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Effect of flumazenil on recovery from sevoflurane anesthesia in children premedicated with oral midazolam before undergoing herniorrhaphy with or without caudal analgesia

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Abstract
Purpose. Oral midazolam is frequently used to treat children, but its effect on recovery from anesthesia is controversial. This study was designed to evaluate the effect of flumazenil on reversal of midazolam during recovery from sevoflurane-induced anesthesia in children who underwent caudal analgesia compared to those who did not.
Methods. A series of 60 children 1–8 years of age, with an American Society of Anesthesiologists (ASA) physical status of 1 or 2, who were scheduled to undergo herniorrhaphy were randomly assigned to one of four groups: group 1, control/placebo; group 2, control/flumazenil; group 3, caudal/placebo; group 4, caudal/flumazenil. After oral administration of midazolam $0.5\,mg \cdot kg^{-1}$, anesthesia was induced and maintained with sevoflurane and nitrous oxide in oxygen via a face mask with spontaneous ventilation. The time from the discontinuation of anesthetics to emergence was recorded, and at the time of discharge from the operating room each patient's recovery characteristics were assessed using a three-point scale.
Results. Emergence from anesthesia was significantly less agitated in the group of children who underwent caudal analgesia without flumazenil compared to the other three groups. Flumazenil shortened the time to emergence regardless of the application of caudal analgesia, and caudal analgesia delayed the time to emergence regardless of flumazenil administration.
Conclusion. Caudal analgesia and avoiding the use of flumazenil synergistically resulted in the emergence from anesthesia in a less agitated state for children who underwent herniorrhaphy after oral midazolam premedication.

Key words Sevoflurane · Caudal analgesia · Benzodiazepine · Pediatrics · Flumazenil

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Introduction

Premedication of children reduces preoperative anxiety and allows their satisfactory separation from parents and the smooth induction of anesthesia. The oral administration of midazolam is widely used for this purpose because of its rapid onset, short duration of action, and lack of significant side effects [1–4]. However, previous studies have shown contradictory effects of oral midazolam premedication on the quality of recovery from sevoflurane-induced anesthesia [5–7].

Flumazenil, a potent benzodiazepine antagonist, reverses the sedative effect of midazolam used for premedication or induction with no significant adverse effects on children [8,9]. Moreover, midazolam occasionally precipitates hostility and violence instead of tranquility, and this paradoxical phenomenon can also be reversed by flumazenil [10,11].

Postoperative agitation is a common problem for children and is a manifestation of acute pain and anxiety [12]. Some investigators have reported that adequate analgesia decreases the incidence of postoperative agitation of children [13,14]. Therefore, we investigated whether flumazenil modulates recovery from general anesthesia of children given oral midazolam premedication with or without caudal analgesia.

Materials and methods

After receiving approval from the institutional review board and obtaining written informed parental consent, we studied 60 children aged 1–8 years, each with an American Society of Anesthesiologists (ASA) physical status of 1 or 2, who were scheduled for elective herniorrhaphy at the Japanese Red Cross Nagoya First Hospital. Children were excluded from the study if they had a history of allergies to the drugs to be used, a previous adverse anesthesia experience, or mental retardation or

if they had been subjected to recent chronic medication that could interact with midazolam.

The children were randomly assigned to one of four groups (15 each) on the basis of a computer-generated random number. The children in groups 1 and 2 did not have caudal analgesia, whereas those in groups 3 and 4 underwent caudal analgesia induced with 0.25% bupivacaine $1\,ml \cdot kg^{-1}$ (maximum 20 ml) before surgery. The children in groups 2 and 4 received flumazenil $0.02\,mg \cdot kg^{-1}$ at the end of surgery, whereas those in groups 1 and 3 received a placebo.

All patients received midazolam $0.5\,mg \cdot kg^{-1}$ orally 30 min before the induction of anesthesia. On entering the operating room, each child's willingness to separate from the parents and the level of sedation were evaluated using two three-point scales. The sedation scale was as follows: 1, asleep; 2, drowsy; 3, awake. The separation scale was rated as: 1, calm; 2, anxious; 3, combative. Anesthesia was induced with 5% sevoflurane and 66% nitrous oxide in oxygen via a face mask. After intravenous cannulation, atropine $0.01\,mg \cdot kg^{-1}$ was administered, and an infusion of Ringer's lactate solution containing 5% dextrose was started. All children breathed spontaneously with manual assistance throughout anesthesia maintained with 3% sevoflurane and 66% nitrous oxide in oxygen via a face mask. For groups 3 and 4, caudal analgesia was induced by placing each child in the right lateral position immediately after the induction of anesthesia, and 0.25% bupivacaine $1\,ml \cdot kg^{-1}$ was administered into the caudal space. During anesthesia, pulse oximetry, anesthetic gas concentrations, noninvasive blood pressure, and rectal temperature were monitored; and electrocardiography was performed.

Sevoflurane was discontinued at the beginning of skin closure, and at the end of surgery nitrous oxide was discontinued and a bolus dose of either flumazenil $0.02\,mg \cdot kg^{-1}$ (groups 2 and 4) or saline $0.2\,ml \cdot kg^{-1}$ (groups 1 and 3) was administered by injection. The time from the discontinuation of nitrous oxide to emergence, defined as the time at which a grimace was observed upon patting the child's forehead, was recorded by an anesthesiologist who was unaware of the group to which the subject belonged. The same anesthesiologist also evaluated the quality of recovery at the time of discharge from the operating room (6.4 ± 2.1 min after emergence from anesthesia) using a three-point recovery scale (1, asleep, calm, or mildly agitated but easily consolable; 2, moderately agitated or restless but inconsolable; and 3, hysterical, crying inconsolably, or thrashing) as reported by Davis et al. [13]. Each child who scored 2 or 3 was categorized as being agitated, after which a rescue dose of rectal acetaminophen or intravenous pentazocin was administered.

The data were analyzed using descriptive statistics, the Cochran-Mantel-Haenszel test, the chi-squared test, and two-way analysis of variance (ANOVA) with replication where applicable. Probability values of $P < 0.05$ indicated statistical significance. A sample of 15 patients per treatment group was selected for calculations to detect a 20% difference in each score and the time to emergence with an α value of 0.05 and a β value of 0.2.

Results

Demographic variables including patient age, sex, weight, the duration of surgery and anesthesia, and the time from premedication to induction and to the end of anesthesia were not significantly different among the four groups. Only one child in group 3 was combative on separation from the parents, and only one in group 2 fell asleep upon entering the operating room. The effects of oral midazolam were not significantly different among the four groups (Table 1).

Emergence from anesthesia was significantly less agitated for the children in group 3 (caudal/placebo) compared to those in the other three groups. Flumazenil shortened the time to emergence regardless of the induction of caudal analgesia, and caudal analgesia delayed the time to emergence regardless of flumazenil administration (Table 2).

Discussion

Some studies have shown that the use of oral midazolam preoperatively decreases the degree of postoperative agitation [5,6], whereas others have noted conflicting results. Viitanen et al. [7] reported that premedication with midazolam delays recovery after ambulatory sevoflurane-induced anesthesia of children but does not affect the incidence of postanesthetic excitement. On the other hand, Massanari et al. [10] found that midazolam given before carrying out endoscopic procedures results in adverse behavioral problems, such as inconsolable crying, combativeness, and agitation; they reported that these problems are reversed by flumazenil, although the incidence of behavioral problem is low (1.4%). These conflicting results may be due to differences in the average age of the patients of the study population, the type of surgical procedure performed, the type of anesthesia and analgesia employed, or the reason for choosing to use midazolam.

We found that the emergence from anesthesia was less agitated when caudal analgesia was applied without flumazenil administration for children premedicated with oral midazolam. Gallinkin et al. [14] found that the use of intranasal fentanyl during sevoflurane-induced

Table 1. Demographic and time interval data

Parameter	Group 1 (control/ placebo) ($n = 15$)	Group 2 (control/ flumazenil) ($n = 15$)	Group 3 (caudal/ placebo) ($n = 15$)	Group 4 (caudal/ flumazenil) ($n = 15$)
Age (years)	2.5 ± 1.8	2.9 ± 1.7	3.4 ± 1.9	3.3 ± 2.2
Weight (kg)	14 ± 4	14 ± 4	16 ± 5	15 ± 4
Sex: no. of males	8 (53%)	8 (53%)	11 (73%)	8 (53%)
Duration of surgery (min)	17 ± 8	17 ± 7	16 ± 5	19 ± 6
Duration of anesthesia (min)	35 ± 12	33 ± 7	39 ± 7	45 ± 9
Time from premedication (min)				
To induction	32 ± 10	30 ± 9	31 ± 7	32 ± 6
To the end of anesthesia	67 ± 18	64 ± 11	70 ± 11	78 ± 11
Effect of oral midazolam premedication on entering the OR				
Sedation (no.): asleep/drowsy/awake	0/2/13	1/1/13	0/2/13	0/1/14
Separation (no.): calm/anxious/combative	14/1/0	14/1/0	14/0/1	13/2/0

OR, operating room
The values are means ± SD except where indicated

Table 2. Recovery characteristics

Patients	Recovery scale 1	2	3	Time to emergence (min)
Group 1 (control/placebo)	2	7	6	4.7 ± 2.5
Group 2 (control/flumazenil)	2	6	7	2.3 ± 1.6*
Group 3 (caudal/placebo)	9	5	1*†	6.1 ± 2.6*
Group 4 (caudal/flumazenil)	2	8	5‡	4.3 ± 1.7†,‡

The values are numbers for the recovery scale and means ± SD for the time to emergence
* $P < 0.05$ vs. group 1; † $P < 0.05$ vs. group 2; ‡ $P < 0.05$ vs. group 3

anesthesia for bilateral myringotomy is associated with diminished postoperative agitation, and Davis et al. [13] reported that ketorolac markedly diminishes the emergence of agitation afterward. Thus, analgesia is a significant contributor to diminishing postoperative agitation. Because caudal analgesia is adequate for lower abdominal surgery [15], we hypothesize that adequate analgesia results in a reduced incidence of agitation. However, Ko et al. [6] suggested that postoperative pain is not the only explanation for emergence agitation because patients who undergo noninvasive examinations under sevoflurane-induced anesthesia also experience emergence agitation. The present observation that not using flumazenil administration decreased agitation after general anesthesia for children who underwent caudal analgesia indicates that the residual sedative effects of midazolam in conjunction with caudal analgesia may have resulted in a lower incidence of postoperative agitation. We believe that sedative and analgesic tools together might be needed to decrease agitation.

However, we could not extrapolate the results of this study to the outcomes for longer surgical procedures, for which the blood concentration of midazolam might significantly decline at the end of surgery. Thus, the results of this study are limited to children who undergo short procedures.

Flumazenil induces rapid recovery in children who receive midazolam $0.5\,mg \cdot kg^{-1}$ orally as premedication and intravenous injection of midazolam $0.5\,mg \cdot kg^{-1}$ during induction [8]. In that study, the mean total dose of flumazenil administered to achieve awakening was $0.024\,mg \cdot kg^{-1}$, whereas other investigators used flumazenil $0.017–0.027\,mg \cdot kg^{-1}$ to antagonize the effect of midazolam [9,16]. Therefore, we administered flumazenil at a fixed dose of $0.02\,mg \cdot kg^{-1}$.

McMillan et al. [2] reported that oral midazolam $0.5\,mg \cdot kg^{-1}$ is safe and effective for premedication and that it induces minimal side effects when given 30 min before patients are separated from their parents. In accordance with this, we administered the same dose of midazolam in the same way. On entering the operating room, only one child was separated from his parents in a combative manner, and only one fell asleep. In terms of making children cooperate without falling asleep,

these results are comparable to those in other reports that investigated the effect of oral midazolam premedication [1,2,13]. After midazolam is administered orally, its serum concentration peaks after 50–60 min and sometimes remains at therapeutic levels for anxiolysis and light sedation up to 2 h after administration [17,18]; this interval coincides with the recovery period from brief anesthesia seen in our study. Therefore, we believe that the residual effects of midazolam still exist on emergence from anesthesia and can be adequately reversed by flumazenil.

Emergence occurred 2 min earlier in the flumazenil group than in the control group. The difference might not be clinically important. In a preliminary study, we found that some children tended to sleep for a significant period of time unless we applied tactile stimulation, which is why we defined emergence as the appearance of grimacing resulting from this type of stimulus. Other definitions regarding the recovery time, such as the time to spontaneous opening of the eyes, self-identification, and ambulation according to age may have been significantly longer if flumazenil had not been administered. However, reversal of the residual effects of midazolam did not necessarily appear to be beneficial because flumazenil administration increased the incidence of agitation, especially when analgesia was induced. Prompt reversal may reduce the monitoring time required for children who remain sedated after a procedure is completed, but children who rapidly emerge from anesthesia are often agitated and therefore require more monitoring. This therefore negates the reduction in monitoring time achieved with prompt reversal.

Conclusion

Caudal analgesia and avoiding the use of flumazenil synergistically resulted in a less agitated emergence from anesthesia for children who underwent herniorrhaphy after oral midazolam premedication.

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