Low- versus high-dose combination of midazolam-ketamine for oral premedication in children for ophthalmologic surgeries

Darlong V, Shende D, Singh M, Garg R, Pandey R, Punj J

ABSTRACT

Introduction: Midazolam and ketamine are useful for oral premedication in children to allay anxiety. We compared the effects of midazolam with a combination of high- and low-dose ketamine-midazolam as an oral premedication.

Methods: This is a randomised, controlled prospective study conducted in 87 children who were scheduled for ophthalmologic surgeries. Group M received oral midazolam 0.5 mg/kg, Group MKL received oral midazolam 0.25 mg/kg and ketamine 3 mg/kg, and Group MKH received midazolam 0.5 mg/kg and ketamine 6 mg/kg. Standard general anaesthesia technique was used. Sedation levels and ease of parental separation were noted.

Results: A linear increasing trend in sedation was seen in the preoperative sedation scores of all the three groups. At 30 minutes, 23 children in Group MKH had good sedation scores as opposed to 20 in Group MKL and 12 in Group M. The best parental separation time was much shorter in the combination groups. There were no statistically significant differences in the parental separation scores, mean response to induction and mask acceptance. The time to reach Aldrete score of 10 was shorter in Group MKL (22 +/− 5 min) and Group M (36 +/− 1 min) compared to Group MKH (52 +/− 2 min). Group MKH had a higher incidence of excessive salivation compared to the other groups.

Conclusion: A combination of low-dose midazolam and ketamine is as effective as high-dose midazolam and ketamine for achieving optimum anxiolysis and a faster recovery, with a lower incidence of excessive salivation in children undergoing ophthalmic surgery.

Keywords: children, combination, high-dose ketamine, low dose, midazolam, premedication

Singapore Med J 2011; 52(7): 512-516

INTRODUCTION

Anaesthesia and surgery are stressful and difficult for both children and their parents, leading to considerable anxiety, especially in the preoperative period. Behavioural and pharmacological interventions are available for treatment of preoperative anxiety in children.[1] Both oral midazolam and oral ketamine are used for premedication in children.[2,3] A combination of midazolam and ketamine has been found to achieve more effective sedation than when either is used alone.[4-6] These two drugs have been used in different dosage combinations with variable effects and outcomes. Lower doses of these drugs, when used in combination, could provide adequate anxiolysis with lesser side effects as compared to higher doses. As studies on optimal dosing for effective anxiolysis have not previously been conducted, we aimed to compare the efficacy of high- and low-dose combinations of midazolam and ketamine for oral premedication in children scheduled for ophthalmologic surgeries.

METHODS

This was a prospective, double-blind, randomised controlled trial conducted in 87 children aged 1–10 years, of American Society of Anaesthesiologists (ASA) physical status I or II and who were scheduled for elective ophthalmologic surgeries. The patients were randomised into three groups using computer-generated random numbers. Children with ASA physical status III or higher, severe mental retardation, upper respiratory tract infection, increased intracranial pressure and documented allergies, as well as those on antiepileptic drugs or sedatives, were excluded from the study. Approval of the institutional ethics committee and parental consent were obtained prior to the commencement of the study.

The children were restricted to an intake of light meal or non-human milk for up to six hours, breast milk

Department of Anaesthesiology and Intensive Care, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India

Darlong V, MD
Associate Professor

Shende D, MD
Professor

Singh M, MD
Ex-Senior Resident

Garg R, MD, DNB
Senior Resident

Pandey R, MD
Assistant Professor

Punj J, MD
Assistant Professor

Correspondence to:
A/Prof Vanlal Darlong
Tel: (91) 986 839 7809
Email: drrgarg@hotmail.com

for four hours and clear fluids for two hours before the surgery. On arrival at the preoperative holding area, oral premedication was given to the children. Group M received midazolam 0.5 mg/kg. Group MKL received a low-dose combination of midazolam (0.25 mg/kg) and ketamine (3 mg/kg), while Group MKH received a high-dose combination of midazolam (0.5 mg/kg) and ketamine (6 mg/kg). The premedication mixture was prepared and mixed with fresh honey up to a maximum volume of 0.5 ml/kg and administered orally 30 minutes prior to surgery. Children who refused to swallow or vomited the premedication mixture were excluded from the study.

Data was collected by an independent observer. Heart rate, blood pressure, respiratory rate and arterial haemoglobin saturation (SpO_2) were recorded every five minutes. The level of sedation was noted by using the sedation score devised by Epstein et al.[7] The ease and optimum time of separation of the child from the parents was recorded at 10-minute intervals. The time taken to achieve the best parental separation score was noted. The child's response to induction of general anaesthesia was also recorded. Mask acceptance was taken as 'good' when there was no resistance to face mask application and 'bad' when there was resistance to mask application. Evaluation scales for preoperative sedation, parental separation score and response to induction scores were adopted from published studies investigating paediatric premedication (Table I).[8-11] To evaluate parental separation, a score of 1 or 2 was considered 'good' and a score of 3 or 4 was deemed to be 'bad'. For preoperative sedation and response to induction, a score of 1 or 2 was taken as 'bad' and a score of 3 or 4 was considered 'good' or 'acceptable'. For sedation, a score of 5 was considered as a 'complication' and noted.

Table I. Evaluation scale.

Score	Sedation score
1	Awake and active
2	Awake, calm and active
3	Drowsy and responds readily to verbal commands and/or gentle stimuli
4	Asleep and responds slowly to verbal commands and/or gentle stimuli
5	Asleep and not readily arousable
	Parental separation score
1	Excellent, unafraid, cooperative or asleep
2	Good, slight fear and/or crying, quiet with reassurance
3	Fair, moderate fear and/or crying, not quiet with reassurance
4	Poor, crying with need for restraint
	Respone to induction score
1	Fear, crying with mask, needs restraint
2	Moderate fear and crying with mask
3	Slight fear with application of mask
4	Unafraid or asleep, readily accepts mask

Inhalational induction was done using sevoflurane in oxygen-nitrous oxide mixture until loss of eyelash reflex. Monitoring was done using electrocardiogram, non-invasive blood pressure, end-tidal carbon dioxide inhalational agent concentration and an FiO_2 (fraction of inspired oxygen) analyser (Datex-Ohmeda, Helsinki, Finland). After obtaining intravenous (IV) access, vecuronium (0.1 mg/kg) and fentanyl (2 mcg/kg) were administered, followed by tracheal intubation using an appropriate-sized endotracheal tube. Anaesthesia was maintained using isoflurane in oxygen-nitrous oxide mixture (MAC 1-1.5) and intermittent positive pressure ventilation. Intraoperative analgesia was provided with intravenous fentanyl as increments of 0.5 mcg/kg, as required to maintain heart rate and systolic blood pressure within 20% of the baseline levels. At the end of the surgery, residual neuromuscular blockade was reversed with neostigmine (50 mcg/kg) and atropine (20 mcg/kg). After adequate neuromuscular recovery and return of airway reflexes, the trachea was extubated. Children were moved to the post-anaesthesia care unit (PACU), where heart rate, blood pressure, respiratory rate and SpO_2 were recorded until the child was fit for discharge using the modified Aldrete criteria. Side effects related to the drugs administered, such as postoperative nausea and vomiting (PONV), excessive salivation, hallucinations, irrelevant talking, breath holding and sedation, were also noted.

The sample size was estimated in order to detect an increase in success rate of optimal sedation and anxiolysis from 60% to 90%, with a power of 80% and alpha error < 5%. Data was entered and analysed using Epiinfo version 6.04d (Centers for Disease Control and Prevention, Atlanta, GA, USA) and the Statistical Package for the Social Sciences version 7.5 (SPSS Inc, Chicago, IL, USA). For continuous variables such as age, weight and duration, one-way ANOVA or Kruskal-Wallis test was applied to compare the data of the three groups, followed by multiple comparison (range) tests. For qualitative data, chi-square test or Fisher's exact test was applied to determine the association among groups (wherever applicable). Chi-square test for proportions was used to compare between the groups, and chi-square trend analyses were performed to determine the trend at different time intervals. Two-way analysis of variance

Table II. Demographics, time intervals and distribution of surgical procedures.

	Group M (n = 29)	Group MKL (n = 29)	Group MKH (n = 29)	p-value
Median age; range (yrs)	3.5; 1–8	4; 1–9	4; 1.5–7	0.172
Median weight; range (kg)	14; 3–21	13; 3–19	15; 3.5–19	0.267
Gender (M/F)	22/7	22/7	20/9	0.789
Mean duration of surgery ± SD; median (min)	50.5 ± 14.9; 45	45.7 ± 10.2; 45	56.93 ± 11.8; 50	0.218
Type of surgery (no.)				
Lens aspiration	18	16	16	0.828
Squint surgery	3	1	3	0.691
Trabeculectomy	3	2	2	1.000
Others	5	10	8	0.367

M: male; F: female; SD: standard deviation

(Freidman test) was applied to determine the change over time, along with multiple comparisons for each group. Statistical significance was defined as $p < 0.05$.

RESULTS

There was no statistically significant difference in the demographic data and distribution of surgical procedures in the three groups (Table II). All the children accepted the premedication mixture well, and no incidence of vomiting or refusal to swallow was noted. A total of 87 children (n = 29 in each group) were included in the study. Haemodynamic parameters remained within 20% of the baseline values throughout, and no significant differences among the groups were observed.

The number of children having 'good' sedation scores increased with time and followed a linear trend (Table III). None of the patients in any group were deeply sedated (sedation score 5). At 30 minutes, the parental separation scores were comparable in the three groups (Table IV). Time to achieve the best parental separation score was much lesser in the combination groups, i.e. Group MKL and MKH as compared to group M (Table IV). None of the children were sedated to an extent that they could not be awakened during the study period. In addition, no episode of apnoea or airway obstruction after premedication or in the postoperative period was noted, except for one child in Group MKH; the child had an episode of breath holding in the PACU, but was managed conservatively and did not require any active pharmacological intervention.

Although there was no statistically significant difference in the responses to induction and mask acceptance, > 90% of children in all three groups had good scores (Table IV). Recovery from anaesthesia was taken as the time of shifting out from the operation room to the time taken to reach a modified Aldrete score of 10 in the PACU. Recovery was faster in Group MKL as compared to Groups M and MKH (Table IV). Group MKH had a significantly higher incidence of excessive salivation in nine children as compared to none in other groups (Table V). There was no significant difference in the PONV in all three groups, although 14 children in Group MKH had PONV, as opposed to ten in Group M and six in the Group MKL. One child in Group M had irrelevant talk (Table V).

Table III. Distribution of 'good' sedation score at different time intervals.

Time interval (min)	No. (%)			p-value
	Group M (n = 29)	Group MKL (n = 29)	Group MKH (n = 29)	
10	1 (3.4)	2 (6.9)	2 (6.9)	0.351
20	6 (20.7)	15 (51.7)	18 (62)	0.004
30	12 (41.4)	20 (69.0)	23 (79.3)	0.008

DISCUSSION

We found that a combination of low-dose midazolam and ketamine (0.25 mg/kg and 3 mg/kg, respectively) is as effective as a combination of high-dose midazolam and ketamine (0.5 mg/kg and 6 mg/kg, respectively) for achieving optimal anxiolysis and faster recovery, with a lower incidence of excessive salivation in children undergoing ophthalmic surgery. Midazolam, a water-soluble benzodiazepine, is one of the most widely used oral premedication drugs in children.[12] It has rapid onset, short duration of action and minimal side effects, although the success rates vary from 60% to 80%.[13] Hence, we used oral midazolam alone as a control vs. two different doses of combination midazolam-ketamine. Ketamine, a phencyclidine derivative, acts on the n-methyl d-aspartate (NMDA) receptor and causes central dissociation of the cerebral cortex while providing analgesia and amnesia. In addition to intravenous and intramuscular routes,

Table IV: Distribution of parental separation, induction score, mask acceptance, time to reach Aldrete 10 and best parental separation time.

	No. (%)			p-value
	Group M (n = 29)	Group MKL (n = 29)	Group MKH (n = 29)	
Parental separation				
Good	25 (86.2)	26 (89.7)	29 (100.0)	0.133
Bad	4 (13.8)	3 (10.3)	0 (0.0)	
Response to induction				
Good	21 (72.4)	21 (72.4)	24 (82.8)	0.568
Bad	8 (27.6)	8 (27.6)	5 (17.2)	
Mask acceptance				
Good	26 (89.6)	27 (93.1)	27 (93.1)	0.856
Bad	3 (10.4)	2 (6.9)	2 (6.9)	
Mean best parental separation time ± SD (min)	27.8 ± 7.63	20.7 ± 8.31	22 ± 8.18	0.003
Mean time to reach Aldrete 10 ± SD (min)	36.4 ± 12.1	22.2 ± 5.7	52.2 ± 21.9	0.001

SD: standard deviation

ketamine has been administered rectally, orally and intranasally with varied effects.[5,8,14]

To our knowledge, dose response studies for optimal dosing of combination ketamine-midazolam for oral premedication in paediatric patients have not been reported in the literature. Moreover, a comparison of two different doses of combination midazolam-ketamine with midazolam as a control has also not been previously conducted. Oral premedication with midazolam 0.75 mg/kg has shown better efficacy than 0.5 mg/kg or 1 mg/kg in terms of acceptable sedation profile and safe recovery characteristics in paediatric patients.[15] Our results are comparable to Darlong et al's study, in which a combination of midazolam 0.25 mg/kg and ketamine 3 mg/kg produced minimal side effects and showed a faster onset and more rapid recovery than ketamine 6 mg/kg or midazolam 0.5 mg/kg for oral premedication in children.[16] Significantly more children were found to be in an awake, calm and quiet state, and were easily separated from their parents with a low-dose combination of midazolam and ketamine (0.25 mg/kg and 2.5 mg/kg, respectively) than with either drug alone.[17] A 90% success rate of satisfactory anxiolysis with low-dose combination midazolam-ketamine has been reported, compared with < 75% success rate with either drug alone.[12]

The use of both ketamine and midazolam has been associated with paradoxical reactions.[13,18] Benzodiazepines have been used in the prevention and treatment of emergence delirium associated with ketamine.[13] A combination of midazolam and ketamine may serve to curtail these paradoxical reactions. In our study, only one child in Group M had an episode of irrelevant talking, with none in the other two groups. A bigger scale study of a larger sample size may be required to further examine this relationship. The combination of midazolam and ketamine may also suggest a possible synergistic action, as preoperative sedation scores and best parental separation scores were attained earlier in the combination group as compared to midazolam alone (Group M). Group MKL, however, showed better results than Group MKH in terms of lesser side effects and more acceptable recovery characteristics. Group MKL had an acceptable sedation profile with rapid onset and offset, minimal side effects and no delay in induction, emergence or discharge from PACU.

We conclude that the combination of midazolam (0.25 mg/kg) and ketamine (3 mg/kg) is an acceptable and effective option for oral premedication in children scheduled for ophthalmologic surgeries when compared to a high-dose combination of midazolam (0.5 mg/kg) and ketamine (6 mg/kg), or midazolam (0.5 mg/kg) alone.

Table V. Incidence of side effects.

	No. (%)			p-value
	Group M (n = 29)	Group MKL (n = 29)	Group MKH (n = 29)	
PONV	10 (34.5)	6 (20.7)	14 (48.3)	0.086
Excessive salivation	0 (0.0)	0 (0.0)	9 (31)	0.001
Irrelevant talking	1 (3.4)	0 (0.0)	0 (0.0)	1.0
Breath holding	0 (0.0)	0 (0.0)	1 (3.4)	1.0

PONV: post-operative nausea and vomiting

REFERENCES

1. Kain ZN, Mayes LC, Wang SM, et al. Parental presence and a sedative premedicant for children undergoing surgery: a hierarchical study. Anesthesiology 2000; 92:939-46.
2. Saarnivaara L, Lindgren L, Klemola UM. Comparison of chloral hydrate and midazolam by mouth as premedicants in children undergoing otolaryngological surgery. Br J Anaesth 1988; 61:390-6.
3. Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic study in children. Anesthesiology 1992; 76:28-33.
4. Beebe DS, Belani KG, Chang PN, et al. Effectiveness of preoperative sedation with rectal midazolam, ketamine or their combination in young children. Anesth Analg 1992; 75:880-4.
5. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric premedicant. Paediatr Anesth 1995; 5:293-5.
6. Lin YC, Moynihan RJ, Hacke A. A comparison of oral midazolam, oral ketamine and oral midazolam combined with ketamine as preanaesthetic medication for paediatric outpatients. Anesthesiology 1993; 79:A1177.
7. Epstein RH, Mendel HG, Witkowski TA, et al. The safety and efficacy of oral transmucosal fentanyl citrate for preoperative sedation in young children. Anesth Analg 1996; 83:1200-5.
8. Cioacă R, Canavea I. Oral transmucosal ketamine: an effective premedication in children. Paediatr Anaesth 1996; 6:361-5.
9. Mitchell V, Grange C, Black A, Train J. A comparison of midazolam with trimeprazine as an oral premedicant for children. Anaesthesia 1997; 52:416-21.
10. Bevan JC, Veall GR, Maenab AJ, Ries CR, Marsland C. Midazolam premedication delays recovery after propofol without modifying involuntary movements. Anesth Analg 1997; 85:50-4.
11. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine. Can J Anaesth 1994; 41:221-6.
12. Funk W, Jakob W, Reidl T, Taeger K. Oral preanaesthetic medication for children: Double blind randomized study of a combination of midazolam and ketamine vs. midazolam or ketamine alone. Br J Anaesth 2000; 84:335-40.
13. Gutstein HB. Potential physiologic mechanism for ketamine-induced emergence delirium. Anesthesiology 1996; 84:474.
14. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth 1996; 77:203-7.
15. Mishra LD, Sinha GK, Bhaskar Rao P, et al. Injectable midazolam as oral premedicant in pediatric neurosurgery. J Neurosurg Anesthesiol 2005; 17:193-8.
16. Darlong V, Shende D, Subramanyam MS, Sunder R, Naik A. Oral ketamine or midazolam or low dose combination for premedication in children. Anaesth Intensive Care 2004; 32:246-9.
17. Ghai B, Grandhe RP, Kumar A, Chari P. Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. Paediatr Anaesth 2005; 15:554-9.
18. Golparvar M, Saghaei M, Sajedi P, Razavi SS. Paradoxical reaction following intravenous midazolam premedication in pediatric patients – a randomized placebo controlled trial of ketamine for rapid tranquilization. Paediatr Anaesth 2004; 14:924-30.