

Reevaluation of Rectal Ketamine Premedication in Children

Comparison with Rectal Midazolam

Makoto Tanaka, M.D., Masayoshi Sato, M.D.,† Atsushi Saito, M.D.,† Toshiaki Nishikawa, M.D.‡*

Background: **Results of previous studies of rectal ketamine as a pediatric premedication are clouded because of lack of dose–response relation, inappropriate time of assessing sedative effects, and previous administration or coadministration of benzodiazepines. Therefore, the authors reevaluated the efficacy of rectally administered ketamine in comparison with 1 mg/kg rectal midazolam.**

Methods: **Sixty-six infants and children (age, 7–61 months) who were American Society of Anesthesiologists physical status I and who were undergoing minor surgeries as in-patients were randomized to receive 5 mg/kg ketamine (n = 16), 7 mg/kg ketamine (n = 16), 10 mg/kg ketamine (n = 17), or 1 mg/kg midazolam (n = 17) via rectum. A blinded observer scored sedation 45 min and 15 min after administration of ketamine and midazolam, respectively, when children were separated from parent(s) for inhalational induction. All children underwent standardized general anesthesia with sevoflurane, nitrous oxide, and oxygen with endotracheal intubation. Blood pressure, heart rate, and oxyhemoglobin saturation were determined before, during, and after anesthesia. Postoperative recovery characteristics and incidence of adverse reactions were also assessed.**

Results: **Most children (88%) who received rectally 10 mg/kg ketamine or 1 mg/kg midazolam separated easily from their parents compared with those (31%) who received 7 or 5 mg/kg rectal ketamine ($P < 0.05$). Similarly, more children who received 10 mg/kg ketamine or 1 mg/kg midazolam underwent mask induction without struggling or crying compared with those who received 7 or 5 mg/kg ketamine ($P < 0.05$). There were no clinically significant changes in blood pressure, heart rate, and oxyhemoglobin saturation after administration of either drug. Immediately after surgery, more children receiving midazolam or 5 mg/kg ketamine were agitated compared with 7 or 10 mg/kg ketamine. Ketamine, 7 and 10 mg/kg, provided postoperative analgesia, but the largest dose of ketamine was associated with delayed emergence from general anesthesia.**

Conclusions: **The results indicate that rectally administered ketamine alone produces dose-dependent sedative effects in children, when evaluated at its predicted peak plasma concentration. Ketamine, 10 mg/kg, has a delayed onset but is as effective as 1 mg/kg midazolam for sedating healthy children before general anesthesia. However, 10 mg/kg rectal ketamine is not recommended for brief surgeries because of prolonged postoperative sedation. (Key words: Anesthetics; hypnotics; preinduction.)**

* Associate Professor, † Resident, ‡ Professor and Chairman.

Received from the Department of Anesthesia, Akita University School of Medicine, Akita, Japan. Submitted for publication November 22, 1999. Accepted for publicaton June 5, 2000. Support was provided solely from institutional and/or departmental sources. Presented in part at the annual meeting of the American Society of Anesthesiologists, Orlando, Florida, October 17–21, 1998.

Address reprint requests to Dr. Tanaka: Department of Anesthesia, Akita University School of Medicine, Hondo 1-1-1, Akita-shi, Akita-ken 010-8543, Japan. Address electronic mail to: mtanaka@med.akita-u.ac.jp.

INHALATION induction may be a stormy procedure in children.[1] In addition, painful and frightening experiences may cause long-term psychologic complications and make subsequent contacts with health professionals more difficult.[2] As a result, a variety of premedications administered *via* various routes have been introduced,[3–14] among which rectal administrations of midazolam and ketamine have been performed with no reported late sequelae, but with varying degrees of success.[3–6,9–14]

Ketamine has well-characterized sedative, anesthetic, and analgesic properties.[15] It also has advantages over other sedative–anesthetic drugs, because it stimulates the cardiovascular system, is usually associated with an unobstructed airway and upper airway reflexes, and causes minimum respiratory depression.[15] On the other hand, oral[16,17] and intramuscular[18] ketamine in children has been associated with increased airway secretions, increased incidence of postoperative nausea or vomiting, and emergence reactions, including delirium, dysphoria, nightmares, and hallucinations. Furthermore, recovery from ketamine may be prolonged.[10,19] Early clinical trials with rectal ketamine in children yielded controversial results.[9–14] Satisfactory preoperative sedation and postoperative adverse effects have been reported after rectal administration of 8–10 mg/kg ketamine.[9–11] However, these studies were confounded by prior or coadministration of diazepam[9,10] or midazolam.[11] In other studies, sedative effects of rectal ketamine were found to be either unacceptable or inferior to rectally administered midazolam.[12,14] However, in these studies a single dose of ketamine was evaluated or compared with rectal midazolam,[14] and does-related effects of rectal ketamine were not assessed. More importantly, evaluations of sedative effects were made 15 or 20 min after rectal ketamine administrations,[12,14] despite the fact that the peak plasma level of ketamine is attained 40–45 min after administration.[10,12]

This randomized, double-blind, dose–response study was designed to test the hypothesis that rectally administered ketamine would produce sedative effects comparable to that produced by rectally administered midazolam when evaluated at its predicted peak plasma concentration. In addition, hemodynamic changes after various doses of rectally administered ketamine were compared with rectally administered midazolam before, during, and immediately after anesthesia, and incidence of postoperative adverse effects and recovery character-

istics were examined in healthy infants and children undergoing minor surgical procedures.

Methods

After obtaining institutional review board approval and informed parental consent, we studied 66 infants and children aged 7–61 months with American Society of Anesthesiologists physical status I who were undergoing minor surgeries for inguinal hernia, undescended testis, hydrocele, and hypospadias with general anesthesia. Exclusion criteria were symptoms of upper airway tract infection within the last 2 weeks, gastrointestinal tract disorders, and history of general anesthesia. No patients were taking medication within the last 2 weeks before surgery. All patients were allowed food *ad libitum* 8 h before surgery, and a maximum of 10 ml/kg clear liquid 4 h before the anticipated time of general anesthesia induction. Patients were randomly assigned to one of the following groups according to computer-generated random numbers: the midazolam group (n = 17) received 1 mg/kg midazolam; the ketamine-5 group received 5 mg/kg ketamine (n = 16); the ketamine-7 group received 7 mg/kg ketamine (n = 16); and the ketamine-10 group received 10 mg/kg ketamine (n = 17). All drugs were administered rectally through a 12-French suction catheter lubricated with 2% sterile lidocaine jelly with its tip 3–4 cm proximal to the anal sphincter. A few milliliters of air were then injected through the catheter before its withdrawal. The buttocks were tightly apposed for 5 min to avoid loss of the drug. These procedures were performed in the preinduction area by attending anesthesiologists in charge of the case, and always in the presence of the child's parent(s). The concentration of midazolam was 5 mg/ml, and that of ketamine was 50 mg/ml in all children. Noninvasive systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), and oxyhemoglobin saturation (Spo_2) were measured before drug administration and immediately before separation from parents. None of the patients received previous cleansing enemas.

A blinded investigator (Dr. Tanaka) who was unaware of the drug, the time of administration, and the dose, observed children at separation from parent(s) (15 min after midazolam and 45 min after ketamine) and graded them as follows: (1) asleep; (2) calm but awake; (3) restless; or (4) agitated, crying, or upset. These observations were repeated by the same investigator when an anesthetic mask was applied and were similarly graded as: (1) asleep; (2) calm but awake and apprehensive; (3) awake and struggling; or (4) agitated or crying with restraint required.

Anesthetic technique was standardized. After standard monitors were applied, including an automated blood pressure (BP) cuff, electrocardiography, a pulse oximeter, and precordial stethoscope, general anesthesia was induced in all patients with sevoflurane and 67% nitrous oxide in oxygen. A Jackson-Rees circuit was used with a fresh gas flow approximately three times the minute ventilation for children weighing less than 15 kg, or a semiclosed circle system was used with a fresh gas flow 6 l/min for children weighing more than or equal to 15 kg throughout the study. The concentration of sevoflurane was gradually increased by 0.5% every 4–5 breaths. When the patient was asleep, a forearm peripheral vein was cannulated, and lactated Ringer's solution containing 2% dextrose was started. Ventilation was first assisted and then controlled to obtain end-tidal carbon dioxide tensions between 30 and 35 mmHg thereafter. End-tidal sevoflurane concentration was maintained at 2% in 67% nitrous oxide in oxygen throughout anesthesia and surgery. When hemodynamic variables were stable and at least 10 min had elapsed after anesthetic induction, 0.01 mg/kg atropine and 0.1 mg/kg vecuronium were administered intravenously in all patients. Another 5 min was allowed to obtain a baseline SBP and HR measurement before the patient's trachea was intubated. The complications of mask induction and endotracheal intubation were noted, including laryngospasm, arterial oxygen saturation less than 90%, and vomiting. Extent of salivation was assessed by the same blinded observer and graded as follows: (1) dry; (2) wet but suctioning not required; or (3) wet and suctioning required during mask ventilation or before endotracheal intubation. At the completion of surgery, residual muscle relaxant was antagonized with 0.02 mg/kg atropine and 0.05 mg/kg neostigmine administered intravenously, and sevoflurane and nitrous oxide were discontinued. The patient's trachea was extubated after confirming spontaneous respiration, sustained muscle contracture for 5 s to tetanus stimulus at 50 Hz to the ulnar nerve, and spontaneous eye-opening or purposeful muscular movements of upper extremities. Time from the discontinuance of sevoflurane and nitrous oxide until extubation was noted. SBP, DBP, HR, and Spo_2 were measured after induction, after atropine administration, after endotracheal intubation, at 5-min intervals throughout the surgery, and 5 min after tracheal extubation. Coefficient of variation (SD/mean) for SBP, DBP, and HR was determined using data obtained at 5-min intervals during surgery.

All children were admitted to our hospital for 24 h unless complications required a longer hospital stay. They were transported from the operating room with their parent(s) directly to the pediatric postanesthesia recovery room on the ward, where they were closely observed by two blinded observers who had 12 and 19 yr of clinical experience in pediatric surgery. Emergence reactions, such as agitation, delirium, dysphoria, and any adverse events, including nausea and vomiting, were noted. The rate of recovery was evaluated using a modified Aldrete score and a modified pain–discomfort scale

Table 1. The Modified Aldrete Score and the Pain/Discomfort Scale

Modified Aldrete Score	Score	Pain/Discomfort Scale	Score
Activity		Crying	
Not moving	0	Not crying	0
Nonpurposeful movement	1	Responding to comforting	1
Moving extremities purposefully	2	Not responding to comforting	2
Respiration		Moving	
Apnea/needs airway support	0	None	0
Shallow or limited	1	Restless	1
Deep breathing/coughing	2	Thrashing	2
Consciousness		Agitation	
Unresponsive	0	Asleep or calm	0
Responding to stimuli	1	Mild agitation	1
Fully awake	2	Severe agitation/hysterical	2
O_2 saturation			
$< 90\%$	0		
90–94%	1		
$> 94\%$	2		

(table 1).[20,21] In addition, time to emergence (spontaneous eye opening without stimulus), time to interaction (responding to comforting by parents), time to full points on the modified Aldrete score, and time to drinking fluids were noted. If the sum on the pain–discomfort scale at any evaluation period was greater than 3, the child was considered to suffer from pain, and acetaminophen suppository (50 mg $\leq$ 1 yr, 1 yr $<$ 75 mg $\leq$ 3 yr, 3 yr $<$ 100 mg $\leq$ 6 yr) was given. If pain relief was inadequate within the next 30 min, pentazocine 0.5 mg/kg was given intravenously as a rescue analgesic. For the purpose of statistical analysis, time to the first analgesic was considered to be 24 h if no analgesic was required within the first 24 h after surgery. Children aged more than or equal to 2.5 yr were specifically questioned about the presence of pain. Approximately 24 h after children returned to the ward, all parents, who accompanied their child overnight after surgery, were interviewed by a blinded observer (Dr. Tanaka) to evaluate their overall satisfaction in anesthetic management, which was graded as excellent, good, fair, or poor. In addition, they were questioned about the general well-being of the child, presence of nightmares, and any behavioral change. Children aged more than or equal to 2.5 yr were specifically questioned about whether they recalled any intraoperative event.

All values are presented as mean $\pm$ SD. Statistical analysis was performed using one-way analysis of variance to compare demographic variables and hemodynamic data among groups. When a significant difference was identified, it was followed by an unpaired Student *t* test with Bonferroni correction to adjust for multiple comparisons. Time to first analgesic and number of analgesic requirements within the first 24 h were compared using the Mann–Whitney test. Intergroup differences in categoric demographic data, the level of sedation, extent of salivation, analgesic requirement, incidence of adverse effects, and parent's satisfaction were also compared using the chi-square test or Fisher exact test as appropriate. Changes in hemodynamic and oxyhemoglobin saturation over time were analyzed by two-way analysis of variance with repeated measures, followed by the Wilcoxon signed rank test. Correlation between the degree of sedation and the extent of salivation was assessed by the Spearman correlation coefficient by rank. A *P* value less than 0.05 was considered statistically significant.

Results

There were no significant differences among the four groups in terms of age, gender distribution, weight, height, duration of surgery and anesthesia, and time from discontinuance of anesthetics until tracheal extu

Table 2. Patients' Demographic, Surgical, and Anesthetic Data

	Midazolam (n = 17)	Ketamine-10 (n = 17)	Ketamine-7 (n = 16)	Ketamine-5 (n = 16)
Age (months)	33 $\pm$ 19	29 $\pm$ 13	26 $\pm$ 12	32 $\pm$ 16
Male/female (n)	10/7	8/9	14/2	9/7
Weight (kg)	13 $\pm$ 4	13 $\pm$ 4	12 $\pm$ 3	13 $\pm$ 4
Height (cm)	89 $\pm$ 13	86 $\pm$ 12	84 $\pm$ 7	86 $\pm$ 12
Duration of surgery (min)	74 $\pm$ 61	86 $\pm$ 73	79 $\pm$ 50	81 $\pm$ 76
Duration of anesthesia (min)	124 $\pm$ 68	149 $\pm$ 79	133 $\pm$ 63	146 $\pm$ 62
Time until tracheal extubation (min)	11 $\pm$ 5	12 $\pm$ 5	12 $\pm$ 6	11 $\pm$ 6

Values are mean $\pm$ SD, or number of patients. No significant differences between groups.

Table 3. Blood Pressure, Heart Rate, and Oxyhemoglobin Saturation before and 15 min after Rectal Midazolam and 45 min after Rectal Ketamine Administration

	Midazolam	Ketamine-10	Ketamine-7	Ketamine-5
Before premedication				
SBP	102 ± 9	105 ± 12	107 ± 8	106 ± 7
DBP	61 ± 12	61 ± 10	64 ± 10	65 ± 11
HR	114 ± 18	111 ± 19	118 ± 10	110 ± 14
Spo_2	98 ± 1	99 ± 1	99 ± 1	98 ± 1
After premedication				
SBP	96 ± 13†	108 ± 12*	116 ± 12*	116 ± 11*
DBP	55 ± 11	63 ± 15	66 ± 13*	60 ± 5
HR	119 ± 21	124 ± 16†	120 ± 8	115 ± 10
Spo_2	98 ± 1	99 ± 1	98 ± 1	98 ± 1

Values are mean ± SD.

* $P < 0.05$ *versus* the midazolam group. † $P < 0.05$ *versus* before premedication.

SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); HR = heart rate (beats/min), Spo_2 = oxyhemoglobin saturation (%).

bation (table 2). In addition, no significant difference was seen with respect to BP, HR, and Spo_2 before premedication among groups (table 3). SBP decreased significantly after rectally administered midazolam and was significantly less than those of the ketamine groups, whereas DBP, HR, and Spo_2 remained unchanged. On the other hand, 10 mg/kg rectal ketamine, but not 7 or 5 mg/kg, increased HR significantly (table 3). No patients developed Spo_2 less than 97% on room air.

At separation from parent(s), significantly greater proportions of children in the midazolam and ketamine-10 groups were classified as being "asleep" and "calm but awake" than in the ketamine-7 and -5 groups (fig. 1). Although two children in the midazolam and ketamine-10 groups were either restless, agitated, crying, or upset at the time of separation, none required restraint when an anesthetic mask was applied for inhalational induction (figs. 1 and 2). On the other hand, 12 children (75%) in the ketamine-5 group required restraint, and smooth induction was accomplished in only 4 (25%; fig. 2). During mask ventilation, a significantly greater proportion of children in the ketamine-5 group were classified as "wet" compared with the ketamine-10 group (fig. 3). Significant negative correlation was observed between the degree of salivation *versus* the degree of sedation at induction ($P = 0.027$) but not *versus* the ketamine dose.

After the induction of anesthesia, there were no significant differences in terms of SBP, DBP, HR, and Spo_2 among groups (table 4). Significant increases in BP and HR were observed after intravenous atropine in all groups but ketamine-5. SBP, DBP, and HR significantly increased after endotracheal intubation in the midazolam and ketamine-5 groups but were unchanged in the ketamine-10 group (table 4). During surgery and after tracheal extubation, there were no significant differences in SBP, DBP, HR, Spo_2, and coefficient of variation for these vital signs among the four groups (table 4).

One patient in the midazolam group aspirated stomach contents immediately after induction of anesthesia. This child did not require antibiotics and recovered 3 days postoperatively. One patient in the ketamine-10 group developed retching 20 min after rectal administration but it was not accompanied by hypotension or hypoxemia. One patient in the ketamine-7 group developed laryngospasm after induction. Postoperatively, time to

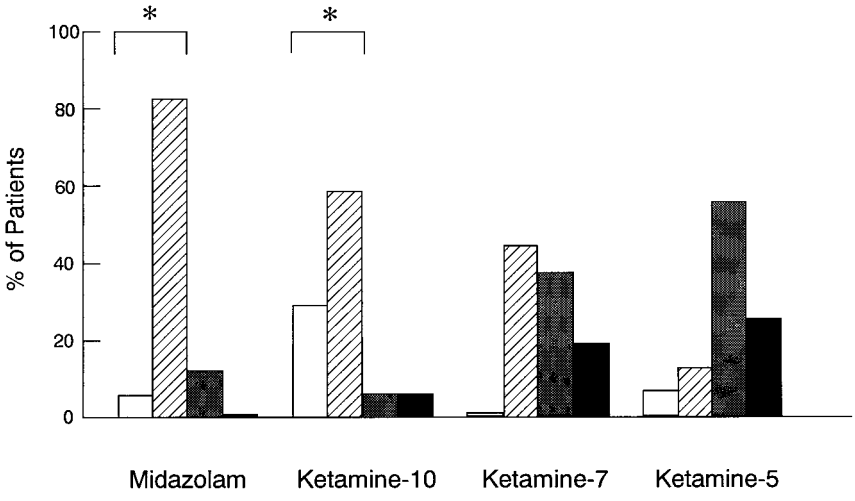

Fig. 1. Percentage of patients in each sedation category at separation from parent(s). Midazolam group = 1 mg/kg midazolam; ketamine-10 = 10 mg/kg ketamine; ketamine-7 = 7 mg/kg ketamine; ketamine-5 = 5 mg/kg ketamine. Patients in the midazolam group were assessed at 15 min and those in the ketamine groups at 45 min after rectal administration. Open bar = asleep; hatched bar = calm but awake; stippled bar = restless; solid bar = agitated, crying, or upset. *$P < 0.05$ *versus* the ketamine-7 and -5 groups.

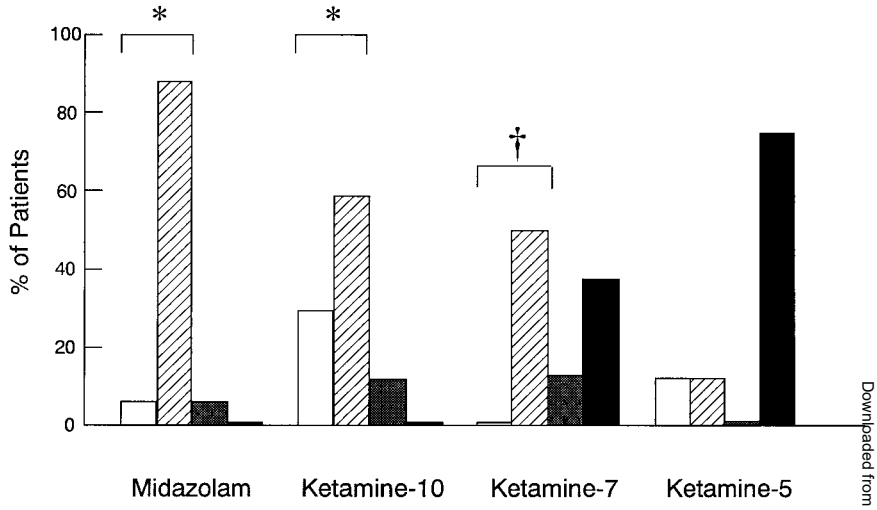

Fig. 2. Percentage of patients in each sedation category at induction of general anesthesia. Midazolam group = 1 mg/kg midazolam; ketamine-10 = 10 mg/kg ketamine; ketamine-7 = 7 mg/kg ketamine; ketamine-5 = 5 mg/kg ketamine. Patients in the midazolam group were assessed at 15 min and those in the ketamine groups at 45 min after rectal adminstration. Open bar = asleep; hatched bar = calm but awake and apprehensive; stippled bar = awake and struggling; solid bar = agitated or crying with restraint required. *$P < 0.05$ *versus* the ketamine-7 and -5 groups; †$P < 0.05$ *versus* the ketamine-5 group.

emergence in the ketamine-10 and -7 groups were significantly prolonged compared with the ketamine-5 group, and time to full points on the modified Aldrete score in the ketamine-10 group was significantly longer than any other group (table 5). However, number of analgesics and proportions of children requiring analgesic in the ketamine-10 and -7 groups were significantly less than those in the midazolam and ketamine-5 groups (table 5). Immediately after surgery, 4 (24%) and 3 (19%) patients in the midazolam and ketamine-5 groups, respectively, and none in the ketamine-10 and -7 groups were severely agitated ($P < 0.05$). All of these children developed a pain–discomfort scale score greater than 4 and received the first dose of analgesic. One in the ketamine-10 group developed delirium 30 min after receiving pentazocine as a rescue analgesic. Mild dysphoria was noted in one patient in each of the ketamine-7 and -5 groups within 6 h after surgery. Nightmare, hallucination, and recall of intraoperative events were not noted. Nausea or vomiting occurred in 4 (24%), 2 (12%), 2 (13%), and 5 (31%) patients in the midazolam and ketamine-10, -7, and -5 groups, respectively. Except for agitation, there were no significant differences in the incidence of any of these adverse effects among groups. Through the postoperative interview, parent(s) reported lethargy on the day of surgery in one child of the midazolam group and appetite loss in one in the ketamine-5 group. However, 88% or 89% of parents in each group graded overall anesthetic management as either excellent or good.

Discussion

The major finding of our study is that rectal ketamine as a sole agent produces a dose-related sedative effect when assessed at its predicted peak plasma levels. Rectal ketamine, 10 mg/kg, reliably eases separation from parent(s) and facilitates a smooth, struggle-free inhalational induction of anesthesia in a manner comparable to that of 1 mg/kg rectal midazolam, which was reported to produce the maximum sedative effect. BP after rectal ketamine administration was well maintained, and an increase in HR after 10 mg/kg ketamine was of a clini

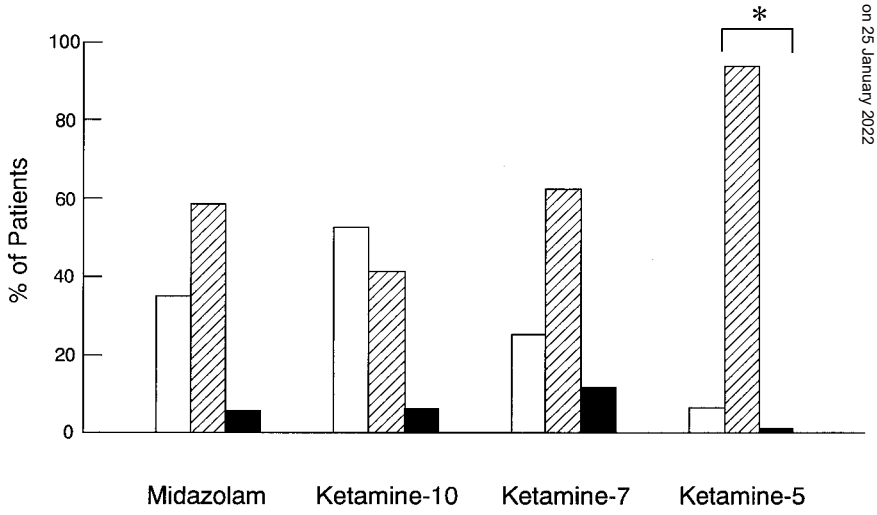

Fig. 3. Incidence (percentage) and severity of salivation of children in each group during mask ventilation or before endotracheal intubation. Midazolam group = 1 mg/kg midazolam; ketamine-10 = 10 mg/kg ketamine; ketamine-7 = 7 mg/kg ketamine; ketamine-5 = 5 mg/kg ketamine. Open bar = dry; hatched bar = wet but suctioning not required; solid bar = wet and suctioning required during mask ventilation or before endotracheal intubation. *$P < 0.05$ *versus* the ketamine-10 group.

Table 4. Blood Pressure, Heart Rate, and Oxyhemoglobin Saturation during and after Surgery, and Intraoperative Coefficient of Variations

	Midazolam	Ketamine-10	Ketamine-7	Ketamine-5
After induction, before atropine				
SBP	87 ± 11	93 ± 9	94 ± 11	96 ± 17
DBP	44 ± 7	46 ± 7	47 ± 12	53 ± 11
HR	114 ± 16	110 ± 16	110 ± 17	118 ± 13
Spo_2	99 ± 1	99 ± 1	99 ± 1	99 ± 1
After atropine				
SBP	95 ± 11*	102 ± 11*	103 ± 15*	101 ± 15
DBP	50 ± 8*	57 ± 11*	55 ± 15*	58 ± 8
HR	147 ± 12*	151 ± 15*	146 ± 20*	146 ± 10*
Spo_2	99 ± 1	99 ± 1	99 ± 1	99 ± 1
After endotracheal intubation				
SBP	103 ± 13†	104 ± 13	110 ± 13†	105 ± 14†
DBP	55 ± 10†	59 ± 12	54 ± 13	55 ± 6†
HR	155 ± 15†	156 ± 14	152 ± 24	154 ± 10†
Spo_2	99 ± 1	99 ± 1	99 ± 1	99 ± 1
After tracheal extubation				
SBP	114 ± 16	108 ± 12	112 ± 11	115 ± 9
DBP	60 ± 9	62 ± 13	67 ± 10	65 ± 7
HR	162 ± 20	153 ± 21	166 ± 28	152 ± 14
Spo_2	99 ± 1	99 ± 1	98 ± 1	99 ± 1
Intraoperative CV				
SBP	6.3 ± 2.0	7.7 ± 3.1	5.6 ± 3.1	5.5 ± 1.9
DBP	10.0 ± 3.7	10.4 ± 4.1	7.6 ± 3.5	8.5 ± 3.9
HR	3.6 ± 1.9	3.1 ± 1.0	4.0 ± 1.6	4.8 ± 3.2

Values are mean ± SD.

* $P < 0.05$ *versus* before atropine. † $P < 0.05$ *versus* after atropine.

SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); HR = heart rate (beats/min), Spo_2 = oxyhemoglobin saturation (%); CV = coefficient of variation (%).

cally acceptable level. In addition, airway complications were uncommon in most children. These results indicate that rectally administered 10 mg/kg ketamine, but not 5 or 7 mg/kg, is a clinically useful tool in the anesthetic management of healthy infants and children. However, whether a larger dose of rectally administered ketamine may reliably produce sedation in a larger proportion of children remains to be determined in future studies.

Our results are in clear contrast with a previous trial, in which an acceptable level of sedation was not obtained in any pediatric patient 20 min after rectal administration of 10 mg/kg ketamine.[12] Similarly, another study showed that significantly more children receiving 3 mg/kg rectal ketamine struggled or cried at separation from parents and during intravenous catheter placement than those receiving 0.5 mg/kg rectal midazolam.[14] In the latter study, clinical effects were also assessed 10–15 min after rectal midazolam or ketamine administration. However, peak plasma concentration after rectal ketamine is attained at 40–45 min,[10,12] whereas that of rectal midazolam occurs at 12–16 min.[4,6] Therefore, inadequate level of sedation in previous trials is considered to be caused, at least in part, by inadequate time elapsed and, hence, insufficient plasma concentration of ketamine achieved at the time of clinical assessment. On the other hand, results of other studies demonstrating adequate sedation after rectal ketamine are flawed with previous administrations of 0.2 mg/kg intramuscular diazepam,

Table 5. Recovery Time from Anesthesia and Analgesic Profile

	Midazolam	Ketamine-10	Ketamine-7	Ketamine-5
Rate of recovery				
Time to emergence (h)	0.6 ± 0.4	1.4 ± 1.4*	1.3 ± 1.2*	0.3 ± 0.2
Time to interaction (h)	1.4 ± 1.0*	1.7 ± 0.6*	1.3 ± 1.0*	0.4 ± 0.3
Time to full Aldrete score (h)	1.7 ± 0.8	3.5 ± 1.7†	2.2 ± 0.9	1.7 ± 1.2
Time to drink fluids (h)	3.8 ± 1.5	4.7 ± 1.5	4.2 ± 1.3	4.0 ± 1.1
Analgesic profile				
Analgesic treatment (yes/no)	11/6	4/13‡	3/13‡	14/2
Time to first analgesic (h)	6.0 ± 10.8	22.4 ± 3.3‡	20.4 ± 7.7‡	5.0 ± 7.7
Number of analgesic within first 24 h	1.0 ± 1.0	0.3 ± 0.6‡	0.2 ± 0.4‡	1.1 ± 0.9

Values are mean ± SD or number.

* $P < 0.05$ *versus* the ketamine-5 group. † $P < 0.05$ *versus* the midazolam, and ketamine-7, and -5 groups. ‡ $P < 0.05$ *versus* the midazolam and ketamine-5 groups.

0.5 mg/kg rectal diazepam,[10] or coadministration of 0.2 mg/kg rectal midazolam.[11] These doses of benzodiazepines alone may be sufficient to produce sedation, because most children (77%) were indeed sedated after 0.5 mg/kg rectal diazepam before ketamine was administered rectally.[10]

Minimum hemodynamic changes after rectal midazolam or ketamine further support the safety of these drugs as a pediatric premedicant. Cardiovascular stimulation caused by endotracheal intubation in patients receiving midazolam and the least dose of ketamine, but not the largest dose of ketamine, suggests that the higher rectal ketamine dose reliably suppresses stress response associated with laryngoscopy and intubation. Although such an extent of hemodynamic alterations after endotracheal intubation may have little clinical importance in otherwise healthy children, this study was conducted to generate data to be used in a future study in children with congenital heart diseases, in which cardiovascular stimulation and minimum respiratory depression by ketamine would favor its use despite adverse effects.[22,23] In the present study, hemodynamic stability as estimated by intraoperative coefficient of variation for BP and HR was demonstrated by the ketamine doses used.

Despite our concern, significant negative correlation between the degree of preoperative sedation, but not the dose of ketamine, *versus* the degree of salivation at the time of induction suggests that prophylactic anticholinergic may not be routinely indicated after rectal ketamine. However, a larger dose–response study is warranted to determine whether salivation is increased by rectal ketamine in children.

Delayed emergence in children receiving 10 or 7 mg/kg rectal ketamine compared with rectal midazolam may be explained by the significant plasma concentration of norketamine, an active metabolite of ketamine that possesses one third of anesthetic potency. Previous studies showed that the terminal half-life of rectal midazolam and rectal ketamine were both approximately 100 min,[6,10] but that of norketamine is longer than ketamine *per se*.[10] Although our hospital regulation required all children in our study to be admitted to the hospital on the day of surgery, it is likely that the time until discharge criteria were met would also be prolonged, especially after 10 mg/kg ketamine, because this dose is associated with significantly longer time to the fullpoints on the modified Aldrete score than the other regimens. Because the incidence of all other side effects were comparable between midazolam and 10 mg/kg ketamine, and ketamine exerts postoperative analgesia, indication of rectal ketamine premedication in children should be carefully weighed against prolonging recovery from general anesthesia and may be confined to in-patients. Several previous studies have reported no effect on recovery characteristics in children after 0.5 mg/kg oral midazolam premedication when using halothane and nitrous oxide,[24,25] whereas other studies showed slightly delayed recovery or discharge after the same dose of oral midazolam when using sevoflurane plus alfentanil or propofol for ambulatory surgery.[26,27] Because elimination half-life of oral midazolam is 70 min,[28] it is conceivable that discharge may be delayed after ambulatory anesthesia using rectal midazolam or ketamine, when compared with no premedication.

There are shortcomings of our study. Although we demonstrated that 10 mg/kg rectal ketamine was roughly equipotent with 1 mg/kg rectal midazolam in sedating pediatric patients, the cost of ketamine per kilogram is approximately 1.7 times that of midazolam in our country. The 30-min additional cost for the preinduction room stay with rectal ketamine would even further increase its cost and therefore limit its usefulness and restrict its use when compared with rectal midazolam. Second, differing volume of ketamine might affect relative distribution of the drug between the portal and systemic drainage, *i.e.*, less volume per dose of the drug would direct greater proportion absorbed from the systemic drainage, and thus the initial sedative effect would be greater than the drug being diluted. These considerations imply that, if a smaller dose of ketamine had been diluted to 0.2 ml/kg, preoperative sedation of a smaller dose of ketamine would have been attenuated because of less systemic drainage, and postoperative recovery possibly affected by norketamine would have been slower because of more first-pass hepatic metabolism. Third, performing regional block or providing infiltration of a local anesthetic might have affected the postoperative analgesic profile. Lastly, preoperative anxiety was not assessed in our study. However, objective evaluation of the level of anxiety in pediatric patients, especially those younger than 12 months, could be especially difficult compared with older children.

In conclusion, ketamine produced dose-dependent sedative effects when evaluated 45 min after rectal administration. Although sedative effect of rectal ketamine at a dose of 10 mg/kg was comparable to that of 1 mg/kg rectal midazolam and provided postoperative analgesia, it was associated with delayed emergence from general anesthesia in children undergoing minor surgical procedures.

References

1. Meursing AEE: Psychological effects of anaesthesia in children. Curr Opin Anaesth 1989; 2:335–8

2. McGraw T: Preparing children for the operating room: Psychological issues. Can J Anaesth 1994; 41:1094–103

3. Spear RM, Yaster M, Berkowitz ID, Maxwell LG, Bender KS, Naclerio R, Manolio TA, Nichols DG: Preinduction of anesthesia in children with rectally administered midazolam. ANESTHESIOLOGY 1991; 74:670–4

4. Malinovsky JM, Lejus C, Servin F, Lepage JY, Le Normand Y, Testa S, Cozian A, Pinaud M: Plasma concentrations of midazolam after i.v., nasal or rectal administration in children. Br J Anaesth 1993; 70:617–20

5. Malinovsky JM, Populaire C, Cozian A, Lepage JY, Lejus C, Pinaud M: Premedication with midazolam in children: Effect of intranasal, rectal and oral routes on plasma midazolam concentrations. Anaesthesia 1995; 50:351–4

6. Saint-Maurice C, Meistelman C, Rey E, Esteve C, de Lauture D, Olive G: The pharmacokinetics of rectal midazolam for premedication in children. ANESTHESIOLOGY 1986; 65:536–8

7. Levine MF, Hartley EJ, Macpherson BA, Burrows FA, Lerman J: Oral midazolam premedication for children with congenital cyanotic heart disease undergoing cardiac surgery: A comparative study. Can J Anaesth 1993; 40:934–8

8. Khalil S, Philbrook L, Rabb M, Wagner K, Jennings C, Chuang AZ, Lemak NA: Sublingual midazolam premedication in children: A dose response study. Paediatr Anaesth 1998; 8:461–5

9. Saint-Maurice C, Languenie G, Couturier C, Goutail-Flaud F: Rectal ketamine in paediatric anaesthesia. Br J Anaesth 1979; 51:573–4

10. Idvall J, Holasek J: Rectal ketamine for induction of anaesthesia in children. Anaesthesia 1983; 38:60–4

11. Holm-Knudsen R, Nygård E, Laub M: Rectal induction of anaesthesia in children: A comparison between ketamine-midazolam and halothane for induction and maintenance of anaesthesia. Acta Anaesthesiol Scand 1989; 33:518–21

12. Pedraz JL, Calvo MB, Lanao JM, Muriel C, Santos Lamas J, Dominguez-Gil A: Pharmacokinetics of rectal ketamine in children. Br J Anaesth 1989; 63:671–4

13. Maltby JR, Watkins DMB: Repeated ketamine anaesthesia of a child for radiotherapy in the prone position. Can Anaesth Soc J 1983; 30:526–30

14. Beebe DS, Belani KG, Chang PN, Hesse PS, Schuh JS, Liao JC, Palahniuk RJ: Effectiveness of preoperative sedation with rectal midazolam, ketamine, or their combination in young children. Anesth Analg 1992; 75:880–4

15. White PF, Way WL, Trevor AJ: Ketamine: Its pharmacology and therapeutic uses. ANESTHESIOLOGY 1982; 56:119–36

16. Gingrich BK: Difficulties encountered in a comparative study of orally administered midazolam and ketamine. ANESTHESIOLOGY 1994; 80:1414–5

17. Meyers EF, Charles P: Prolonged adverse reactions to ketamine in children. ANESTHESIOLOGY 1978; 49:39–40

18. Hollister GR, Burn JMB: Side effects of ketamine in pediatric anesthesia. Anesth Analg 1974; 53:264–7

19. Gutstein HB, Johnson KL, Heard MB, Gregory GA: Oral ketamine preanesthetic medication in children. ANESTHESIOLOGY 1992; 76:28–33

20. Viitanen H, Baer G, Annila P: Recovery characteristics of sevoflurane or halothane for day-case anaesthesia in children aged 1-3 years. Acta Anaesthesiol Scand 2000; 44:101–6

21. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS: Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. ANESTHESIOLOGY 1987; 66: 832–4

22. Audenaert SM, Wagner Y, Montgomery CL, Lock RL, Colclough G, Kuhn RJ, Johnson GL, Pedigo NW: Cardiorespiratory effects of premedication for children. Anesth Analg 1995; 80:506–10

23. Morray JP, Lynn AM, Stamm SJ, Herndon PS, Kawabori I, Stevenson JG: Hemodynamic effects of ketamine in children with congenital heart disease. Anesth Analg 1984; 63:895–9

24. Weldon BC, Watcha MF, White PF: Oral midazolam in children: Effect of time and adjunctive therapy. Anesth Analg 1992; 75:51–5

25. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J: Premedication of children with oral midazolam. Can J Anaesth 1992; 39:545–50

26. Viitanen H, Annila P, Viitanen M, Tarkkila P: Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children. Anesth Analg 1999; 89:75–9

27. Bevan JC, Veall GRO, Macnab AJ, Ries CR, Marsland C: Midazolam premedication delays recovery after propofol without modifying involuntary movements. Anesth Analg 1997; 85:50–4

28. Payne K, Mattheyse FJ, Liebenberg D, Dawes T: The pharmacokinetics of midazolam in paediatric patients. Eur J Clin Pharmacol 1989; 37:267–72