Effect of esmolol and lidocaine on agitation in awake phase of anesthesia among children: a double-blind, randomized clinical study

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Abstract

Background: Sevoflurane is widely used to anesthetize children because of its rapid action with minimal irritation of the airways. However, there is a high risk of agitation after emergence from anesthesia. Strabismus surgery, in particular, can trigger agitation because patients have their eyes covered in the postoperative period. The aim of this study was to determine whether or not esmolol and lidocaine could decrease emergence agitation in children.

Methods: Eighty-four patients aged 3 to 9 years undergoing strabismus surgery were randomly assigned to a control group (saline only), a group that received intravenous lidocaine 1.5 mg/kg, and a group that received intravenous esmolol 0.5 mg/kg and lidocaine 1.5 mg/kg. Agitation was measured using the objective pain score, Cole 5-point score, and Richmond Agitation Sedation Scale score at the end of surgery, on arrival in the recovery room, and 10 and 30 min after arrival.

Results: The group that received the combination of esmolol and lidocaine showed lower OPS and RASS scores than the other two groups when patients awoke from anesthesia (OPS = 0 (0-4), RASS = -4 [(-5)-1]) and were transferred to the recovery room (OPS = 0 (0-8), RASS = -1 [(-5)-3]) (P < 0.05). There was no significant difference in the severity of agitation among the three groups at other time points (P > 0.05).

Conclusions: When pediatric strabismus surgery is accompanied by sevoflurane anesthesia, an intravenous injection of esmolol and lidocaine could alleviate agitation until arrival in the recovery room.

Trial registration: Clinical Research Information Service, No. KCT0002925; https://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=11532

Keywords: Agitation; Esmolol; Lidocaine; Sevoflurane

Introduction

In recent years, sevoflurane has become a popular anesthetic agent, affording hemodynamic stability, low-level stimulation of the airway, and low blood-gas solubility and permitting rapid induction of anesthesia and emergence. The rapid recovery from sevoflurane anesthesia reduces the risks of coughing and respiratory complications. However, a high incidence of agitation on emergence from anesthesia (50%–80%) has been reported in children who receive sevoflurane. Postoperative agitation not only causes pain and delays discharge from the recovery room, but also requires medical treatment. Several factors, including anxiety, young age, and pain, cause agitation in children. Several agents, including midazolam and dexmedetomidine, are used to

mitigate agitation.^[4] However, these drugs are not safe for use in children; midazolam delays postoperative awakening, and dexmedetomidine can trigger side effects, such as hypotension, bradycardia, and asystole.^[5,6]

Lidocaine relieves postoperative sore throat and reduces emergence agitation and coughing, ^[7,8] and has been used to alleviate agitation in children during both induction of anesthesia and when awakening. However, it is not yet clear whether lidocaine reduces agitation.

Esmolol is often used to maintain hemodynamic stability; it also relieves stress during surgery and lowers the requirement for narcotics postoperatively. [9,10] However, the use of esmolol to alleviate agitation in children has received little research attention. Many children become

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agitated after strabismus surgery because the eyes are covered postoperatively, although the exact reason remains unclear. [11] We hypothesized that agitation would be alleviated by the analgesic and sedating effects of esmolol and attenuation of airway stimulation by lidocaine.

Methods

Ethical approval

This double-blind, prospective, randomized, controlled clinical trial was approved by the Institutional Review Board of Soon Chun Hyang University Cheonan Hospital (No. 2017–05–026–002), and conducted in accordance with the tenets of *Declaration of Helsinki*. This study was registered in the Clinical Research Information Service (No. KCT0002925). Written informed consent was obtained from the parents of children.

Patients enrollment

Eighty-four children undergoing strabismus surgery aged 3 to 9 years with American Society of Anesthesiologists physical status I or II between June 2017 and February 2018 were enrolled. Patients with a cardiac disorder, respiratory disease, or mental disorder were excluded. The study participants were randomly assigned to a control (saline) group, a lidocaine group, or an esmolol and lidocaine (EL) group using a computerized random sequence generator program (www. random.org). The investigator who was involved in drug administration was blinded to group allocation. A non-blinded nurse prepared the study drugs in the recovery room and handed syringes containing the drugs to the investigator. Drug administration and patient evaluation were performed by a single investigator.

Method of anesthesia

All patients received intramuscular injections of glycopyrrolate 0.01 mg/kg as premedication. Heart rate, mean arterial pressure, and the SpO₂ level were monitored, and thiopental 5 mg/kg and rocuronium 0.6 mg/kg were administered immediately prior to induction. Vital signs were then checked at 5-minute intervals. At intubation, esmolol 0.5 mg/kg was injected intravenously and anesthesia was maintained with 2% sevoflurane in a mixture of oxygen and air (FiO₂ 0.5) and maintenance of normocapnia. Dexamethasone 0.5 mg/kg was injected before surgery. The inhalation anesthetic levels were elevated or nicardipine was administered if the patient's blood pressure (BP) or heart rate rose by >25% of the baseline value, and atropine 0.01 mg/kg was administered if bradycardia developed. All patients received 1:4 saline dextrose.

Protocols for three groups

The control group received saline at a volume equivalent to that of 1.5 mg/kg of lidocaine at the end of surgery and saline at a volume equivalent to that of 0.5 mg/kg of esmolol when they started to move voluntarily. The lidocaine group received 1.5 mg/kg lidocaine intravenously at the end of surgery and saline at a volume equivalent to that of 0.5 mg/kg of esmolol when they started to move

voluntarily after the gas was turned off. The EL group received 1.5 mg/kg of lidocaine at the end of surgery and 0.5 mg/kg of esmolol when they started to move voluntarily after the gas was turned off. The esmolol dose used in this study was determined from the dose administered when esmolol is used as an adjunct to opioids, which is generally 0.5 mg/kg. [12] The lidocaine dose was determined based on reports of lidocaine being effective in reducing airway stimulation when administered at a dose of 1.5 mg/kg. [13,14] The primary outcome was the effect of esmolol and lidocaine on the severity of postoperative agitation in children who have received sevoflurane anesthesia. The secondary outcomes were vital signs, severity of pain, amount of fentanyl used, extubation time, and recovery time. All patients were monitored from the end of surgery to the time of discharge from the recovery room.

Outcome measures

Agitation was measured using the objective pain score (OPS), Cole 5-point score (CPS), and Richmond Agitation Sedation Scale (RASS) [Tables 1-3], starting when the patients awoke from anesthesia and initiated spontaneous breathing at 6 to 8 ml/kg. Even though the Pediatric Anesthesia Emergence Delirium (PAED) scale is typically used to measure agitation in children, we opted to use the OPS instead because the children's eyes were covered, thereby preventing use of the PAED scale. Although the OPS is an instrument that measures pain, given a report [6] showing that an OPS score of ≥ 4 is similar to the 4-point PAED scale item "The child is restless" while a score of 5 means "The child is inconsolable," we decided that an OPS score of \geq 4 indicated agitation rather than a pain response and, strabismus surgery is known to be associated with little pain. [6] Thus, we determined that the OPS would be useful for measuring agitation.

Postoperative care

All patients were extubated and transferred to the recovery room when spontaneous breathing at 5 to 8 ml/kg was stable and head elevation was possible. The extubation time was the interval between the completion of surgery and extubation. The recovery time was the interval between arrival in and departure from the recovery room after recovering from anesthesia. The OPS, CPS, and RASS were applied; heart rate, BP, and blood oxygen saturation were measured on arrival in the recovery room and at 10 and 30 min after arrival. When the objective OPS score was 3 to 4 for up to 10 min after arrival in the recovery room, verbal sedation was attempted, given that the symptoms were not considered to be pain responses but rather agitation after awaking from anesthesia. Symptoms were considered to be pain responses if verbal sedation failed, and fentanyl 1 µg/kg was administered after 10 min.

Statistical analysis

In the study by Cao *et al*,^[15] the results were statistically significant when OPS scores differed by more than two points, and they calculated that the number of patients required for an alpha of 0.5, a beta of 0.1 (power of 90%), and a dropout rate of 20% would be 28. The incidence of

severe agitation was 30% in that study. Based on the values of OPS in the control group [median (range), 2 (0–6); mean \pm standard deviation (SD), 2 ± 1.5] and dexmedetomidine group [median (range), 0 (0–7); mean \pm SD, 0 \pm 1.75] in the previous study, ^[15] the sample size was calculated using the Bonferroni method. First, we assessed the descriptive summary statistics (the mean ± SD values for age, weight, operating time, duration of anesthesia, and extubation and recovery times; sex distributions and proportion of patients who received fentanyl; and the median OPS, CPS, and RASS scores). The three study groups were compared using the Pearson chi-square test, the Bonferroni method, analysis of variance (ANOVA), or the Kruskal-Wallis test, as appropriate. All statistical analyses were performed using SPSS software (version 21.0; IBM Corp., Armonk, NY, USA). All tests were twotailed and a P-value < 0.05 was considered statistically significant.

Results

Enrollment and exclusion

Figure 1 shows the CONSORT flow diagram for the pediatric patients in this study. Eighty-four patients were enrolled. Ten patients with fever and upper respiratory

tract infection were excluded on the day of surgery, and three who developed nausea and vomiting after surgery.

Comparison of agitation incidence

When the incidence of agitation from awakening to the arrival at the recovery room is defined as an OPS score of 4 or higher, the incidence was 20% in the EL group, 63% in the Lidocaine group, and 45% in the Control group. Compared to the Control group, the EL group had a significantly lower incidence (P=0.01), and when compared to the Lidocaine group, the EL group also had a significantly greater reduction of incidence (P=0.00). Although the Lidocaine group had a higher incidence, there was no statistically difference in incidence between the Lidocaine group and Control group (P=0.515).

Demographic data and characteristics

There was no statistically significant between-group difference in patients' age (P=0.085), weight (P=0.369), sex (P=0.784), operation duration (P=0.999), anesthesia duration (P=0.978), extubation time (P=0.175), recovery time (P=0.163), fentanyl use (P=0.316) [Table 4]. Furthermore, there was no significant difference in extubation time among the three groups (P=0.316) [Table 4].

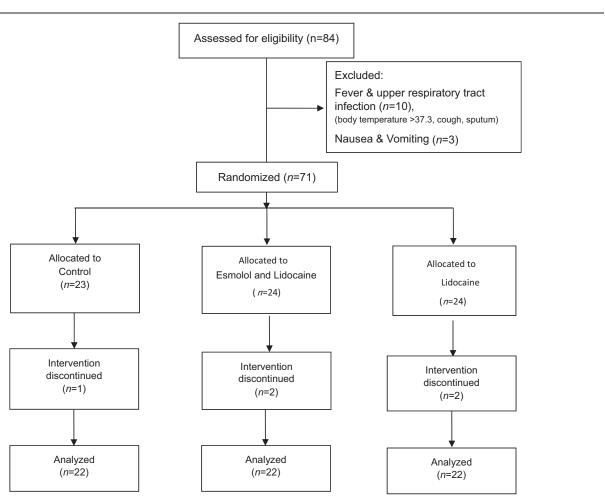


Figure 1: Consort flow diagram of this study.

0.175), likely because neither esmolol nor lidocaine has a marked effect on the level of sedation. As shown in Table 5, although the EL group showed a statistically significant decrease in systolic blood pressure (113.5 \pm 17.4 mmHg, P<0.05) and heart rate (113.9 \pm 8.9 beats/min, P<0.05) on awakening, there were no hemodynamic changes over

Table 1: The Objective pain score (OPS). Criteria **Parameters** Score Systolic blood Increase <20% of preoperative blood 0 pressure pressure Increase 20% to 30% of preoperative 1 blood pressure Increase >30% of preoperative blood 2 pressure 0 Not crying Crying Responds to age appropriate 1 nurturing (tender loving care) Does not respond to nurturing 2 No movements, relaxed 0 Movements Restless, moving about in bed 1 constantly Thrashing (moving widely) 2 Agitation Asleep or calm 0 Can be comforted to lessen the 1 agitation (mild) 2 Cannot be comforted (hysterical) Complains of 0 Asleep pain 0 States no pain Cannot localize 1

Table 2: The cole 5-point scale (CPS) score.			
Behavior	Score		
Sleeping	1		
Awake, calm	1		
Irritable, crying	3		
Inconsolable crying	4		
Severe restlessness, disorientation	5		

Localizes pain

time in any of the study groups that could be attributed to the short duration of action of esmolol.

Comparison of agitation score

Although the lidocaine group and control group did not differ significantly in terms of the severity of agitation [Table 6], the EL group had lower OPS and RASS scores than the other two groups when patients awoke from anesthesia (OPS = 0 (0-4), RASS = -4 [(-5)-1]) and were transferred to the recovery room (OPS = 0 (0-8), RASS = -1 [(-5)-3]) (P < 0.05). After being transferred to the recovery room, if the pediatric patient shows agitation, 10 min of verbal relaxation was attempted. If this failed, fentanyl was administered regardless of the level of agitation. Therefore, agitation scores measured at 30 min were not statistically significant (P > 0.05). Unlike the OPS and RASS scores, there was no significant difference in the CPS score among the three groups at the time of arrival in the recovery room (P > 0.05), likely because its criteria are not as detailed as those for the OPS

Table 3: Richmond agitation and sedation scale (RASS).			
Score		Description	
+4	Combative	Violent, immediate danger to staff	
+3	Very Agitated	Pulls at or removes tubes, aggressive	
+2	Agitated	Frequent non-purposeful movements, fights ventilator	
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous	
0	Alert & Calm	Č	
-1	Drowsy	Not fully alert, sustained awakening to voice (eye opening & contact >10 s)	
-2	Light sedation	Briefly awakens to voice (eye opening & contact <10 s)	
-3	Moderate sedation	Movement or eye-opening to voice (no eye contact)	
-4	Deep sedation	No response to voice, but movemen or eye opening to physical stimulation	
5	Unarousable	No response to voice or physical stimulation	

Table 4: Characteristics of patients undergoing strabismus surgery among three different groups.					
Characteristics	Control group (n=22)	Lidocaine group (n=22)	Esmolol+lidocaine group (n=22)	<i>P</i> value	
Age (years)	5.4 ± 1.6	6.5 ± 2.2	6.4 ± 1.9	0.085	
Weight (kg)	23.0 ± 8.5	26.4 ± 9.0	25.4 ± 8.9	0.369	
Sex (male/female)	11/11	11/11	13/9	0.784	
Operation duration (min)	24.3 ± 3.9	24.5 ± 4.6	25.5 ± 6.9	0.999	
Anesthesia duration (min)	43.2 ± 4.2	43.6 ± 6.9	44.3 ± 6.8	0.978	
Extubation time (min)	9.4 ± 1.3	9.2 ± 1.8	8.5 ± 1.7	0.175	
Recovery time (min)	30.5 ± 0.7	30.3 ± 0.7	30.8 ± 1.2	0.163	
Fentanyl, n (%)	8 (36.4)	11 (50.0)	13 (59.1)	0.316	

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Data are expressed as number of patients, mean \pm standard deviation, or n (%).

Items	I (0)	A (0)	R (0)	R (10)	R (30)
SBP (mmHg)					
Control group	111.6 ± 14.3	131.1 ± 20.2	120.1 ± 14.5	113.5 ± 10.4	110.3 ± 9.6
Lidocaine group	109.7 ± 12.8	123.2 ± 15.6	115.4 ± 14.5	109.5 ± 10.1	109.3 ± 10.2
Esmolol+lidocaine group	110.3 ± 17.3	$113.5 \pm 17.4^*$	114.9 ± 15.6	112.0 ± 15.6	114.3 ± 16.3
DBP (mmHg)					
Control group	64.6 ± 9.3	85.9 ± 17.1	74.6 ± 13.1	70.3 ± 10.9	68.6 ± 8.8
Lidocaine group	65.4 ± 10.8	77.0 ± 17.0	68.5 ± 11.8	66.0 ± 11.4	66.5 ± 10.6
Esmolol+lidocaine group	67.1 ± 14.8	73.2 ± 18.5	70.9 ± 16.0	70.8 ± 18.0	70.0 ± 16.1
HR (beat/min)					
Control group	108.2 ± 17.6	123.2 ± 14.0	114.5 ± 15.1	108.6 ± 7.4	105.3 ± 11.4
Lidocaine group	99.9 ± 21.3	119.8 ± 14.5	110.9 ± 16.7	108.7 ± 14.9	106.8 ± 14.1
Esmolol+lidocaine group	108.0 ± 18.2	$113.9 \pm 8.9^*$	109.8 ± 12.2	106.8 ± 10.3	107.0 ± 9.8
SpO ₂ (%)					
Control group	99.7 ± 0.6	99.7 ± 0.6	99.7 ± 0.6	99.7 ± 0.6	99.7 ± 0.6
Lidocaine group	99.5 ± 1.0	99.5 ± 0.9	99.4 ± 1.1	99.6 ± 0.7	99.6 ± 0.7
Esmolol+lidocaine group	99.4 ± 0.7	99.4 ± 0.7	$99.2 \pm 0.9^*$	99.4 ± 0.8	99.4 ± 0.7

Data are expressed as mean \pm standard deviation. I (0): during induction; A (0): immediately after waking from anesthesia; R (0): immediately after arriving in recovery room; R (10): 10 min after arriving in recovery room; R (30): 30 min after arriving in recovery room. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; SpO₂: Blood oxygen saturation. $^*P < 0.05$, Esmolol+lidocaine group, Lidocaine group compared to Control group.

Table 6: Postanesthesia agitation data of patient undergoing strabismus surgery ($n=22$ in each group).				
Items	A (0)	R (0)	R (10)	R (30)
OPS				
Control group	4 (0–9)	3 (0–9)	5 (0-8)	0 (0-7)
Lidocaine group	4 (0-8)	4 (0-7)	4 (0-7)	3 (0–8)
Esmolol+lidocaine group	0 (0–4)*,†	0 (0–8)*,†	3 (0-7)	0 (0-8)
CPS				
Control group	3 (1–3)	2 (1–4)	3 (1–4)	1 (1-4)
Lidocaine group	3 (1–4)	3 (1–4)	3 (1–4)	1 (1-4)
Esmolol+lidocaine group	1 (1–3)*,†	1 (1–4)	3 (1–4)	2 (1-4)
RASS				
Control group	1 [(-4)-3]	1 [(-4)-3]	2[(-4)-3]	-4[(-5)-3]
Lidocaine group	2[(-5)-3]	2[(-5)-3]	1[(-5)-3]	1[(-5)-3]
Esmolol+lidocaine group	$-4 [(-5)-1]^{*,\dagger}$	$-1 [(-5)-3]^{*,\dagger}$	-1 [(-4)-3]	1 [(-4)-3]

Data are expressed as median (range). I (0): during induction; A (0): immediately after waking from anesthesia; R (0): immediately after arriving in recovery room; R (10): 10 min after arriving in recovery room R; (30): 30 min after arriving in recovery room. OPS: Objective pain score; CPS: Cole 5-point score; RASS: Richmond-agitation-sedation scale. $^*P < 0.05$, Esmolol+lidocaine group, Lidocaine group compared to Control group. $^\dagger P < 0.05$, Esmolol+lidocaine group compared to Lidocaine group.

and RASS. Although emergence agitation delayed discharge from the recovery room, we found that the time spent in the recovery room was similar among the three groups (P > 0.05); most children stabilized and their pain had resolved at 30 min after arrival in the recovery room.

Discussion

Children in the group that received an intravenous injection of esmolol and lidocaine at the end of surgery were less agitated than those in the other two groups from the time of awakening in the operating room to arrival in the recovery room. The incidence of postoperative

agitation differs between school-aged children and preschool-aged children. However, we did not distinguish between these age groups and enrolled children aged 3 to 9 years. This is unlikely to have affected the outcomes, given that the three groups did not differ significantly in terms of age, and the lidocaine group had a greater OPS score after arrival in the recovery room, although there were more preschool-aged children in the control group (19 of 22) than in the lidocaine group (14 of 22).

Postoperative agitation is common in children. It is known that several factors, including the anesthetic agent, anxiety, young age, and pain, cause postoperative agitation in this age group. It can cause many problems, including the risk of additional injury, a need for increased staffing, and

delays in recovery. [6] Therefore, many studies have explored the use of opioids, midazolam, and analgesics to reduce postoperative agitation. Opioids are the agents used most often to alleviate agitation. However, their use is associated with a high risk of postoperative nausea and vomiting, as well as risks of urinary retention, respiratory depression, and delayed emergence from anesthesia. [16,17] Therefore, many studies have explored ketorolac, acetaminophen, and midazolam as alternatives to opioid to attenuate emergence agitation. [18] Some studies found that children premedicated with midazolam were less agitated after surgery while others reported that airway sensitivity to midazolam delayed discharge from the recovery room.^[5] Midazolam worsened pain because of its anti-analgesic effects, [19] limiting use of the drug in children. The rationale for use of ketorolac and acetaminophen to lessen agitation is that alleviation of pain reduces agitation. However, these two drugs cannot be used only to mitigate agitation; many studies have found that agitation can develop in the absence of pain. [3,20-23] For example, covering the eyes after strabismus surgery may trigger anxiety and agitation.

Sevoflurane, an inhaled anesthetic often used in children, is associated with rapid induction and emergence; its blood solubility is low and there is no airway stimulation. However, sevoflurane has been associated with various complications, including agitation on emergence, [1,18,24] particularly after pediatric ophthalmic surgery (the eyes are covered postoperatively). One study found that 44% of pediatric patients who underwent strabismus surgery showed emergence agitation. [25]

Although it is unclear why agitation is prevalent after strabismus surgery, it may be attributable to anxiety or airway stimulation rather than pain. Although intravenous infusion of lidocaine may delay recovery, postoperative sore throat is reduced, possibly lessening agitation. ^[7,8] The mechanism by which lidocaine relieves sore throat and cough remains unclear, but it is known that the drug reduces secretion of neuropeptides in the brainstem and airway by inhibiting stimulation of sensory C fibers in the airway and reducing stimulation of the mucosa in the airway by the tracheal tube. One study found that lidocaine reduced agitation by lessening airway stimulation^[8] and another found that the drug had no effect on agitation. [27] In the former study, 1 mg/kg of 1% lidocaine or 2 mg/kg of 2% lidocaine was administered after return of spontaneous breathing; in the latter study, lidocaine 1.5 mg/kg was administered at the end of anesthesia. Therefore, it is difficult to determine the effects of lidocaine on agitation. In this study, we explored whether lidocaine 1.5 mg/kg alone (to relieve sore throat) mitigated agitation, or whether lidocaine 1.5 mg/kg (to relieve sore throat) and additional use of esmolol (to reduce anxiety) was helpful. Moreover, the study included patients undergoing strabismus surgery, which is associated with only low-level pain.

Esmolol is a beta-blocker that is generally used to lower the heart rate after intubation or surgical stimulation. [28,29] In this study, esmolol was administered not only on awakening but also during induction. However, we believe that esmolol administered at the time of induction would exert only a minimal effect; the mean operating time was

only 30 min, and the peak effect of esmolol occurs within 5 to 10 min and lasts for only 10 to 20 min. Beta-blockers also reduce surgical stress and the levels of anesthetics and opioids required. Beta-agonists increase wakefulness and excitation by activating the reticular activating system in the brain, [30] in turn reducing cortical arousal, which is how esmolol reduces agitation. [30,31] Several studies found that esmolol reduced the need for analgesics and sedatives, but most researchers have reported that esmolol is more effective when combined with other drugs than when administered as monotherapy. [10,22,32,33] For this reason, we combined esmolol with lidocaine, which relieves sore throat. Strabismus surgery in children is known to cause minimal pain, [25,34] so we attempted to determine whether injection of lidocaine can reduce agitation by attenuating stimulation of the airway. And also, we predicted that because esmolol not only maintains hemodynamic stability but also suppresses wakefulness, [30] using the two agents in combination would achieve a greater reduction in agitation. Therefore, we compared an EL group with a lidocaine group, and found that only the patients in the EL group had a statistically significant reduction in agitation. However, there is a limitation that esmolol alone has not been compared. Therefore, further studies on the effect of using esmolol alone are needed. It can be inferred that agitation was decreased by a combination of the ability of esmolol to block beta receptors and decrease wakefulness^[30] and the ability of lidocaine to lessen airway stimulation in children.^[14] Infusions of esmolol are not commonly used in pediatric patients because their safety is not confirmed.

Unlike other studies in which esmolol was administered as a bolus for induction, infused during anesthesia, or administered as a further bolus at the end of surgery, [9,10,31,32,35-38] we delivered boluses on induction and awakening. Therefore, it is possible that the duration of any effect of esmolol on agitation was less than if the drug had been administered via a continuous infusion. The extent and duration of esmolol-mediated effects require further examination.

We used the RASS rather than the more popular PAED because it contains an item measuring the extent of eye contact with the caregiver. Our patients were blindfolded after surgery, so were unable to make eye contact. Furthermore, the RASS affords a more detailed measure of pediatric agitation when used in conjunction with the OPS and CPS.

This study has some limitations. First, we did not distinguish between patients in whom one or both eyes was/were covered. Second, agitation that persisted for 10 min after arrival in the recovery room was considered to be a pain response. Such patients received fentanyl regardless of symptom severity and we did not explore the possibility of a relationship between severity of agitation and administration of fentanyl. Third, the RASS can be used to subclassify agitation in children. However, the RASS is generally employed to measure sedation and agitation in patients in the intensive care unit. Therefore, items commonly used to measure agitation in children were not perfectly matched with RASS items. Fourth, the bispectral index is not used in children at our institution.

However, we maintained the state of anesthesia at 1 MAC from induction to emergence from anesthesia. Furthermore, although there were no tools available to measure the consumption of sevoflurane, the duration of anesthesia and the concentration of sevoflurane were similar in the three study groups. We believe that these factors had no significant impact on the results of our study. Fifth, we did not use the PAED, which is commonly used to measure the severity of agitation in pediatric patients, because one of the items in the PAED checks for eye movement and the patients in this study had their eyes covered after strabismus surgery. Therefore, given that OPS score >4 indicates symptoms of anxiety and agitation in children in other study, [6] and, strabismus surgery is known cause minimal pain, [22] we determined that if an OPS score was >4, any agitation would have a cause other than pain.

In conclusion, administration of both lidocaine and esmolol at the end of anesthesia reduced agitation when pediatric patients awoke from anesthesia and were transferred to the recovery room. This effect was helpful even though it was of short duration; because when patients are transferred from the operating room to the recovery room, further reducing the risk of fall-related accidents. Further studies should explore whether such treatment is useful after procedures other than pediatric strabismus surgery.

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Conflicts of interest

None.

References

- 1. Ravi PR, Nanda HS, Anant S. Comparative study of recovery after sevoflurane versus halothane anaesthesia in adult patients. Med J Armed Forces India 2008;64:325–328. doi: 10.1016/s0377-1237 (08)80011-1.
- Bakhamees HS, Mercan A, El-Halafawy YM. Combination effect of low dose fentanyl and propofol on emergence agitation in children following sevoflurane anesthesia. Saudi med J 2009;30:500–503.
- Beskow A, Westrin P. Sevoflurane causes more postoperative agitation in children than does halothane. Acta Anaesthesiol Scand 1999;43:536–541. doi: 10.1097/00000542-199709001-01061.
- Ozcengiz D, Gunes Y, Ozmete O. Oral melatonin, dexmedetomidine, and midazolam for prevention of postoperative agitation in children. J Anesth 2011;25:184–188. doi: 10.1007/s00540-011-1099-2.
- Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. Anesthesiology 1990;73:831–834.
- Bedirli N, Akcabay M, Emik U. Tramadol vs dexmedetomidine for emergence agitation control in pediatric patients undergoing adenotonsillectomy with sevoflurane anesthesia: prospective randomized controlled clinical study. BMC Anesthesiol 2017;17:41. doi: 10.1186/s12871-017-0332-4.
- Navarro RM, Baughman VL. Lidocaine in the endotracheal tube cuff reduces postoperative sore throat. J Clin Anesth 1997;9:394–397. doi: 10.1016/S0952-8180 (97)00068-8.
- Lee JY, Kim CH, Kim SH, Kim JS, Lee KY. Intravenous lidocaine prior to extubation reduces emergence agitation and cough in pediatric adenotonsillectomy under sevoflurane anesthesia. Korean J Anesthesiol 2007;53:458–462. doi: 10.4097/kjae.2007.53.4.458.
- 9. Haghighi M, Sedighinejad A, Mirbolook A, Naderi Nabi B, Farahmand M, Kazemnezhad Leili E, *et al.* Effect of intravenous intraoperative esmolol on pain management following lower limb orthopedic surgery. Korean J Pain 2015;28:198–202. doi: 10.3344/kjp.2015.28.3.198.

- Chia YY, Chan MH, Ko NH, Liu K. Role of beta-blockade in anaesthesia and postoperative pain management after hysterectomy. Br J Anaesth 2004;93:799–805. doi: 10.1093/bja/aeh268.
- 11. Cho EJ, Yoon SZ, Cho JE, Lee HW. 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. Anesthesiology 2014;120:1354–1361. doi: 10.1097/aln.0000000000000181.
- Gelineau AM, King MR, Ladha KS, Burns SM, Houle T, Anderson TA. Intraoperative esmolol as an adjunct for perioperative opioid and postoperative pain reduction: a systematic review, meta-analysis, and meta-regression. Anesth Analg 2018;126:1035–1049. doi: 10.1213/ ANE.0000000000000002469.
- 13. Subedi A, Tripathi M, Pokharel K, Khatiwada S. Effect of intravenous lidocaine, dexamethasone, and their combination on postoperative sore throat: a randomized controlled trial. Anesth Analg 2018. [Epub ahead of print]. doi: 10.1213/ANE.000000000003842.
- 14. Khattak R, Haq IU, Abbasi T, Ahmad A, Khan SA, Raja MH, *et al.* Efficacy of intravenous lignocain vs sevoflurane in prevention of coughing and desaturation at extubation in children. J Ayub Med Coll Abbottabad 2018;30:167–170.
- 15. Cao JL, Pei YP, Wei JQ, Zhang YY. Effects of intraoperative dexmedetomidine with intravenous anesthesia on postoperative emergence agitation/delirium in pediatric patients undergoing tonsillectomy with or without adenoidectomy: A CONSORT-prospective, randomized, controlled clinical trial. Medicine 2016;95:e5566. doi: 10.1097/md.000000000000005566.
- Efune PN, Minhajuddin A, Szmuk P. Incidence and factors contributing to postdischarge nausea and vomiting in pediatric ambulatory surgical cases. Paediatr Anaesth 2018;28:257–263. doi: 10.1111/pan.13333.
- 17. Forrest WH Jr, Bellville JW. The effect of sleep plus morphine on the respiratory response to carbon dioxide. Anesthesiology 1964;25:137–141.
- 18. Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg 2003;96:1625–1630.
- Oxorn DC, Ferris LE, Harrington E, Orser BA. The effects of midazolam on propofol-induced anesthesia: propofol dose requirements, mood profiles, and perioperative dreams. Anesth Analg 1997;85:553–559.
- Wells LT, Rasch DK. Emergence "delirium" after sevoflurane anesthesia: a paranoid delusion? Anesth Analg 1999;88:1308– 1310. doi: 10.1213/00000539-199906000-00020.
- Holzki J, Kretz FJ. Changing aspects of sevoflurane in paediatric anaesthesia. Paediatr Anaesth 1999;9:283–286. doi: 10.1046/j.1460-9592.1999.00415.x.
- 22. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatr Anaesth 2000;10:419–424. doi: 10.1046/j.1460-9592.2000.00560.x.
- Uezono S, Goto T, Terui K, Ichinose F, Ishguro Y, Nakata Y, et al. Emergence agitation after sevoflurane versus propofol in pediatric patients. Anesth Analg 2000;91:563–566. doi: 10.1213/00000539-200009000-00012
- 24. Lapin SL, Auden SM, Goldsmith LJ, Reynolds AM. Effects of sevoflurane anaesthesia on recovery in children: a comparison with halothane. Paediatr Anaesth 1999;9:299–304. doi: 10.1046/j.1460-9592.1999.00351.x.
- Przybylo HJ, Martini DR, Mazurek AJ, Bracey E, Johnsen L, Cote CJ. Assessing behaviour in children emerging from anaesthesia: can we apply psychiatric diagnostic techniques? Paediatr Anaesth 2003;13:609–616. doi: 10.1046/j.1460-9592.2003.01099.x.
- 26. Xu YJ, Wang SL, Ren Y, Zhu Y, Tan ZM. A smaller endotracheal tube combined with intravenous lidocaine decreases post-operative sore throat a randomized controlled trial. Acta Anaesthesiol Scand 2012;56:1314–1320. doi: 10.1111/j.1399-6576.2012.02768.x.
- 27. Jang YH, Oh SR. Intravenous lidocaine does not reduce emergence agitation or pain after sevoflurane anesthesia in children. Korean J Anesthesiol 2005;49:S14–S19. doi: 10.4097/kjae.2005.49.6. S14.
- 28. Rajbhandari PK. Lignocaine and esmolol on stress response to laryngoscopy and intubation. JNMA J Nepal med Assoc 2014;52:775–779. doi: 10.31729/jnma.2729.
- 29. Besir A, Cekic B, Kutanis D, Akdogan A, Livaoglu M. Comparison of surgical conditions in 2 different anesthesia techniques of esmolol-induced controlled hypotension in breast reduction surgery. Medicine 2017;96:e6254. doi: 10.1097/md.0000000000006254.

- Asouhidou I, Trikoupi A. Esmolol reduces anesthetic requirements thereby facilitating early extubation; a prospective controlled study in patients undergoing intracranial surgery. BMC Anesthesiol 2015;15:172. doi: 10.1186/s12871-015-0154-1.
- Harless M, Depp C, Collins S, Hewer I. Role of esmolol in perioperative analgesia and anesthesia: a literature review. AANA J 2015;83:167–177.
- 32. Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol potentiates reduction of minimum alveolar isoflurane concentration by alfentanil. Anesth Analg 1998;87:671–676. doi: 10.1213/0000539-199809000-00034.
- Lopez-Alvarez S, Mayo-Moldes M, Zaballos M, Iglesias BG, Blanco-Davila R. Esmolol versus ketamine-remifentanil combination for early postoperative analgesia after laparoscopic cholecystectomy: a randomized controlled trial. Can J Anaesth 2012;59:442–448. doi: 10.1007/s12630-012-9684-x.
- 34. Song IA, Seo KS, Oh AY, Baik JS, Kim JH, Hwang JW, et al. Dexmedetomidine injection during strabismus surgery reduces emergence agitation without increasing the oculocardiac reflex in children: a randomized controlled trial. PLoS One 2016;11: e0162785. doi: 10.137/journal.pone.0162785.
- 35. Moon YE, Hwang WJ, Koh HJ, Min JY, Lee J. The sparing effect of low-dose esmolol on sevoflurane during laparoscopic gynaecological

- surgery. J Int Med Res 2011;39:1861–1869. doi: 10.1177/147323001103900529.
- Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. Anesth Analg 2001;92:352–357. doi: 10.1213/00000539-200102000-00014
- Collard V, Mistraletti G, Taqi A, Asenjo JF, Feldman LS, Fried GM, et al. Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. Anesth Analg 2007;105:1255–1262. doi: 10.1213/01.ane.0000282822.07437.02.
- 38. Aono J, Mamiya K, Manabe M. Preoperative anxiety is associated with a high incidence of problematic behavior on emergence after halothane anesthesia in boys. Acta Anaesthesiol Scand 1999;43:542–544. doi: 10.1034/j.1399-6576.1999.430509.x.

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