Comparison of the Effects of 0.03 and 0.05 mg/kg Midazolam with Placebo on Prevention of Emergence Agitation in Children Having Strabismus Surgery

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ABSTRACT

Background: Midazolam has been widely studied for preventing emergence agitation. The authors previously reported that in children with sevoflurane anesthesia, intravenous administration of midazolam (0.05 mg/kg) before the end of surgery reduced the incidence of emergence agitation but prolonged the emergence time. This study was designed to test the hypothesis that a lower midazolam dose could suppress emergence agitation with minimal disturbance of the emergence time in children with sevoflurane anesthesia.

Methods: In this randomized, double-blind, placebo-controlled trial, 90 children (1 to 13 yr of age) having strabismus surgery were randomized to 1:1:1 to receive 0.03 mg/kg of midazolam, 0.05 mg/kg of midazolam, or saline just before the end of surgery. The primary outcome, the incidence of emergence agitation, was evaluated by using the pediatric anesthesia emergence delirium scale and the four-point agitation scale. The secondary outcome was time to emergence, defined as the time from sevoflurane discontinuation to the time to extubation.

Results: The incidence of emergence agitation was lower in patients given 0.03 mg/kg of midazolam (5 of 30, 16.7%) and patients given 0.05 mg/kg of midazolam (5 of 30, 16.7%) compared with that in patients given saline (13/ of 30, 43.3%; $P = 0.036$ each). The emergence time was longer in patients given 0.05 mg/kg of midazolam (17.1 ± 3.4 min, mean ± SD) compared with that in patients given 0.03 mg/kg of midazolam (14.1 ± 3.6 min; $P = 0.0009$) or saline (12.8 ± 4.1 min; $P = 0.0003$).

Conclusion: Intravenous administration of 0.03 mg/kg of midazolam just before the end of surgery reduces emergence agitation without delaying the emergence time in children having strabismus surgery with sevoflurane anesthesia. **(ANESTHESIOLOGY 2014; 120:1354-61)**

SEVOFLURANE is a popular anesthetic agent for pediatric patients because it facilitates a rapid and smooth induction and emergence from anesthesia, has hemodynamic stability, and does not irritate airways.[1] However, sevoflurane has been associated with a high incidence (up to 80%) of emergence agitation in children.[2] Emergence agitation can include restlessness, agitation, disorientation, hallucination, delusion, inconsolable crying, and cognitive impairment.[3] Restless recovery from anesthesia may not only cause injury to the child or to the surgical site but also lead to the accidental removal of surgical dressings and intravenous catheters. Extra nursing care is often necessary. Furthermore, supplemental sedatives and/or analgesic medications in the postanesthesia care unit (PACU) may be needed to control emergence agitation, which could delay patient discharge from the hospital. Although the pathogenesis of postoperative emergence agitation remains unclear, children having ophthalmic surgery may experience a high incidence of emergence agitation due to visual disturbances.[4]

Various pharmacological agents have been tested for their ability to reduce the incidence of emergence agitation, including α_2 adrenergic receptor agonists,[5] opioids,[6,7] and sedative agents (propofol[8] and midazolam[9]). At present, midazolam is the most widely used premedication for pediatric anesthesia, and it has been evaluated for the prevention of emergence agitation. Several studies have suggested that midazolam can benefit patients by decreasing the incidence of postoperative agitation,[10,11] whereas others reported no such

What We Already Know about This Topic

- Midazolam 0.05 mg/kg given at the end of surgery reduces emergence agitation, but prolongs emergence time in children under sevoflurane anesthesia
- The authors tested the hypothesis that 0.03 mg/kg of midazolam suppresses emergence agitation without prolonging emergence time in children having strabismus surgery with sevoflurane anesthesia, comparing 0.05 mg/kg, 0.03 mg/kg, and placebo

What This Article Tells Us That Is New

- Both midazolam groups significantly and comparably reduced the risk of emergence agitation, and the 0.03 mg/kg dose did so without prolonging emergence time

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effect on emergence agitation.[12,13] Because midazolam has a short half-life, we considered the possibility that midazolam premedication is unable to maintain a residual effect until the end of longer procedures.[13] According to a previous report, combined premedication with midazolam and diazepam, a relatively long-acting benzodiazepine, improved the emergence condition from sevoflurane anesthesia compared with midazolam alone.[14] On the basis of this background, we gave the study agents just before the end of surgery and not as premedication in our studies that evaluated the prevention of emergence agitation.

We previously reported that administration of propofol or midazolam (0.05 mg/kg) before the end of surgery reduced the occurrence of emergence agitation in children having strabismus surgery.[9] However, the emergence time was 4 min longer in the midazolam and propofol groups than that in the control group. In this study, we could not eliminate the possibility that the patients had been reanesthetized during recovery because a midazolam dose of 0.05 mg/kg is a sedative dose in pediatric patients having invasive and/or time-consuming procedures[15] and the elimination half-life of midazolam in children usually ranges from 1 to 2 h.[16] The concerns about reanesthetization of patients due to administration of midazolam before the end of surgery could be put to rest if it could be concluded that a smaller dose of midazolam effectively suppresses emergence agitation without delaying the emergence time.

Therefore, we designed a follow-up study to test the hypothesis that a midazolam dose less than 0.05 mg/kg suppresses emergence agitation with minimal effects on the emergence time. The primary endpoint of the current study was to evaluate whether 0.03 mg/kg of midazolam is as effective as 0.05 mg/kg of midazolam given just before the end of strabismus surgery in reducing the incidence of emergence agitation after sevoflurane anesthesia in children. The secondary endpoint was to examine whether 0.03 mg/kg of midazolam given just before the end of strabismus surgery affects the emergence time.

Materials and Methods

The trial was approved by the Ethics Committee of the Korea University Anam Hospital Institutional Review Board (Seoul, Korea) (ref: ED12083) and was registered at ClinicalTrials.gov Protocol Registration System (ref: NCT01680471). Written consent was obtained from parents, and assent was obtained from children who were old enough to understand the concept of research. The study was implemented in accordance with the principles of the Helsinki Declarations.

This prospective, randomized, double-blind, placebo-controlled, parallel-group, single-site trial was conducted from May to September 2012. The patients were Korean children (1 to 13 yr of age) with American Society of Anesthesiologists physical status of I or II who were admitted and had elective strabismus surgery at Korea University Anam Hospital. The participants were recruited through the strabismus clinic of Korea University Anam Hospital. Exclusion criteria included known adverse reactions to midazolam, neurological illness, developmental delay, previous anesthesia experience, or parental refusal.

The 90 enrolled patients were randomized to 1:1:1 by using a computer-generated randomization program (Excel; Microsoft, Redmond, WA) to receive 0.03 mg/kg of midazolam (n = 30), 0.05 mg/kg of midazolam (n = 30), or isotonic saline (n = 30). Independent researchers who were not involved in the anesthesia procedures or outcome assessment conducted patient enrollment, generated the random allocation, and prepared a sealed envelope. All patients, care providers, outcome assessors, and data analysts were blinded to patient assignment.

Intravenous access for anesthesia was obtained on the night before the surgery. All patients fasted for 8 h and received intramuscular atropine (0.01 mg/kg) as premedication 30 min before induction of anesthesia. The number of children who were agitated or inconsolable during induction of anesthesia was recorded in each group.

After patients arrived in the operating room, the study agents were prepared according to the order sealed in an envelope by a research nurse who was not involved in data collection. Noninvasive blood pressure, electrocardiogram, heart rate, pulse oxygen saturation, end-tidal carbon dioxide, and end-tidal sevoflurane concentrations (Cato edition; Drager, Lubeck, Germany) were monitored throughout the surgery.

Anesthesia was induced by using intravenous thiopental sodium (5 mg/kg) and was maintained with an end-tidal concentration of 2 to 3% sevoflurane (Abbott laboratories S.A., Abbott Park, IL) and 50% nitrous oxide in oxygen. Intravenous rocuronium bromide (0.6 mg/kg) was used to facilitate tracheal intubation. After induction of anesthesia, patients were given intravenous paracetamol (10 mg/kg) for postoperative pain relief.

Just before the end of surgery, the patients were given the study drug in accordance with the allocated study group. On completion of the surgery, all anesthetic gases were discontinued and the fraction of inspired oxygen was increased to 100%. All patients received eye ointment in the operated eye without an eye patch. The tracheal tube was removed when the patient demonstrated purposeful movement, facial grimacing, and spontaneous and regular breathing. After extubation, the patients were transferred to the PACU.

In the PACU, the patients were monitored for heart rate, noninvasive blood pressure, and pulse oxygen saturation and were cared for by one of their parents and the PACU nurses. Behavior on emergence, which was determined by using the pediatric anesthesia emergence delirium scale devised by Sikich and Lerman[3] (table 1) and a four-point agitation scale described by Aono *et al.*[17] (1 = calm; 2 = not calm, but could be easily calmed; 3 = not easily calmed, moderately

Table 1. The Pediatric Anesthesia Emergence Delirium Scale Devised by Sikich and Lerman[3]

Item	Score
The child makes eye contact with caregiver	4 = not at all
The child's actions are purposeful	3 = just a little
The child is aware of his/her surroundings	2 = quite a bit
	1 = very much
	0 = extremely
The child is restless	0 = not at all
The child is inconsolable	1 = just a little
	2 = quite a bit
	3 = very much
	4 = extremely

The scores of each item are summed to obtain a total pediatric anesthesia emergence delirium scale score. The severity of emergence agitation increased proportional to the total score.

Reproduced, with permission, from Sikich N, Lerman J. Anesthesiology 2004; 100:1138–45.

Table 2. Four-point Agitation Scale Described by Aono *et al.*[17]

Score	Behavior	Emergence Agitation
1	Calm	No
2	Not calm but could be easily calmed	
3	Not easily calmed, moderately agitated, or restless	Yes
4	Excited or disorientated	

Reproduced, with permission, from Aono *et al.* Anesthesiology 1997; 87:1298–300.

agitated or restless; and 4 = excited or disoriented) (table 2), was recorded every 5 min for the first 30 min, and then every 10 min for the remainder of the stay in the PACU.

The primary outcome variable included behavior on emergence scored using the pediatric anesthesia emergence delirium scale and the four-point agitation scale. Two researchers (one research anesthesiologist and one nurse) who were unaware of group assignment evaluated all the patients in the PACU. The anesthesiologist assessed the scores on the pediatric anesthesia emergence delirium scale and the nurse evaluated the scores on the four-point scale. Agitation scores were measured starting immediately after extubation and continuously thereafter until no agitation was evident. The highest score for each patient was recorded. Patients were considered agitated if they had a score of 3 or 4 on the four-point scale during their stay in the PACU. Severely agitated patients (score = 4) were treated with intravenous fentanyl (1 μg/kg).

The secondary outcome variable was the time to emergence, defined as the time from the discontinuation of sevoflurane to the time of extubation. Measurements also included the duration of surgery, anesthesia, and sevoflurane administration. The duration of anesthesia was defined as the time from induction to extubation. The duration of sevoflurane administration was defined as the time from induction to the discontinuation of sevoflurane.

Table 3. The Modified Aldrete Scoring System for Determining When Patients Are Ready for Discharge from the Postanesthesia Care Unit[18]

Discharge Criteria	Score
Activity: able to move voluntarily or on command	
Four extremities	2
Two extremities	1
Zero extremities	0
Respiration	
Able to deep breathe and cough freely	2
Dyspnea, shallow or limited breathing	1
Apneic	0
Circulation	
Blood pressure ± 20 mm of preanesthetic level	2
Blood pressure ± 20–50 mm preanesthesia level	1
Blood pressure ± 50 mm of preanesthesia level	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responding	0
oxygen saturation	
Able to maintain oxygen saturation >92% on room air	2
Needs oxygen inhalation to maintain oxygen saturation >90%	1
oxygen saturation <90% even with oxygen supplementation	0

A score 9 was required for discharge.

Reproduced, with permission, from Aldrete JA. J Clin Anesth 1995; 7:89–91.

We assessed postoperative pain by using a numerical rating scale (0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain; and 4 = the worst imaginable pain). This was assessed after the patients were able to make eye contact with the caregiver or nurse to exclude emergence agitation. Rescue medication in the form of intravenous fentanyl (1 μg/kg) was given on parental request or to treat pain whenever the intensity of pain was judged to be greater than 2.

Patients were discharged from the PACU after a modified Aldrete score[18] (table 3) of 9 was attained without pain or agitation in an hour. Adverse events were recorded, including postoperative nausea or vomiting, laryngospasm, and respiratory depression.

Statistical Analysis

By using power analysis based on the results of our previous study,[9] we deduced that a sample size of 30 patients per group would have a significance level of 5% (two-tailed) and a power of 80% in detection of 30% difference in emergence agitation incidence among the groups. According to our previous results, emergence agitation occurred in 74.3% (26 of 35) of the patients in the saline group and in 45.5% (30 of 66) of those in the pharmacologically treated group, and the time to emergence was 14.3 ± 3.8 min in the midazolam-treated group and 11.3 ± 2.9 min in the saline group.

Continuous variables are reported as means with the SD; these variables were analyzed by one-way ANOVA.

Nonparametric data such as the pediatric anesthesia emergence delirium scale scores are reported as medians and interquartile ranges; these data were compared by using the Kruskal–Wallis test. Categorical variables, such as the incidence of emergence agitation, are reported as numbers and percentages; these variables were compared among groups by using the chi-square test or Fisher exact test, as appropriate. Multiple comparisons were obtained using false discovery rate *post hoc* analysis. Accordingly, the primary outcome (incidence of emergence agitation) was analyzed by using the chi-square test followed by the false discovery rate, and the secondary outcome (emergence time) was analyzed by using ANOVA with the false discovery rate.

SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL), was used for all statistical analyses, and a P value of less than 0.05 was considered statistically significant.

Results

Of the 100 patients who were initially assessed, 90 who were randomized to their allocated intervention completed the trial. The three patient groups did not differ in age, sex distribution, body weight, type of surgical procedures (1 or 2 eyes), and durations of surgery and anesthesia (table 4). Similarly, the rates of preoperative agitation did not differ among the three patient groups (table 4).

The incidence of emergence agitation was 16.7% each in the patients given 0.03 mg/kg of midazolam and the patients given 0.05 mg/kg of midazolam (5 of 30 each) and was 43.3% in the patients given saline (13 of 30). The differences between the patients given 0.03 mg/kg of midazolam, the patients given 0.05 mg/kg of midazolam, and the patients given saline were statistically significant (P = 0.036 each; table 5). The pediatric anesthesia emergence delirium scale score was lower in both the patients given 0.03 mg/kg of midazolam (mean, 10 [range, 8 to 15]) and patients given 0.05 mg/kg of midazolam (mean, 10 [range, 8 to 17]) compared with that in the patients given saline (mean, 12 [range, 9 to 19]; P = 0.0165 each). Similarly, the percentages of patients with the pediatric anesthesia emergence delirium scale scores 10 or greater and 13 or greater were lower in the patients given 0.03 mg/kg of midazolam and the patients given 0.05 mg/kg of midazolam compared with that in the patients given saline (P = 0.03 and P = 0.015 in patients with pediatric anesthesia emergence delirium scale scores ≥10, P = 0.036 and P = 0.036 in patients with pediatric anesthesia emergence delirium scale scores ≥13). In addition, the incidence of pediatric anesthesia emergence delirium scale

Table 4. Demographic, Surgical, and Anesthetic Data

	Midazolam 0.03 mg/kg (n = 30)	Midazolam 0.05 mg/kg (n = 30) 30)	Normal Saline (n = 30)	*P* Value
Age (mo)	96 ± 27	94 ± 22	97 ± 25	0.896
Sex (male/female)	10/20	13/17	9/21	0.532
Weight (kg)	31 ± 13	27 ± 8	30 ± 11	0.275
Eyes operated, 1/2	15/15	17/13	21/9	0.277
Duration of surgery (min)	46 ± 26	45 ± 23	47 ± 25	0.963
Duration of anesthesia (min)	82 ± 30	83 ± 26	86 ± 27	0.878
Duration of sevoflurane administration (min)	60 ± 30	59 ± 26	65 ± 27	0.694
Incidence of preoperative agitation	4 (13.3%)	7 (23.3%)	8 (26.7%)	0.420

Data are presented as mean ± SD or number of patients (percentages). None of these parameters differed significantly among the three groups.

Table 5. Incidence of Emergence Agitation, Pediatric Anesthesia Emergence Delirium Scale Score, and Emergence Time

	Midazolam 0.03 mg/kg (n = 30)	Midazolam 0.05 mg/kg (n = 30)	Saline (n = 30)	*P* Value
Incidence of emergence agitation*	5 (16.7%)	5 (16.7%)	13 (43.3%)	0.024
Pediatric anesthesia emergence delirium scale score†	10 (8–17)	10 (8–17)	12 (9–19)	0.004
No. of patients with pediatric anesthesia emergence delirium score ≥10‡	21 (70%)	19 (63.3%)	28 (93.3%)	0.018
No. of patients with pediatric anesthesia emergence delirium score ≥13§	5 (16.7%)	5 (16.7%)	13 (43.3%)	0.024
Emergence time (min)‖	14.1 ± 3.6	17.1 ± 3.4	12.8 ± 4.1	<0.001

Data are presented as numbers of patients (percentage), median (range), or mean ± SD. Multiple comparisons using false discovery rate were obtained as follows:

* Midazolam 0.03 mg/kg *vs.* saline (P = 0.036), midazolam 0.05 mg/kg *vs.* saline (P = 0.036), midazolam 0.03 mg/kg *vs.* midazolam 0.05 mg/kg (P = 1).
† Midazolam 0.03 mg/kg *vs.* saline (P = 0.0165), midazolam 0.05 mg/kg *vs.* saline (P = 0.0165), midazolam 0.03 mg/kg *vs.* midazolam 0.05 mg/kg (P = 1).
‡ Midazolam 0.03 mg/kg *vs.* saline (P = 0.03), midazolam 0.05 mg/kg *vs.* saline (P = 0.015), midazolam 0.03 mg/kg *vs.* midazolam 0.05 mg/kg (P = 0.584).
§ Midazolam 0.03 mg/kg *vs.* saline (P = 0.036), midazolam 0.05 mg/kg *vs.* saline (P = 0.036), midazolam 0.03 mg/kg *vs.* midazolam 0.05 mg/kg (P = 1).
‖ Midazolam 0.03 mg/kg *vs.* saline (P = 0.385), midazolam 0.05 mg/kg *vs.* saline (P = 0.0003), midazolam 0.03 mg/kg *vs.* midazolam 0.05 mg/kg (P = 0.0009).

Table 6. Postoperative Adverse Events, Rescue Medication, Pain Score

	Midazolam 0.03 mg/kg (n = 30)	Midazolam 0.05 mg/kg (n = 30)	Normal Saline (n = 30)
Nausea, vomiting	0	0	0
Laryngospasm	1	0	0
Desaturation	0	0	0
Needing fentanyl for severe agitation	5 (16.7%)	4 (13.3%)	9 (30.0%)
Mean fentanyl consumption (μg) for severe agitation	4.67	3.5	7.17
Mean pain score	0.37 ± 0.12	0.57 ± 0.13	0.57 ± 0.16
Mean fentanyl consumption (μg) for postoperative pain control	3	2.5	3.3

Data are presented as number of postoperative adverse events, number of patients (percentage), mean doses (μg), or mean ± SD. Severely agitated patients who had a score of 4 on the four-point scale were treated with intravenous fentanyl (1 μg/kg). Postoperative pain was assessed by using a numerical rating scale (0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain; 4 = the worst imaginable pain). Rescue medication of intravenous fentanyl (1 μg/kg) was given on parent's request or to treat pain whenever the intensity of pain was judged to be >2. All data showed no significant difference among the three groups.

scores 13 or greater corresponded exactly to the incidence of emergence agitation (table 5).

The emergence time was longer in the patients given 0.05 mg/kg of midazolam compared with that in the patients given 0.03 mg/kg of midazolam (P = 0.0009) and the patients given saline (P = 0.0003) but was similar in the patients given 0.03 mg/kg of midazolam and the patients given saline (table 5).

The incidence of severe agitation requiring pharmacologic treatment, the mean fentanyl consumption, and the incidence of postoperative adverse events, including nausea or vomiting, laryngospasm, and respiratory depression, did not differ among the three patient groups (table 6). The mean patient pain score (0.03 mg/kg of midazolam, 0.37 ± 0.12; 0.05 mg/kg of midazolam, 0.57 ± 0.13; and saline, 0.57 ± 0.16), the number of patients who required rescue fentanyl for postoperative pain control (0.03 mg/kg of midazolam, four patients; 0.05 mg/kg of midazolam, three patients; and saline, four patients), and the mean fentanyl consumption (0.03 mg/kg of midazolam, 3 μg; 0.05 mg/kg of midazolam, 2.5 μg; and saline, 3.3 μg) were not statistically different among the patient groups.

Discussion

This study demonstrated that giving 0.03 mg/kg of midazolam to children having strabismus surgery with sevoflurane anesthesia just before the end of surgery reduced the incidence of emergence agitation without delaying the emergence time or increasing postoperative adverse events.

The etiology of emergence agitation is unclear. Several studies proposed that emergence agitation is related to a variation in the neurologic recovery rate in different brain areas and to the immaturity of neurons.[19] Inhalation anesthetics have been known to exert transient paradoxical excitatory effects in both animals and human patients, especially in children. Sevoflurane directly excites neurons in the locus ceruleus of rats, which may be associated with emergence agitation.[20] The γ-aminobutyric acid receptor is the target depressant effect site of most anesthetic drugs including sevoflurane.[21] We previously examined the effect of midazolam and propofol, which are γ-aminobutyric acid receptor inhibitors, on emergence behavior and reported that giving intravenous propofol or midazolam to children having strabismus surgery before the end of surgery decreases the occurrence of emergence agitation, but 0.05 mg/kg of midazolam prolongs emergence.[9]

Although midazolam is a commonly used premedication for children having operations, its effects on emergence behavior are unclear. Several studies have suggested that midazolam can benefit patients by decreasing the incidence of postoperative agitation. According to Lapin *et al.*,[10] preoperative oral midazolam decreased the amount of postoperative agitation in children having myringotomy surgery with sevoflurane anesthesia. However, patients given oral midazolam premedication had significantly longer recovery times. In contrast, others studies reported no effect on emergence agitation.[12,13] Breschan *et al.*[12] reported that midazolam premedication did not result in a reduced incidence of emergence agitation after sevoflurane anesthesia during minor surgery.[12] According to Cohen *et al.*,[13] intravenous 0.1 mg/kg of midazolam given at the induction of anesthesia did not reduce the incidence of emergence agitation, but it did delay emergence and recovery having an adenotonsillectomy. Therefore, the effects of midazolam premedication on emergence behavior are controversial. Because midazolam has a short half-life, we considered the possibility that midazolam premedication is unable to maintain a residual effect until the end of longer procedures.[13] Arai *et al.*[14] reported that a combined premedication with midazolam and diazepam, a relatively long-acting benzodiazepine, improves the emergence condition from sevoflurane anesthesia compared with midazolam alone. On the basis of this background, we gave intravenous midazolam just before the end of surgery and not as premedication, hence its effects may have lasted through the postoperative recovery period.

Premedication using sedative agents may delay recovery from anesthesia. For example, both 0.1 mg/kg of midazolam and 2 mg/kg of propofol premedication prolonged extubation 5 to 7 min compared with controls in children having adenotonsillectomy.[13] In addition, premedication with oral

0.5 mg/kg midazolam delayed eye opening and prolonged the time to discharge from the recovery room in patients with halothane anesthesia.[22] Similarly, we found that giving intravenous 0.05 mg/kg of midazolam or 1 mg/kg of propofol before the end of surgery delayed emergence after sevoflurane anesthesia.[9] Sedation with intravenous midazolam (0.05 to 0.1 mg/kg), with a maximum single dose of 2 mg and a maximum total dose of 4 mg, was shown to be safe and effective in pediatric patients having invasive and/or time-consuming procedures.[15] Because our previous study used a midazolam dose of 0.05 mg/kg and the elimination half-life of midazolam in children is usually 1 to 2 h,[16] we could not eliminate the possibility that these patients had become reanesthetized. Thus, we designed the current study to test the hypothesis that a dose of midazolam less than 0.05 mg/kg suppresses emergence agitation while having a minimal effect on the emergence time. Our current results indicate that intravascular 0.03 mg/kg of midazolam reduces the incidence of agitation without delaying emergence and confirms that 0.05 mg/kg of midazolam prolongs emergence. Therefore, it seems reasonable that the possibility of reanesthetization can be excluded when 0.03 mg/kg of midazolam is given intravenously before the end of surgery.

Emergence agitation is a common problem in pediatric patients emerging from anesthesia. Agitated patients typically kick, tilt their bodies, extend their heads, and demonstrate little eye contact and they are inconsolable.[23,24] The causes of emergence agitation include rapid awakening in a hostile environment, pain, preschool age, preoperative anxiety, sevoflurane or desflurane anesthesia, and head and neck procedures.[25,26] No single factor can be the cause of emergence agitation.

Pain is widely regarded as a major contributing factor to emergence agitation because adequate analgesia with regional blockade, opioids, and nonsteroidal anti-inflammatory drugs decreases the incidence of emergence agitation in children.[27,28] Although pain has been described as a contributing factor to emergence agitation, some recent studies have reported the occurrence of emergence agitation when pain was treated effectively[29] or even in the absence of any painful stimuli.[30] Despite the controversy over pain being a risk factor for agitation, we attempted to reduce postoperative pain by giving 10 mg/kg intravenous paracetamol to all patients after anesthesia induction to exclude any possible effect of postoperative pain on the occurrence of emergence agitation. According to a recent report, intravenous 15 mg/kg paracetamol is associated with similar analgesic properties to that of intravenous 1.0 mg/kg tramadol after adenotonsillectomy in children.[31] Therefore, we presumed that intravenous 10 mg/kg paracetamol was sufficient for controlling immediate postoperative pain in strabismus surgery. The mean pain score in the current study was 0.37 ± 0.12 in the patients given 0.03 mg/kg of midazolam, 0.57 ± 0.13 in the patients given 0.05 mg/kg of midazolam, and 0.57 ± 0.16 in the patients given saline. Because the average pain score was less than 1 throughout the study, we believe that postoperative pain did not have an important influence on the agitation scores.

Research on emergence agitation has been complicated by the use of various agitation rating systems and observational differences in defining the stages of agitation.[3] The limitations of previous scales led to the development of the pediatric anesthesia emergence delirium scale, which improved the reliability and validity of emergence agitation diagnoses in children. The interobserver reliability of the pediatric anesthesia emergence delirium scale was 0.84 and the internal consistency was 0.89 (95% CI, 0.76 to 0.90).[3] The sensitivity and specificity analyses using the receiving operator characteristics revealed an area under the curve of 76.6% with a threshold of 10 or more, giving a sensitivity of 64% and a specificity of 86%. These results support the reliability and validity of the pediatric anesthesia emergence delirium scale. Numerous studies have evaluated emergence agitation with this scale since the publication of these results, and the pediatric anesthesia emergence delirium scale is currently regarded as the general evaluation tool for emergence agitation. Although the authors of the pediatric anesthesia emergence delirium scale provided sensitivity and specificity data for a score of 10, they suggested that "further attempts to determine a cutoff point are needed"; however, until recently, no consensus has been reached regarding an appropriate cutoff pediatric anesthesia emergence delirium scale score for emergence agitation.[8,32,33] Many other studies have used both the pediatric anesthesia emergence delirium scale and Aono's four-point scale for evaluating emergence agitation.[8,34,35] Patients were considered agitated if they had a score of 3 or 4 on the four-point scale. Therefore, to determine whether the patients were agitated, we evaluated emergence agitation by using both the pediatric anesthesia emergence delirium scale and Aono's four-point scale. However, the usefulness of the pediatric anesthesia emergence delirium scale may be limited for measuring emergence agitation after ophthalmology procedures because item 1, which concerns eye contact, may be misinterpreted due to the visual disturbance caused by eye ointment and postoperative pain. Although a pediatric anesthesia emergence delirium score 10 or greater has been regarded as the cutoff for emergence agitation from anesthesia,[3] our findings suggest that a pediatric anesthesia emergence delirium score 13 or greater indicated the occurrence of agitation, which may have been due to the artifactually high score for item 1.

Our study had several limitations. The first limitation is that the age range of the study participants was wide (1 to 13 yr). It is well known that emergence agitation is prevalent in the preschool age population, but the majority of patients in the current study (62 of 90, 69%) were of school age (>84 months). Therefore, the overall incidence of emergence agitation of the current study was lower than that of our previous study[9] (control group; 43.3 *vs.* 71.4%). However, the primary purpose of the current study was to

evaluate whether midazolam given before the end of surgery is effective in suppressing emergence agitation, not to evaluate the overall incidence of emergence agitation. Therefore, we believe that the skewed age range of this study population did not affect the results of the current study.

The second limitation is that atropine premedication could also affect perioperative agitation. Atropine is used widely as preanesthetic medication before surgical procedures. Due to its anticholinergic action, it can prevent bradycardia, bronchoconstriction, and the vasovagal reaction and can reduce secretions.[36] By reducing the cholinergic activity in the central nervous system, an anticholinergic drug can cause central anticholinergic syndrome, which consists of confusion, hallucination, agitation, delirium, drowsiness, and coma.[37,38] In our study, we gave 0.01 mg/kg of atropine intramuscularly 30 min before anesthesia induction for all our patients, and this may have been responsible for perioperative agitation in these pediatric patients by causing anticholinergic syndrome. However, central anticholinergic syndrome is a rare adverse drug reaction of atropine, and these reactions have considerable interpersonal variation based on individual susceptibility to atropine (idiosyncrasy).[38] Only a few cases have been reported[39,40] and a correlation between atropine premedication and central anticholinergic syndrome has not yet been proven in a controlled study. Furthermore, according to a previous report,[40] central anticholinergic syndrome was never observed in patients premedicated with atropine intramuscularly, and the authors concluded that the intramuscular route was safer than the intravascular route for premedication with atropine. Therefore, we believe that central cholinergic syndrome due to atropine premedication was less likely to occur because we used the intramuscular route.

The third limitation is that both doses (0.03 and 0.05 mg/kg) of midazolam had no effect on the incidence of severe emergence agitation requiring pharmacologic treatment. In the current study, the incidence of emergence agitation was reduced at both doses of midazolam compared with the placebo, and the emergence time was different between the two doses. Therefore, the significance of this study is that we found that a lower dose (0.03 mg/kg) of midazolam could suppress emergence agitation with minimal disturbance of the emergence time. Nevertheless, further studies on suppression of severe agitation are needed because severe agitation can create a disruptive and dangerous situation.

Finally, we compared our outcomes by using the false discovery rate *post hoc* analysis for multiple comparisons. The false discovery rate[41] control is a statistical method used in multiple hypotheses testing to correct for multiple comparisons, and this method is at least as powerful as the well-known Bonferroni adjustment. This stepwise algorithm sorts the *P* values and sequentially rejects the hypotheses starting from those with the smallest *P* value. In our primary outcomes, the *P* values obtained using the chi-square test for comparisons of the incidence of emergence agitation were both 0.011 between the patients administered 0.03 mg/kg of midazolam and those administered saline and between the patients administered 0.05 mg/kg of midazolam and those administered saline. Furthermore, the *P* values obtained using the Kruskal–Wallis test for the pediatric anesthesia emergence delirium scale score were both 0.024 between the patients administered 0.03 mg/kg of midazolam and those administered saline and between the patients administered 0.05 mg/kg of midazolam and those administered saline. Both *P* values were less than the 0.025 level after applying the Bonferroni correction for multiple comparisons (*i.e.*, 0.05/2 = 0.025); therefore, the outcomes remained statistically significant and the application of the false discovery rate control did not change the interpretations of these data.

In conclusion, this study showed that giving 0.03 mg/kg of midazolam before the end of surgery reduces the incidence of emergence agitation in children having strabismus surgery without delaying the emergence time or causing adverse events.

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Competing Interests

The authors declare no competing interests.

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