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EFFECTS OF INTRAVENOUS MIDAZOLAM AFTER ANESTHESIA INDUCTION ON EMERGENCE AGITATION IN SEVOFLURANE-NITROUS OXIDE ANESTHESIA FOR CHILDREN

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ABSTRACT
Emergence agitation is one of the biggest problem in pediatric anesthesia. The purpose was to investigate the effects of intravenous midazolam after induction of anesthesia with sevoflurane and nitrous oxide on emergence agitation in children. Seventy-five children aged 4 to 8 years for adenoidectomy or tonsillectomy were divided into three groups. Diazepam syrup 0.6 mg/kg was administered 2 hours before, and anesthesia was induced with halothane 4 % (H group), or sevoflurane 5% (S and M groups) in 50% nitrous oxide. Saline 5 mL (including midazolam 0.1 mg/kg in the M group only) was administered. At the end of surgery, nitrous oxide and halothane or sevoflurane were stopped. Hemodynamics and patients' condition at induction and emergence of anesthesia, especially emergence agitation, were compared among the groups. Only S group showed increase in blood pressure after intubation. M group had significantly lower blood pressure than S group at extubation. Induction was faster in the M group than the H group. Emergence was slower in the H group than other two groups. Number of children with emergence agitation was significantly lower in the M group than the S group. In conclusion, intravenous midazolam 0.1 mg/kg at induction of anesthesia decreased emergence agitation in sevoflurane anesthesia lasted for about one hour in children aged 4 to 8 years without delaying emergence.

KEYWORDS: pediatric anesthesia, inhalation anesthetic, intravenous anesthetics, emergence from anesthesia, agitation.

1. INTRODUCTION
Emergence agitation is a common problem in pediatric anesthesia. Agitated children cry, kick, or move vigorously, which have a risk of injury. The causes of emergence agitation include rapid awakening from anesthesia, pain, preoperative anxiety, etc.[1]

In recent decades, sevoflurane is usually used for pediatric anesthesia because it induces more rapid induction and emergence from anesthesia than halothane. However, emergence agitation was larger with sevoflurane than with halothane.[2] Therefore, many attempts were made to decrease emergence agitation in pediatric anesthesia.[3-6] The present study was performed to investigate the effects of intravenous midazolam after induction of anesthesia with sevoflurane and nitrous oxide on emergence agitation in children in comparison with induction with sevoflurane-nitrous oxide or halothane -nitrous oxide.

2. MATERIALS AND METHODS
After informed consent from parents and approval from ethics committee of the hospital, 75 children aged 4 to 8 years scheduled for adenoidectomy or tonsillectomy were divided into three groups at random by an envelope method. Power analysis was performed to detect the inter- group differences of number of agitation with power of 0.95 and effect size of 0.5 using the G Power™ software (University Mannheim, Germany). Power analysis showed 62 patients were necessary. Considering exclusion by agitation before induction, 75 children were enrolled. Those with previous anesthetic experience, mental retardation, developmental delays, or chronic diseases were excluded from the study. In addition, those who were crying or agitated before induction were also excluded.

As a premedication, diazepam syrup 0.6 mg/kg was administered 2 hours before entering the operation room. One of the parents was present through induction of anesthesia. Anesthesia was induced with halothane increased to 4% by 0.5% as 2 to 3 breaths (H group), or sevoflurane increased to 5% by 0.5% as 2 to 3 breaths (S group and M group). Intravenous route was secured after loss of eyelash reflex in all patients and saline 5 mL (including midazolam 0.1 mg/kg in the M group only)

was administered. In all patients, nitrous oxide 3 L/min and oxygen 3 L/min was also used during induction. Without muscle relaxants, oro-tracheal intubation was performed at 7 min. after start of induction. During maintenance, concentration of halothane or sevoflurane was adjusted to keep blood pressure in ± 20% of the control. Ventilation was controlled to keep end-tidal carbon dioxide concentration between 30 to 40 mmHg. At the end of surgery, nitrous oxide and halothane or sevoflurane were stopped.

Blood pressure, heart rate, number of children with body movement, and laryngospasm at induction, time to return of spontaneous respiration and eyelash reflex from the end of surgery, number of children with emergence agitation were compared among the groups. Four-point agitation scale (FPAS) was used to evaluate agitation at 10 minutes after surgery. The FPAS scale is as follows: 1 = quiet and calm, 2 = crying but consolable, 3 = moderately agitated, screaming and crying, 4 = aggressive, must be physically restrained to avoid harm.[7] The scale 3 and 4 were judged as agitated.

Data were shown as mean ± standard deviation or number of patients. Statistical analysis was performed with factorial analysis of variance (ANOVA) and chi-square test for demographic data and number of patients and repeated measures ANOVA followed by Student-Newman-Keuls test for measured parameters. The p value less than 0.05 was considered to be statistically significant.

3. RESULTS

Twelve children were deleted because they were crying or agitated before induction, then 63 patients were studied. Demographic data were not different among the groups (Table 1).

Blood pressure and heart rate were expressed as % changes of the control value of each patient. Only S group showed significant increase in blood pressure at 1 minute after intubation (Fig.1). M group had significantly lower blood pressure than S group at extubation (Fig.1). Heart rate were not significantly different among the groups (Fig.2).

At induction, time to loss of eyelash reflex was significantly shorter in the M group than the H group (Table 2). Movement at induction were not different among the groups and no laryngospasm was observed in this study (Table 2). At emergence, time to return of spontaneous respiration and eyelash reflex were significantly longer in the H group than other 2 groups (Table 2). Number of children with emergence agitation was significantly lower in the M group than the S group (Table 2).

Table 1: Demographic data.

	H group	S group	M group
Age (years)	6 ± 2	5 ± 1	6 ± 1
Body weight (kg)	21.2 ± 5.1	22.4 ± 4.8	21.0 ± 4.2
Height (cm)	118.3 ± 7.1	119.6 ± 6.3	114.9 ± 6.7
Gender (Male/Female)	12/9	12/10	9/11
Surgery			
adenoidectomy	9	11	7
tonsillectomy	12	11	13
Duration of surgery (min)	53 ± 12	48 ± 10	50 ± 15

Mean ± standard deviation or number of patients.

Table 2: Results.

	H group	S group	M group
Time to loss of eyelash reflex (sec)	96 ± 10	73 ± 8	68 ± 9*
Number of children with movement at induction	3	5	2
Number of children with laryngospasm	0	0	0
Time to return of spontaneous respiration (sec)	335 ± 39	247 ± 42*	269 ± 53*
Time to return of eyelash reflex (sec)	352 ± 41	259 ± 48*	277 ± 57*
FPAS scale 3/4	4/4	5/8	4/1^{+}

Mean ± standard deviation or number of patients
*: P < 0.05 vs. H group, $^{+}$: P < 0.05 vs. S group

The FPAS scale is as follows: 1 = quiet and calm, 2 = crying but consolable, 3 = moderately agitated, screaming and crying, 4 = aggressive, must be physically restrained to avoid harm.[7]

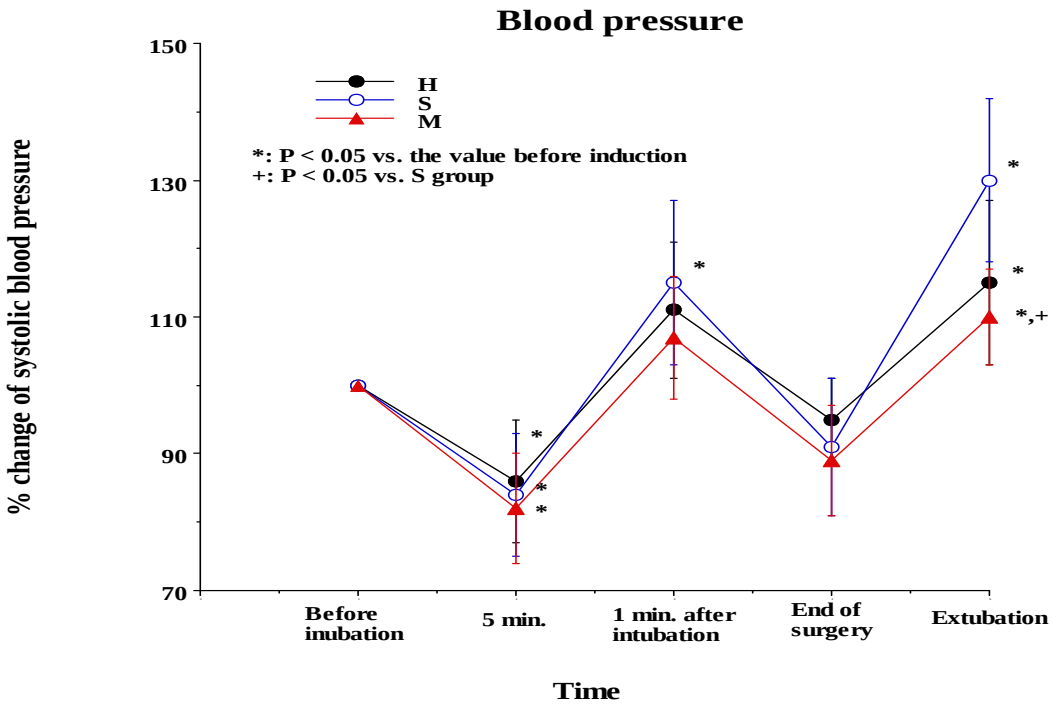

Fig.1 Blood pressure: Systolic blood pressure is shown as % change against each control value before induction. H, Halothane group; S, Sevoflurane group; M, Midazolam group; Bars indicate standard deviation.

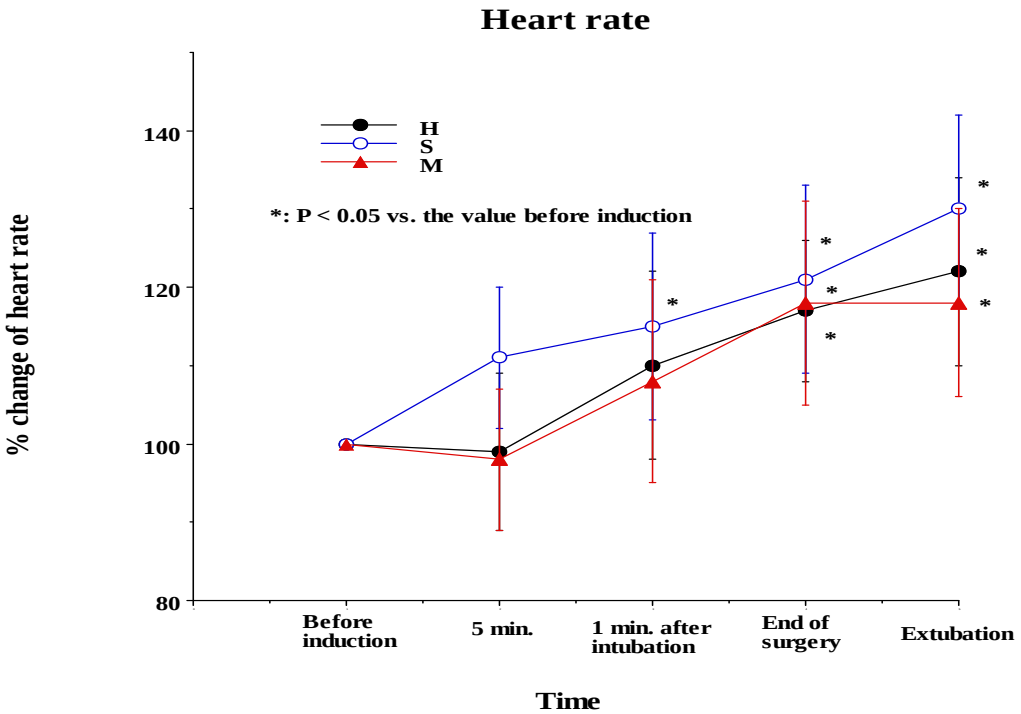

Fig.2 Heart rate: Heart rate is shown as % change against each control value before induction. H, Halothane group; S, Sevoflurane group; M, Midazolam group; Bars indicate standard deviation.

4. DISCUSSION

The present study showed that intravenous midazolam 0.1 mg/kg at induction of anesthesia decreased emergence agitation in sevoflurane-nitrous oxide anesthesia lasted for about one hour in children aged 4 to 8 years without delaying emergence. There are some limitations of this study. We used halothane 4% and sevoflurane 5% and induction time was 7 minutes in all groups. Considering differences of minimum alveolar concentration and blood gas partition coefficients, all groups might have different anesthetic depth at intubation. However, we followed our routine clinical

practice and major point was emergence agitation. Therefore, different anesthetic depth at induction might have few influences on the purpose. Children with agitation at induction had higher incidence of emergence agitation.[8] We excluded these children from the study, therefore, our results might not show true incidence of emergence agitation. However, including these children might make difference of backgrounds of the patients among the groups, therefore, we deleted these children in this study. Adding nitrous oxide to sevoflurane decreased emergence agitation,[5] but we used nitrous oxide in all groups, therefore, the effects of nitrous oxide might be negligible.

Blood pressure and heart rate increased at intubation in sevoflurane induction, while they did not increase in halothane induction in the study by Piat et al.[9] These hemodynamic changes were consistent with the results of the present study. Intravenous midazolam 0.1 mg/kg did not have significant effects on hemodynamics at induction, while it decreased blood pressure at extubation in the present study. This is also one of the benefit of administration of midazolam.

Zand et al.[3] showed that postoperative agitation was significantly decreased by oral midazolam premedication in halothane anesthesia, but not in sevoflurane anesthesia. Longer awakening time increased emergence agitation,[8] therefore, midazolam premedication might have significant effects with halothane, but not with sevoflurane.

However, it is controversy whether premedication with midazolam prevent[10] emergence agitation or not[11] in sevoflurane anesthesia in children. Emergence agitation occurs by many factors,[12] therefore, the discrepancy in these studies might be due to different backgrounds of children studied. Arai et al.[13] reported that premedication of midazolam and diazepam was more effective to decrease emergence agitation than midazolam alone probably due to long action of diazepam. We used diazepam as premedication in all patients, therefore, premedication might have some effects to decrease agitation in the present study.

Expecting more reliable effects, administration of midazolam intravenously at the end of surgery was much studied. Postoperative midazolam 0.025 mg/kg and 0.05 mg/kg decreased emergence agitation without any side effects, but prolonged stay at post-anesthesia care unit.[4] Intravenous midazolam 0.03 mg/kg just before the end of surgery decreased emergence agitation without delaying emergence time in children, but 0.05 mg/kg delayed emergence.[6] Sub-hypnotic dose of propofol or midazolam at the end of sevoflurane anesthesia decreased emergence agitation.[14] Delayed emergence is the most important problem of these methods.

Afraiding delayed emergence, some studied focused on induction of anesthesia. Anesthesia induction with barbiturates decreased emergence agitation compared to inhalation induction with sevoflurane.[7,15] However, induction with thiopental induced more acute anxiety at induction and slower emergence from anesthesia than induction with sevoflurane.[16] Propofol induced less agitation than sevoflurane.[17] However, propofol is not recommended to use in children and it induces severe injection pain. Therefore, propofol should not be used for induction of anesthesia in children. In addition, intravenous induction need intravenous catheter insertion before anesthesia, which might be stressful for children. Thus, we induced anesthesia with sevoflurane and nitrous oxide and then intravenous midazolam was administered.

Our study showed intravenous midazolam decreased emergence agitation in sevoflurane anesthesia, but still some children were agitated. Paradoxical reactions to intravenous midazolam are restlessness, violent behavior, physical assault, act of self-injury, and need for restraints, and may occur after premedication especially with higher doses.[12] Emergence agitation in some children in this study might be due to these effects.

We studied only one dose, 0.1 mg/kg, in this study, which dose was selected after some trials before the study. Further studies are necessary to investigate different doses and different duration of surgery to confirm the effective dose of midazolam.

5. CONCLUSION

Intravenous midazolam 0.1 mg/kg at induction of anesthesia decreased emergence agitation in sevoflurane anesthesia lasted for about one hour in children aged 4 to 8 years without delaying emergence.

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