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ORIGINAL ARTICLE

# Comparing the use of Preoperative Ketamine or Midazolam or Ketamine versus Oral Dextromethorphan for Reducing Sevoflurane Emergence Agitation among Preschool Children Undergoing Adenotonsillectomy

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## ABSTRACT

**Background:** An increased risk of dangerous emergence agitation (EA) has been linked to the use of sevoflurane.

This study aims to compare the the use of preoperative ketamine, midazolam or Oral Dextromethorphan for reducing sevoflurane emergence agitation among preschool children undergoing adenotonsillectomy.

**Methods:** This randomized controlled double-blinded study was carried out at Zagazig University Hospitals on 56 children who were divided into 4 equal groups; 14 patients in each: Group (C): received 10ml oral placebo (clear fluid) 1 hour before the general anesthesia induction. Group (D): Patients received at a dose of 0.5mg/kg 1 hour from oral dextromethorphan before the general anesthesia induction. Group (K): received a dose of 0.5mg/kg 1 hour of oral ketamine before the general anesthesia induction. Group (M): received a dose of 0.5 mg/kg 1 hour of oral Midazolam before the general anesthesia induction.

**Results:** Regarding heart rate (HR); group (K) was significantly highest compared to other groups. ($p<0.001$). The postoperative agitation incidence >4 was significantly lowest in the ketamine group in comparison to the other groups ($p=0.02$). Group M was found to be significantly lowest in post-operative pain occurrence in comparison to the other groups ($p=0.02$). Group K was found to be significantly lowest in the amount of fentanyl consumption in comparison to the other groups ($p=0.004$).

**Conclusion:** Ketamine premedication is more effective for EA prevention among children during the early emergence time after sevoflurane c ompared to midazolam and dextromethorphan anethesia.

**Keywords:** Preoperative Oral Dextromethorphan, Ketamine, Midazolam, Sevoflurane Emergence Agitation.

## INTRODUCTION:

A common anesthetic inhalation drug that is used to induce and maintain anesthesia in children is sevoflurane. Its low blood solubility enables quick induction of general anesthesia and recovery from it. However, it is associated with higher rates of emergence agitation (EA), which can be dangerous for patients when administered as the only anesthetic agent [1]. It is unclear what triggers EA, although some hypotheses include rapid anesthesia withdrawal, a lack of experience with new environments, separation anxiety, heightened pain sensitivity, and sympathetic hyperactivation. [2].

To lower the prevalence of EA, numerous writers used a variety of medications, such as propofol,

opioids, and alpha 2-agonists such as dexmedetomidine or clonidine [3].

Numerous studies have demonstrated that oral or intravenous use of ketamine, which is a competitive N-methyl d-aspartate (NMDA) receptor antagonist, can minimize the EA occurrence [4].

Dextromethorphan is another non-competitive NMDA receptor antagonist commonly used as a cough suppressant and analgesic adjuvant. It is the D-isomer of the codeine analogue levorphanol. Its analgesic and antitussive properties have been attributed to its codeine-like structure and its ability to block NMDA receptors. The harmful effects result from its active metabolite, dextrorphan, which is produced in the liver. Dextrorphan acts on phencyclidine receptors [5].

Therapeutic effects of midazolam, an agonist at aminobutyric acid A receptors, range from anxiolytic to hypnotic, and are regulated less by drug concentrations in the blood than by the ratio of receptor occupancy. It is also used to prevent EA after sevoflurane anesthesia [6].

Midazolam, a common pediatric sedative, is effective in reducing pediatric EA. Oral midazolam administered before sevoflurane anesthesia reduces both preoperative separation anxiety as well as the extent of EA [6].

The blood-brain barrier is quickly crossed by ketamine, which takes one minute to attain its peak effects. Oral ketamine (6 mg/kg) used before desflurane anesthesia for adenotonsillectomy in children has been shown to reduce EA without compromising surgical outcomes. Also, 1 mg/kg ketamine i.v. followed by 1 mg/kg ketamine i.v. per hour after sevoflurane anesthesia for juvenile strabismus surgery reduces EA. In children, the combination of ketamine and midazolam was more powerful in sedating cases during a brief, painful procedure than ketamine alone [7].

The objectives of this study were to assess and compare the incidence and degree of postoperative emergence agitation among preschool children who were undergoing adenotonsillectomy when using preoperative oral dextromethorphan, ketamine, or midazolam. To assess and compare the time of the first dose of analgesic, and also to assess and compare the side effects of the used drugs such as nausea, vomiting, hallucination, and respiratory center depression.

## PATIENTS AND METHODS

The present study was a prospective, randomized, controlled, double-blinded study Zagazig University. Institutional Review Board approval (ZUIRB#: 6702/ 17-3-2021) was obtained. Patients were enrolled from June 2021 to December 2022, after having been informed of written parental consent from all patients.

**Sample size**

Using, open EPI, the sample size was calculated to be 56 (14 in each group). Assuming that sevoflurane emergence agitation among the control group was 52% and among the dextromethorphan group was 10.6% [8] and cases to control ratio 3:1 at 80% power of study and 95% confidence interval.

**Randomization**

Cases were assigned to one of four similar groups at a random way (14 patients in each) using computer-generated randomization tables, the randomization sequence was concealed in sealed envelopes picked by parents.

**Group (C):** 14 patients received a 10ml oral placebo (clear fluid) 1 hour before the general anesthesia induction.

**Group (D):** 14 patients received a dose of 0.5mg/kg oral dextromethorphan (Triaminic Cold and Cough syrup Novartis pharma 1mg/ml) 1 hour before the general anesthesia induction.

**Group (K):** 14 patients who received a dose of 0.5mg/kg oral ketamine (Ketalar Pfizer 5 mg/ml) 1 hour before the general anesthesia induction.

**Group (M):** Including 14 patients received a dose of 0.5mg/kg oral Midazolam (Dormicum 5 mg/ml Hoffman-la Roche Ltd, Switzerland) at 1 hour before the general anesthesia induction.

**Inclusion criteria:**

Parent's acceptance to keep their kids part of the study, children age to be preschool children (3-6) years from both sexes with physical status: American Society of Anesthesiologists (ASA) I&II.

**Exclusion criteria:**

Any case with developmental delay (mental retardation), hypersensitivity to any type of used drugs, congenital heart disease, or neurological disease associated with symptoms of agitation.

**Preoperative preparation:**

Informed written parental consent was taken from all participants. Medical history and complete clinical examination were done on all cases. Routine laboratory investigation including Complete blood count (CBC), Coagulation profile, and C reactive Protein (CRP).

Preoperative fasting times:

The cases should be fasting for 6 hours for solid foods and 2 hours for clear fluids. Premedication with IM 0.01 mg/kg atropine was done 1hr before surgery.

**Intraoperative management**

When the patient was taken into the operating room (OR), regular monitoring equipment was used to take readings from the patient's

electrocardiogram (ECG), noninvasive atrial blood pressure monitor, and pulse oximeter. IV line (24-22G) was inserted, and the ringer's lactate solution was infused according to the child's weight. The Parents were allowed to attend the induction of anesthesia until the child went to sleep. The patient was given 2 mg/kg of propofol IV, 1µg/kg of fentanyl IV, and 0.6 mg/kg of rocuronium IV to induce anesthesia and allow for easier tracheal intubation for CMV monitoring throughout surgery.

Sevoflurane 1-2% was used for maintenance of the anesthesia. Depth of anesthesia was monitored according to hemodynamics including the heart rate (HR) as well as the blood pressure (BP).

At fifteen minutes before the end of surgery, acetaminophen suppository 10mg/kg was used as a standard analgesia. At the end of surgery, Neostigmine (0.05 mg/kg IV) and atropine (0.01mg/kg) were used to reverse the effects of the non-depolarizing muscle relaxant in all individuals. Patients were extubated after fulfilling the criteria of extubation (regular spontaneous respiration, spo2 >92% on room air, able to follow commands, and full reversal of neuromuscular blockade with minimal cough), then the patients were shifted to Post Anesthetic Care unit (PACU).

**Postoperative management**

In PACU, agitation and pain scores were evaluated and parents attended the recovery of the child.

A five-point scale was used to evaluate agitation every 5 min. for 1hr. postoperative. Scoring from one to five corresponding to [1= asleep, 2= is calm as he is awake, 3= crying and irritable, 4 inconsolable, and 5= disoriented and restless] [9] Children with agitation score ≥ 4 were given IV increments of fentanyl (1ug/kg), children were evaluated to assess the respiratory depression signs with a minimum 10-minute interval between doses.

The Children and Infants Postoperative Pain Scale (CHIPPS) [10] was utilized for the assessment of postoperative pain in children every 15 min for 2 hours postoperative. Children with a score ≥ 4 were given diclofenac (25-50 mg rectal suppository according to the age) and the time to the first dose of analgesia (from discontinuation of sevoflurane till CHIPPS to be 4) was recorded.

**Post-operative adverse effects were recorded and treated such as:-**

Postoperative nausea and vomiting (PONV) were managed by ondansetron 0,15 mg/kg which could be repeated up to the total dose of 4mg. Bradycardia was managed by I.V. atropine at a dose of 0.01 mg/kg. Hypotension was managed by IV. Ringer's lactate solution according to the pediatric formula of I.V fluid infusion 4-2-1.

Children then were discharged from PACU to the ward when they had a score ≥9 of the Modified Aldert Score [11].

**Data collection and outcome measures**

Patient characteristics and operative data: age, Sex, ASA, Body weight, Duration of anesthesia, surgery, non-invasive blood pressure (NIBP), Heart rate (HR), and Oxygen saturation (SPO2), were recorded every 5 min intraoperatively, Side effects of used drugs eg. nausea, vomiting, hallucination, respiratory depression, Agitation was evaluated by a five-point scale, Emergence time (min.) from sevoflurane discontinuation to extubation (T1), Post-operative pain was assessed by Children and Infants Postoperative Pain Scale (CHIPPS), Time (min.) of eye-opening to verbal stimuli (discharge time) from the operating room (T2), Modified Aldert Score, to assess the discharge criteria.

**Statistical Analysis**

The statistical work was performed in SPSS 28. (IBM Co., Armonk, NY, USA). The Chi-square, t-t-paired, and ANOVA tests were used to examine categorical data, which were then displayed as frequencies and percentages.

## RESULTS

A total of sixty-five cases were enrolled; however, 56 patients aged 3-6 years of both sex admitted to Zagazig University Hospital for adenotonsillectomy, and finally included in the study after their parents' consent (Figure 1), Patients were randomly allocated into 4 groups,14 in each group.

Non-statistically significant differences were found as regards patients' characteristics, duration of surgery, and anesthesia among the studied groups (Table 1).

Heart rate was significantly higher in the ketamine group ($p<0.001$). As regards O2, systolic, diastolic blood pressure, and side effects, no statistically significant differences were found among the studied groups (Tables 2 &3).

The incidence of postoperative agitation >4 is higher in the control, with high significant decrease in the ketamine group ($p=0.02$). Group M was found to be significantly lower in agitation occurrence in comparison to the other groups ($p=0.02$) (Table 4).

Group M was found to be significantly lower in post-operative pain occurrence when compared to the other groups with the longest time for 1st analgesic request ($p=0.02$). Group K was found to be significantly lower in the amount of fentanyl consumption compared to the other groups ($p=0.004$) (Table 5).

Time from discontinuation of sevoflurane till the time of extubation (T1) was not significantly different among the studied groups, with T2 M/K groups longer than C and D groups (Table 6).

**Table (1):** Patients' characteristics, duration of anesthesia and duration of surgery.

| | | Group (C) (No= 14) | Group (D) (No= 14) | Group (K) (No= 14) | Group (M) (No= 14) | P. value |
|---|---|---|---|---|---|---|
| **Age (years)** | | 3-6 | 3-6 | 3-6 | 3-6 | 0.236# |
| | | 4.2 ± 0.9 | 4.6 ± 1.1 | 4.1± 0.9 | 3.99 ± 0.7 | |
| **Sex** | **Male** | 8 (57.1%) | 7 (50%) | 7 (50%) | 7 (50%) | 0.214^ |
| | **Female** | 6 (42.9%) | 7 (50%) | 7 (50%) | 7 (50%) | |
| **Body weight (Kg)** | | 14-22 | 14-22 | 14-22 | 14-22 | 0.475# |
| | | 18 ± 3.5 | 17 ± 3.6 | 19± 4.5 | 17 ± 3.9 | |
| **Duration of anesthesia(min)** | | 35-50<br>39 ± 4.3 | 36-50<br>38 ± 6.3 | 36-52<br>40 ± 4.5 | 35-50<br>39 ± 3.6 | 0.748# |
| **Duration of surgery(min)** | | 30-37 | 29-40 | 32-40 | 33-40 | 0.669# |
| | | 35 ± 5.3 | 34 ± 4.6 | 36± 5.6 | 36 ± 4.2 | |

Group C = control group, Group D= dextromethorphan group, Group K=ketamine group , Group M=midazolam group, no = Total number of subjects in each group
Data were expressed as mean ± SD; number (percentage).
#: ANOVA test. ^: Chi-square test.
P <0.05 is significant.

**Table (2):** Intraoperative hemodynamic data and O2 saturation

| variables | Group (C) (No= 14) | Group (D) (No= 14) | Group (K) (No= 14) | Group (M) (No= 14) | P. value # |
|---|---|---|---|---|---|
| **HR** | 85 ± 5.3<br>a | 86 ± 7.6<br>a,b | 95± 8.6<br>c | 75 ± 2.8<br>d | <0.001 |
| **Systolic blood pressure** | 95 ± 3.3 | 94 ± 4.6 | 93± 3.6 | 95 ± 3.8 | 0.466 |
| **Diastolic blood pressure** | 65 ± 4.4 | 66 ± 5.2 | 64± 3.7 | 64 ± 4.6 | 0.598 |
| **O2** | 99.5 ± 4.5 | 99.4 ± 4.3 | 99.4±4.4 | 99.6 ± 5.1 | 0.999 |

Group C = control group, Group D = dextromethorphan group, Group K= ketamine group , Group M=midazolam group, no = Total number of subjects in each group
Data were expressed as mean ± SD
#:ANOVA Test.
P <0.05 is significant.

**Table (3): postoperative side effect**

| Side effect | Group (C) (No= 14) | Group (D) (No= 14) | Group (K) (No= 14) | Group (M) (No= 14) | P. value ^ |
|---|---|---|---|---|---|
| **Nausea&Vomiting** | 2 (14.3%) | 1 (7.14%) | 1(7.14%) | 2 (14.3%) | 0.862 |
| **Hypotension** | 0 | 1 (7.14%) | 0 (0.0%) | 1 (7.14%) | 0.557 |
| **Respiratory center depression** | 0 | 0 | 1(7.14%) | 2 (14.3%) | 0.275 |
| **bradycardia** | 1 (7.14%) | 1 (7.14%) | 0 | 1 (7.14%) | 0.787 |

Group C = control group, Group D = dextromethorphan group, Group K= ketamine group , Group M=midazolam group, no = Total number of subjects in each group
Data were expressed as mean ± SD; number (percentage).
^: Chi-square test.
P <0.05 is significant.

**Table (4):** Postoperative agitation

| Agitation >4 | Group (C) (No= 14) | Group (D) (No= 14) | Group (K) (No= 14) | Group (M) (No= 14) | P. value |
|---|---|---|---|---|---|
| **Yes** | 8 (57.1%) | 4 (28.6%) | 3(21.4%) | 1 (7.14%) | **0.02** |

Group C = control group, Group D = dextromethorphan group, Group K= ketamine group , Group M=midazolam group, no = Total number of subjects in each group
Data were expressed as number (percentage).
^: Chi-square test.
P <0.05 is significant.

Chi-square for trend test was used to compare between each two groups separately.

**Table (5):** Postoperative pain and fentanyl consumption.

| | Group (C) (No= 14) | Group (D) (No= 14) | Group (K) (No= 14) | Group (M) (No= 14) | P. value |
|---|---|---|---|---|---|
| **postoperative pain>4** | 7 (50%) | 2 (14.3%) | 1 (7.14%) | 2 (14.3%) | **0.02^** |
| **fentanyl consumption** | 9.9±4.4 a | 7.2±5.4 a,b | 2.9±5.1 a,b,c | 6.9±4.5 a,b | **0.004#** |

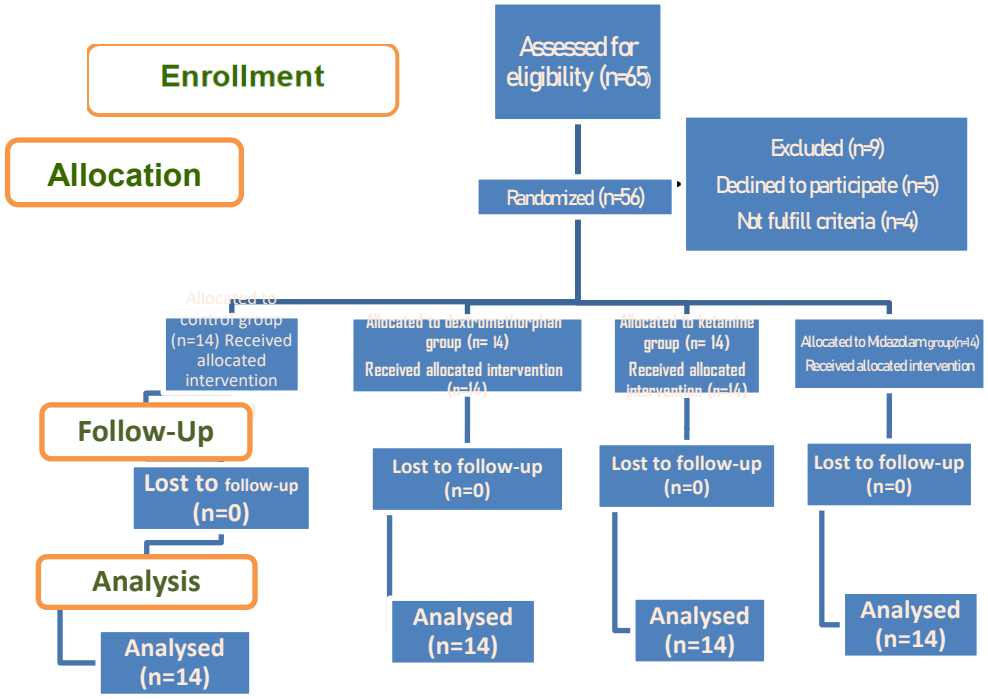
Group C = control group, Group D = dextromethorphan group, Group K= ketamine group , Group M=midazolam group, no = Total number of subjects in each group
Data were expressed as mean ± SD
^: Chi-square test.
#:ANOVA Test.
P <0.05 is significant.
Chi-square for trend test was used to compare between each two groups separately.

**Table (6):** Comparison between group C, group D, group K and group M regarding discharge time.

| | Group (C) (No= 14) | Group (D) (No= 14) | Group (K) (No= 14) | Group (M) (No= 14) | P. value # |
|---|---|---|---|---|---|
| **T1** | 8.7 ±2.5 | 9.4± 1.9 | 10.6± 3.1 | 10.3± 2.1 | 0.167 |
| **T2** | 10.3± 1.4 a | 10.5± 1.1 a,b | 12.7± 2.8 c,d | 12.1± 2.2 c,d | **0.004** |
| **Time to 1st analgesic request** | 51± 3.1 a | 70± 4.2 b | 82.1± 4.1 c | 71.4 ± 5.1 b,d | **<0.001** |

Group C = control group, Group D = dextromethorphan group, Group K= ketamine group , Group M=midazolam group, no = Total number of subjects in each group,T1=time from discontinuation of sevoflurane till time of extubation,T2=time from discontinuation of sevoflurane till eye opening and verbal stimuli discharge from operating room.
Data were expressed as mean ± SD.
#:ANOVA Test.
Independent samples student's t-test.
P <0.05 is significant.

**Figure 1**: Consort flow



## DISCUSSION

For both induction and maintenance of anesthesia in children, sevoflurane is a common inhalational anesthetic of choice. However, when used as the sole anesthetic, it is linked to a high incidence of emergence agitation (EA), which can lead to serious side outcomes for patients [10].

This study aimed to compare the use of preoperative ketamine midazolam or ketamine versus oral dextromethorphan for reducing sevoflurane emergence agitation among preschool children undergoing adenotonsillectomy.

Findings of the current study showed that non-statistically significant differences were found as regards patients' characteristics, duration of surgery, and anesthesia among the studied groups.

In harmony with our results, Kim et al. [12] aimed to assess the impact of the use of midazolam preoperatively versus ketamine on the emergence of agitation (EA) occurrence among children after sevoflurane anesthesia. They stated that no demographic or clinical data showed a statistically significant between-group difference.

This agreed with Abdelmawgoud and Mohy [8] who assessed the effectiveness of dextromethorphan and ketamine in treating agitation caused by sevoflurane. Regarding sex, weight, age, and surgery time, they revealed that the three groups were comparable.

The current findings showed that heart rate was significantly higher in the ketamine group ($p<0.001$). While as regards O2, systolic, diastolic blood pressure, and side effects, no statistically significant differences were found among the studied groups.

This disagreed with Mohammed et al. [13] who observed that postoperative measures, particularly those taken at 5 and 10 minutes, revealed a significant increase in mean arterial pressure (MAP) as well as heart rate in the midazolam group when compared to the nalbuphine group, which was linked to the midazolam group's higher incidence of EA.

This disagreed with Ozcan et al. [14] who investigated The effects of ketamine and midazolam on EA following sevoflurane anesthesia in children with caudal block, and while there were no significant differences between the groups, the midazolam group showed a greater increase in postoperative MAP and HR compared to the ketamine group.

The current study showed that respiratory center depression did not differ significantly between the studied groups.

This coincided with Mohammed et al. [13] who revealed that there were no statistically significant changes in respiratory rate (RR) and no apnea observed at all time intervals in the two studied groups.

In agreement with our findings, Cho et al. [15] found that respiratory depression was not seen in patients given either 0.03 or 0.05 mg/kg midazolam.

In this study, no significant difference in adverse events was found between the two groups. After analyzing the safe pediatric doses in prior papers, we decided to utilize dextromethorphan at a dose of 1 mg/kg in children. There were no adverse effects recorded [16].

This agreed with Abdelmawgoud and Mohy [8] who concluded that usage of ketamine and dextromethorphan hadn't been associated with any negative side effects [17]. The low bioavailability of dextromethorphan upon oral dosing (10%) explains this phenomenon [18], Because of the significant hepatic first-pass impact, the metabolite nor-ketamine, which produces sedation and analgesia without the hallucinations seen with the parenteral route, has a bioavailability of 16% after oral administration of ketamine [19].

Mohammed et al. [13] found that It was found that the severity and the incidence of EA were significantly lower in the nalbuphine group (11%) compared to the midazolam group (33%), as measured by Aono's four-point scale, the Paediatric Anaesthesia Emergence Delirium (PAED) scale, and the significantly lower need for postoperative rescue medication (propofol) (which is within the usual range of EA after sevoflurane anesthesia).

Cho et al. [15] agreed with our findings, as they reported that Preoperative administration of 0.03 mg/kg of midazolam reduces the risk of EA in children undergoing squint surgery.

In addition, Chen et al. [20] discovered that the larger dose of midazolam in their trial may explain why the incidence and severity of EA during cataract surgery could be reduced by administering a combination of 0.05 mg/kg midazolam and 0.5 g/kg fentanyl at the end of surgery. By adding fentanyl at a dose of 0.5 g/kg to midazolam, we were able to further reduce the occurrence and severity of EA.

Preventative analgesic effects of ketamine and a lower risk of EA after adenotonsillectomy in children [21].

In harmony with our results, Kim et al. [12] found that Premedication with ketamine, as opposed to midazolam, decreased the occurrence of EA in the early emerging phase (10-20 min) and the necessity for rescue drugs. In their trial, midazolam and ketamine both had an impact on lowering pre-anesthesia separation anxiety. They showed that premedicating children undergoing

ocular surgery with intravenous ketamine rather than midazolam reduced the incidence of EA.

Others, however, discovered that midazolam given intravenously did not lessen the prevalence of EA [22]. A systematic review of pediatric pharmacological EA prevention concluded that midazolam was ineffective in this context [23].

In contrast to the findings of Ozcan et al. [14], who found that Under sevoflurane anesthesia, neither ketamine nor midazolam increased caudal block or altered EA, the present investigation found that midazolam reduced the incidence of sevoflurane EA. Rectal midazolam administered 10–15 minutes before surgery is not effective in treating EA, according to the research of Breschan et al. [22] When using sevoflurane anesthesia for dental work in children, Abu-Shahwan and Chowdary [4] found that 34.2% of the kids experienced EA despite being premedicated with midazolam.

Oral premedication with midazolam did not reduce the rate of EA after sevoflurane anesthesia in studies that compared it to other medications [24].

**Limitations of the study:**

There are certain limitations to this study, such as the necessity to increase the sample size due to the small number of patients included. Only patients who had an adenotonsillectomy while under general anesthesia were included in the current study.

## CONCLUSION:

Ketamine premedication is more effective for EA prevention among children during the early emergence time after sevoflurane compared to midazolam and dextromethorphan anesthesia.

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