR, Munster P, Werner C, Brambrink AM. Isoflurane is associated with a similar incidence of emergence agitation/delirium as sevoflurane in young children—a randomized controlled study. *Paediatr Anaesth.* 2007;**17**(1):56-60. doi: [10.1111/j.1460-9592.2006.01998.x](https://doi.org/10.1111/j.1460-9592.2006.01998.x). [PubMed: [17184433](https://pubmed.ncbi.nlm.nih.gov/17184433/)].
- Singh R, Kharbanda M, Sood N, Mahajan V, Chatterji C. Comparative evaluation of incidence of emergence agitation and post-operative recovery profile in paediatric patients after isoflurane, sevoflurane and desflurane anaesthesia. *Indian J Anaesth.* 2012;**56**(2):156-61. doi: [10.4103/0019-5049.96325](https://doi.org/10.4103/0019-5049.96325). [PubMed: [22701207](https://pubmed.ncbi.nlm.nih.gov/22701207/)]. [PubMed Central: [PMC3371491](https://pubmed.ncbi.nlm.nih.gov/PMC3371491/)].
- Kim YH, Yoon SZ, Lim HJ, Yoon SM. Prophylactic use of midazolam or propofol at the end of surgery may reduce the incidence of emergence agitation after sevoflurane anaesthesia. *Anaesth Intensive Care.* 2011;**39**(5):904-8. doi: [10.1177/0310057X1103900516](https://doi.org/10.1177/0310057X1103900516). [PubMed: [21970137](https://pubmed.ncbi.nlm.nih.gov/21970137/)].
- Chen J, Li W, Hu X, Wang D. Emergence agitation after cataract surgery in children: A comparison of midazolam, propofol and ketamine. *Paediatr Anaesth.* 2010;**20**(9):873-9. doi: [10.1111/j.1460-9592.2010.03375.x](https://doi.org/10.1111/j.1460-9592.2010.03375.x). [PubMed: [20716081](https://pubmed.ncbi.nlm.nih.gov/20716081/)].
- Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. The effect of fentanyl on the emergence characteristics after desflurane or sevoflurane anesthesia in children. *Anesth Analg.* 2002;**94**(5):1178-81. table of contents. doi: [10.1097/00000539-200205000-00023](https://doi.org/10.1097/00000539-200205000-00023). [PubMed: [11973185](https://pubmed.ncbi.nlm.nih.gov/11973185/)].

22. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology*. 2004;**100**(5):138-45. doi: [10.1097/00000542-200405000-00015](https://doi.org/10.1097/00000542-200405000-00015). [PubMed: [15114210](https://pubmed.ncbi.nlm.nih.gov/15114210/)].
23. Ringblom J, Wahlin I, Proczkowska M. A psychometric evaluation of the Pediatric Anesthesia Emergence Delirium scale. *Paediatr Anaesth*. 2018;**28**(4):332-7. doi: [10.1111/pan.13348](https://doi.org/10.1111/pan.13348). [PubMed: [29508484](https://pubmed.ncbi.nlm.nih.gov/29508484/)].
24. Park JH, Lim BG, Lee IO. The effect of sedation on the pediatric anesthesia emergence delirium scale. *Paediatr Anaesth*. 2014;**24**(9):1014-5. doi: [10.1111/pan.12471](https://doi.org/10.1111/pan.12471). [PubMed: [25092448](https://pubmed.ncbi.nlm.nih.gov/25092448/)].
25. Janssen NJ, Tan EY, Staal M, Janssen EP, Leroy PL, Lousberg R, et al. On the utility of diagnostic instruments for pediatric delirium in critical illness: an evaluation of the pediatric anesthesia emergence delirium scale, the delirium rating scale 88, and the delirium rating scale-revised R-98. *Intensive Care Med*. 2011;**37**(8):1331-7. doi: [10.1007/s00134-011-2244-y](https://doi.org/10.1007/s00134-011-2244-y). [PubMed: [21567109](https://pubmed.ncbi.nlm.nih.gov/21567109/)]. [PubMed Central: [PMC3136686](https://pubmed.ncbi.nlm.nih.gov/PMC3136686/)].
26. Kramer S, Krebs M, Spies C, Ghamari S, Hohne C, Becke K, et al. [Drama in the recovery unit: Paediatric emergence delirium]. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 2018;**53**(11-12):766-76. German. doi: [10.1055/a-0575-0473](https://doi.org/10.1055/a-0575-0473). [PubMed: [30458574](https://pubmed.ncbi.nlm.nih.gov/30458574/)].