

Oral Premedication for Pediatric Cardiac Surgery: A Comparison of Midazolam, Ketamine and Midazolam plus Ketamine

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Abstract

Background- Although midazolam and ketamine are widely administered as oral premedications for children, only a few studies have investigated the cardiovascular, respiratory and sedative effects of these drugs in children with congenital heart disease (CHD).

Methods- We compared three methods of administering midazolam and ketamine and a combination of these two drugs as an oral premedication in 165 children with CHD, ASA class II-III, aged 2-8 years, and candidates for cardiac surgery. In this prospective, randomized double-blinded study, we examined hemodynamics, respiratory rate, hemoglobin oxygen saturation, degree of sedation, adverse events such as nausea, vomiting, hallucinations and finally face-mask acceptance or IV line insertion reaction at induction time in three groups. Patients received midazolam 0.5 mg/kg, ketamine 6 mg/kg, or midazolam 0.25 mg/kg plus ketamine 3 mg/kg, 45 minutes before the induction of anesthesia.

Results- Heart rate, respiratory rate and hemoglobin oxygen saturation were stable in all three groups. However, systolic and diastolic blood pressure were significantly higher in the ketamine group than those in the other two groups ($p=0.001$). Sedation score was gradually increased in all the groups, with maximum rate after 45 minutes. After 30 minutes, the midazolam+ketamine group had significantly higher sedation than the other groups ($p=0.04$). All patients in the three groups had satisfactory separation from their parents. At the time of induction, the cooperation score for face mask acceptance was 81 to 84% among the groups, with no significant differences. However, cooperation at IV line insertion time in the ketamine and the midazolam+ketamine groups (23%, 24%) was better than that in the midazolam group (12%, $p=0.03$). There were six episodes of emesis in the ketamine group and one episode of nausea in the midazolam+ketamine group.

Conclusion- Midazolam and ketamine alone or as a mixed combination are safe oral premedicants in children with CHD undergoing cardiac surgery (*Iranian Heart Journal 2007; 8 (4): 17-23*).

Key words: premedication ■ pediatric cardiac surgery ■ congenital heart disease

Midazolam, a water soluble, short acting 1.4 benzodiazepine, -amino-butyric acid (GABA) receptor inhibitor, is the most common premedication drug for pediatric patients.¹

Ketamine, a phencyclidine derivative, long used as an intravenous or intramuscular sedative, can also be effective when given by the oral route.²

Received July 27, 2006; Accepted for publication November 11, 2007.

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The preoperative period is a stressful time for children and their parents. The most preferable premedication is one that reduces anxiety, eases separation from parents and facilitates patient acceptance of the face mask or IV insertion during the induction of anesthesia without increasing cardio-respiratory instability and prolonging the recovery period.³ It may be administered by various routes like oral, rectal, intranasal and intramuscular. Oral route is used widely and provides effective sedation in children. However, bioavailability of midazolam by this route ranges from 30% to 45% with an appreciable first pass effect.^{4,5} In fact, the fat solubility of midazolam is pH-dependent, and at a pH>4.5, there is a greater physiologically active proportion of drug, so bioavailability is sensitive to changes in pH.⁶ Since the introduction of the commercially-prepared midazolam syrup, both it and mixtures based on the IV formulation remain in clinical use.⁷ Ketamine is also used as an oral premedication in pediatric patients. However, oral ketamine is not marketed, and the commercially available IV solution can be used. Intravenous solutions mix with a variety of additives, to mask the bitter taste.⁸ An oral combination of midazolam and ketamine has been shown to be a safe and effective replacement for the standard premedication for healthy children.⁹ The efficacy of oral midazolam and ketamine alone in children with CHD has been previously investigated in a few studies with small sample sizes.^{10,11} The purpose of this study was to compare the safety and efficacy of three methods of oral premedication in children with CHD undergoing cardiac surgical procedures.

Methods

The study was approved by the ethical committee of Shaheed Rajaei Cardiovascular Center. Written, informed parental consent was obtained for each child.

One hundred sixty-five ASA physical status II–III children, weighing less than 20 kg, aged 2-8 years, scheduled for elective cardiac surgery, were enrolled in this prospective, randomized and double-blinded study. Patients were excluded if there were central nervous system disorders and gastrointestinal disorders that affected drug absorption. Because midazolam is a known substrate of cytochrome p450 3A4 enzyme system,¹² patients taking cytochrome p450 3A4 enzyme inducers (e.g., phenobarbital, phenytoin, rifampin or corticosteroids)¹³ or inhibitors (e.g., grapefruit juice, imidazole derivatives, erythromycin, or cimetidine)^{14,15} were excluded.

Forty-five minutes before the induction of anesthesia, the patients were taken to the waiting area beside the operating room. The parents and a nurse were present throughout the study. Children were assigned to one of three groups based on a computer-generated random numbers table. Group A with 59 patients, received midazolam 0.5mg/kg, group B with 56 patients, received ketamine 6mg/kg, and group C with 50 patients, received midazolam 0.25mg/kg plus ketamine 3mg/kg. Each dose was mixed with atropine 0.02mg/kg. Finally, the medications were diluted with apple juice to a total volume of 5 to 8 ml with pH 5-5.5. All patients were observed at the time of medication administration to verify the ingestion of the entire dose. Taste acceptability was evaluated on a four–point scale (1=accepted readily, 2=accepted with grimace, 3=accepted with verbal complaint, 4= rejected entirely); a score of 1-3 was considered satisfactory.

All children were monitored with the use of a pulse oxymeter throughout the study. Vital signs (blood pressure, heart rate, respiratory rate, and hemoglobin oxygen saturation) were recorded before drug administration (base line) and then each 15 min. until the transfer of the patient into the operating room. A doctor blinded to the group assignment performed all tests.

Sedation score was assessed at similar time intervals with a four-point scale: 1=sleepy/calm, 2=awake/calm, 3=awake/anxious, 4=very anxious/combative. Children with a score of 1 or 2 were considered to have a satisfactory level of sedation; those with a score of 3 or 4 were considered to be unsatisfactorily sedated.¹⁶

After 45 minutes, children were separated from their parents. At the time of separation, the child's willingness to separate from the parents was evaluated on a different four-point scale with 1=easy separation, 2=whimpers but is easily reassured, not clinging, 3=cries and cannot be easily reassured, but not clinging to parents, and 4=crying and clinging to parents. Children with score of 1 or 2 were considered to have an acceptable separation; those with scores of 3 or 4 were considered to have difficult separations.¹⁶

After the patient had entered the operating room, anesthesia was induced using IV anesthetic drugs after IV insertion or sevoflurane in oxygen via a face mask. Behavior at induction was evaluated using a four-point scale, where 1=excellent (unafraid, cooperative), 2= good (slight fear, easily reassured), 3=fair (moderate fear, not calmed with reassurance), and 4=poor (terrified, crying, combative). Children with scores of 1 or 2 were designated as satisfactory, and scores of 3 or 4 were considered unsatisfactory.¹⁶

Statistical analysis was performed with SPSS (version 11) statistical software. Qualitative variables were analyzed with χ^2 test, and quantitative variables were analyzed via one-way ANOVA between the groups. A P value of <0.05 was considered statistically significant.

Results

One hundred sixty-five patients were enrolled in this study and divided randomly into three groups. No children had refused the

premedication, and taste acceptance was satisfactory in all children.

Demographic characteristics such as age, weight, and gender were similar across the groups (Table I). The numbers of the patients with cyanotic heart lesions were similar among the groups and included 15 patients in each group.

Table I. Demographic data

	A	B	C	
Premed:	Midaz.	Ket.	Midaz. + Ket.	P value
Number (n)	59	56	50	
Age (yr)	3.8± 2.8	4.5±2.9	3.5±2.5	NS
Weight (kg)	12.4±5.4	13.5±5.2	12.4±5.5	NS
Gender (M/F)	35/24	30/26	29/21	NS

Values are presented as mean±SD, or number. No P value is significant.

There were no significant differences in baseline blood pressure, heart rate, respiratory rate, hemoglobin oxygen saturation (SpO2) values or sedation scores before the administration of the preanesthetic medication (Tables II, III).

Table II. Comparison of vital signs

Variables	Midazolam	Ketamine	Midazolam	P value
Heart rate (bpm)				
0 min	114±16	114±15	113±12	NS
15 min	114±15	113±16	113±12	NS
30 min	110± 21	112± 16	111± 12	NS
45 min	110± 16	109± 19	109± 12	NS
Respiratory rate (min)				
0 min	27±2		27± 2	NS
15 min	27± 2	27±3	27±4	NS
30 min	27±2	27±2	27±2	NS
45 min	27±3	27±3	27±3	NS
Systolic blood pressure (mmHg)				
0 min	94±7	96±8	92±9	NS
15 min	93±13	103±18	92±8	0.001
30 min	93±11	103±19	92±10	0.001
45 min	90±12	101±18	90±9	0.001
Diastolic blood pressure (mmHg)				
0 min	56±14	56±16	54±8	NS
15 min	55±12	65±14	54±8	0.001
30 min	53±11	65±14	53±9	0.001
45 min	53±11	64±14	53±8	0.001
Hemoglobin oxygen saturation values (%)				
0 min	88±7	89±6	86±6	NS
15 min	89±6	90±5	87±5	NS
30 min	89±5	89±6	87±6	NS
45 min	89±6	89±6	86±5	NS

Values are presented as mean±SD, P value < 0.05

No patient developed hypotension, bradycardia, or decreased SpO2 value during the time from drug administration to the start of induction of anesthesia. Although no differences were noted between the groups in heart rate, respiratory rate and SpO2 values during the study, there were significant increases in systolic and diastolic blood pressure in the ketamine group compared with the two other groups (Table II). These increased values, however, were at the normal ranges for the patients.

Although the number of patients with satisfactory sedation increased in all three groups with time, the distribution of satisfactory sedation in the three groups was significantly different. At 30 minutes, a greater number of patients in the midazolam+ketamine group (98%) exhibited satisfactory sedation compared with midazolam (86%) and ketamine (83%) groups (p=0.04, Table III). However, 93% of the midazolam group patients; and 87% of the ketamine group patients reached satisfactory sedation score at 45 minutes after drug administration.

Table III. Comparison of satisfactory sedation

	A	B	C	
Premed	Midaz.	Ketamine	Midaz+ Ketam	P value
	n = 59	n = 56	n =50	
Satisfactory sedation(%)				
0 min	21/59(35%)	19/56(34%)	17/50(34%)	NS
15 min	44/59(74%)	40/56(71%)	40/50(80%)	NS
30 min	51/59(86%)	47/56(83%)	49/50(98%)	0.04
45 min	55/59(93%)	49/56(87%)	49/50(98%)	NS

Values are presented as no (%); P value < 0.05

Cooperation at separation from parents was satisfactory in 100% of subjects; no differences were noted between the three groups. At induction time, the children were significantly more distressed at IV insertion compared to face mask acceptance. Patients who received ketamine or midazolam + ketamine were more cooperative with IV insertion compared to midazolam group (23%, 24% vs. 12%; p=0.03, Table IV). Nonetheless, cooperation score for face mask

acceptance showed satisfactory rate of 81 to 84% among groups, with no significant differences.

Finally, adverse events were recorded. No child experienced respiratory complications before induction. Six patients in the ketamine group vomited and one had hallucination, while one patient in the midazolam+ketamine group experienced nausea.

Table IV. Comparison of incidence of satisfactory separation and induction score

	A	B	C	P value
Premed	Midazolam	Ketamine	Midaz+ Ketam	
	n = 59	n = 56	n =50	
Separation score (%)	59/59 (100%)	56/56 (100%)	50/50 (100%)	NS
Induction score (%)				
IV line insertion acceptance	7/59 (12%)	13/56 (23%)	12/50 (24%)	0.03
Face mask Acceptance	42/52 (81%)	36/43 (84%)	31/38 (82%)	NS

Values are presented as no. (%); P value < 0.05

Discussion

The goal of premedication is to achieve adequate sedation in a non-traumatic fashion and to maintain respiratory and hemodynamic stability. In children with CHD, the use of a heavy premedication is advocated to diminish myocardial consumption, improve oxygen saturation and promote a satisfactory induction of anesthesia.¹⁷ However, transient oxygen desaturation episodes may occur following premedication in these patients.¹⁸ The type of premedication and the route of administration have important roles in determining preinduction stability. Evidence exists that oxygen saturation transiently decreases more frequently after intramuscular than after oral premedication.¹⁹

Oral midazolam has become the most commonly used premedication for children.²⁰ Midazolam normally exists in an equilibrium of an open and a closed ring structure that is sensitive to pH changes. At a pH of >4.5, the molecule exists almost entirely in the lipophilic closed ring configuration, which is the physiologically active form.²¹ We used IV formulation of midazolam and ketamine in

apple juice as a diluent with pH=5-5.5. Although only 16% of ketamine is bioavailable orally, the plasma concentration of norketamine, an active metabolite with one-third the potency of ketamine, is twice as high after the oral administration of ketamine compared with intramuscular administration.² We used atropine (0.02mg/kg) in all three regimens. The main reasons for the use of atropine were attenuation of vagal reflex during induction and decreasing secretions with using ketamine.

Several investigators have reported oral midazolam as a preanesthetic medication in doses of 0.5-1mg/kg to achieve satisfactory sedation and improve induction in most pediatric patients.^{5,7,22,23} Gutstein et al. found that oral ketamine (6mg/kg) as premedication provided satisfactory sedation in 15-20 min with few minor side effects.² Warner et al. noted that an oral mixture of ketamine (4mg/kg) + midazolam (0.4mg/kg) was an effective preanesthetic medication in children without cardiac or respiratory effects.⁹

In most previous studies, patients were healthy children and data cannot be extrapolated to situations involving children with underlying cardiopulmonary diseases.

Although in all our study groups sedation increased gradually within 45 minutes after premedication, at 30 minutes more midazolam + ketamine patients (98%) than midazolam (86%) and ketamine (83%) groups had a satisfactory sedation. Some investigators demonstrated that peak sedation was at 20-30 min. after receiving midazolam 0.5mg/kg as premedication.^{24,25} The ketamine group exhibited a significantly higher blood pressure compared with the other two groups. However in general, these regimens provided satisfactory sedation without cardiovascular instability. There was also no episode of oxygen desaturation at any time during the study even in cyanotic patients.

These findings are similar to those of other studies on midazolam and ketamine premedication in children with CHD. Levine et al. showed safety of oral midazolam

(0.75mg/kg) in 15 patients with congenital cyanotic heart disease.¹⁰ Stewart et al. demonstrated the cardiorespiratory stability of 10mg/kg oral ketamine in 20 pediatric cardiac patients.¹¹ Furthermore, the combination of midazolam and ketamine has been used successfully in cardiac catheterization procedures in children.²⁶

Cote et al. noted that cooperation at separation from parents was satisfactory in 88.2% of subjects who received oral midazolam as premedication.²⁷ Of interest, we found satisfactory separation scores in all patients and it may have been related to the peak sedation effect of premedication in children at separation time. Assessing the behavior score at induction has shown that children were more distressed at IV insertion than at separation (12-24% vs. 100%). In contrast to our findings, Griffith et al. found more cooperation at IV insertion with 0.2mg/kg intranasal midazolam as premedication.²⁸ In addition to the unpleasant experience of intranasal midazolam for most children,²⁸ in our opinion, the requirement to achieve such a deep sedation may not be safe for children with cardiac diseases.

There were no significant differences in the incidence of behavioral changes with induction via face mask (81 to 84%). Similarly, Weldon et al. reported that cooperation score for face-mask acceptance was satisfactory in 86%.¹⁶ In this study, six patients of ketamine and one patient of midazolam + ketamine group experienced nausea and vomiting; these events may have been related to the drug. Nevertheless, it is difficult to separate a true pharmacodynamic effect from the psychologic response of a child.

In summary, the data demonstrated that IV formulation midazolam and ketamine with apple juice were accepted well by all children. These three premedication regimens were equally effective in children with CHD without altering the cardiovascular or oxygen saturation values. Furthermore, the oral combination of midazolam + ketamine was

superior to midazolam or ketamine alone in greater sedation effects in a shorter period of time.

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