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## A randomized clinical trial of oral ketamine with midazolam versus oral ketamine as premedication in children

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### Abstract

Midazolam is among one of the most popular pediatric Premedicant. It's onset is rapid, duration of action is short, side effects are not significant and effects are predictable Ketamine has also been investigated as an alternative oral Premedicant because after oral administration it has similar pharmacodynamics This was a double-blinded, prospective, randomized and comparative study done. In this study, the time of recovery in both groups were comparable.

**Keywords:** Midazolam, ketamine, pediatric Premedicant

### Introduction

Surgery and anesthesia procedure produce considerable emotional stress on children and parents [1]. When the children are separated from their parents, fears of injections, operation, peculiar operation theatre environment and physicians invariably produces traumatic experiences in young children [2]. Premedication is used in children to facilitate anxiety-free and smooth separation from the parents and smooth induction of anesthesia. Children's ideal premedication should be available in a preparation that is easily accepted by children, have expected outcome, and no side effects (respiratory obstruction, hemodynamic instability or delayed recovery) [3]. The oral route is generally preferred (esp. in children) because it is less traumatic than others, but it requires 20–45 min to achieve desired effect [4].

The goal of oral premedication has been changing. In 2000 A.D., Funk *et al.* [5] had considered low success for awake state, but in 2005 Ghai B *et al.* [6] considered excellent for awake state as long as there is good anxiolysis allowing successful separation. They accepted calm, quiet and awake child as a good result because it avoids loss of head control or balance, loss of airway control and hypoxemia, etc. associated with deeply sedated child.

Midazolam is among one of the most popular pediatric premedicant. It's onset is rapid, duration of action is short, side effects are not significant and effects are predictable [3] A compliant child separating from parents without crying can be obtained by oral dose of 0.25 to 0.33 mg/kg (maximum, 20 mg) [7].

Ketamine has also been investigated as an alternative oral premedicant because after oral administration it has similar pharmacodynamics. It has been used as a sedation medication in doses of 5 to 6 mg/kg for 1 to 6 years children [8]. Maximal sedation occurred within 20 minutes. However, it may cause dysphoria and hallucinations, excessive secretions, nausea and vomiting [5].

The midazolam and ketamine combination has also been used as an oral sedative. This study was designed to compare efficacy of a combination of oral ketamine 2 mg/kg and midazolam 0.2 mg/kg with ketamine 4 mg/kg alone for achieving calm, quiet and awake child allowing smooth parental separation, accepting mask and having minimal recovery time.

### Methods

This was a double-blinded, prospective, randomized and comparative study done. Conducted in department of Anesthesia of Maharajah's institute of Medical Sciences between 03.8.17 – 30.08.18 after obtaining approval from Institutional ethics committee and written informed consent from the guardians, the children were recruited in the study. Hundred children of ASA I and II aged 1 to 6 years undergoing elective ophthalmological procedures under general anesthesia were randomized with lottery method and divided into two groups (A and B).

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Exclusion criteria were refusal by guardian, any contraindications to any of the drugs used and ASA III or higher. Randomization was done in blocks of 10 using computer generated sequence. Group allocation was kept in serially numbered opaque envelopes, decoding was done later after completion of all data collection. Group A were given 4 mg/kg oral ketamine (50 mg/ml parental form) and group B were given 2 mg/kg oral ketamine with 0.2 mg/kg oral midazolam (1 mg/ml parental form). Both the medications were mixed in 25% Dextrose solution (total approx 10 ml) in a bowl by the anesthesiologist and given to parents to feed their child. The time of drug administration was noted and monitored clinically for sedation. Once the child was sedated, between 20 to 30 minutes, another anesthesiologist evaluated the preoperative sedation score, the child was separated from their parents and parental separation score was evaluated, taken to Operation Table and mask was given, mask acceptance score was evaluated as per on Table 1.

Anesthesia induction done with oxygen and nitrous oxide (50:50) and halothane administered via the anesthetic face mask and pediatric breathing circuit titrating according to response. Intravenous access was achieved. Intravenous fluid (DNS) was given as calculated by 4-2-1 formula. LMA of appropriate size was inserted. For analgesia Inj Paracetamol 15 mg/kg iv slowly was given. Anesthesia was maintained with oxygen, halothane (0.5–1%), titrated to clinical response and spontaneous assisted ventilation.

Monitoring done with pulse oximeter, noninvasive blood pressure measurement, electrocardiogram, eye ball movement and precordial stethoscope. At the end of surgery halothane was discontinued. LMA was removed. Suctioning of oral cavity was done as required and was shifted to postanesthesia recovery unit (PACU). In the PACU, time taken to achieve Modified Aldrete score (Table 2) of  $\geq 9$  and presence of nausea and vomiting or other complications, if any, was noted. The primary variable of this study was sedation score and secondary variables were parental separation score, mask acceptance score and recovery time.

## Results

A total of 100 patients who met the inclusion criteria were included in this study. None of the patients were excluded from the study. In sedation score, 38 (76%) children in group A and 42 (84%) children in group B were awake, calm and quite. In parental separation score, 40 (80%) children in group B and 36 (72%) children in group A have good separation, awake and calm. In mask acceptance score, 40 (80%) children in B group and 24 (48%) children in group A were calm, awake, cooperative, accepting mask. The time of recovery in group A was  $18.12 \pm 5.98$  min whereas in group B was  $18.10 \pm 4.22$  min.

## Discussion

Adequate preoperative planning and medication facilitate smooth perioperative course<sup>[10]</sup>. Out of the various goals of premedication, relief of anxiety and production of are most important. Premedication is widely used in pediatric anesthesia in order to provide anxiolysis, sedation, reduction in emotional stress and to facilitate smooth induction. Different routes of drug administration are available, but for children oral is considered good as it is not painful but associated with slow onset or be spit out; drug taste and child cooperation are the main determinants of success. In

this study 100 children undergoing procedures under general anesthesia were selected and randomly divided into two groups as group A- ketamine and B-midazolam + ketamine group of 50 each. The demographic data such as age, sex, weight and ASA were comparable. There was no statistical difference in time interval between premedication and induction and also between duration of surgery.

In this study, sedation score in both groups were good and comparable. 38 children (76%) in group A and 42 children (84%) in group B were calm, quite and awake (score 3). No significant difference in sedation between the two groups were noted.

Darlong V *et al.*<sup>[11]</sup> in 2011 at AIIMS, in their study, they concluded that the combination of low-dose ketamine (3 mg/kg) and midazolam (0.25 mg/kg) (MKL group) is as effective as high-dose ketamine (6 mg/kg) and midazolam (0.5 mg/kg) (MKH group) for achieving optimum anxiolysis than midazolam alone (0.5 mg/kg) (M group). The number of children having 'good' sedation scores increased with time and followed a linear trend i.e. in MKL group 20 (69%), in MKH group 23 (79.3%) & in M group 12 (41.4%) children have good sedation score at 30 min than at 20 min [15 (51.7%) in MKL group, 18 (62%) in MKH group & 6 (20.7%) in M group]. They studied their score at 30 minutes after premedication, which is practically not feasible. In pretesting of 8 children, we found the children get sedated at around 20 minutes of premedication, so we have studied the sedation score at 20-30 minutes. The children were of 1-10 years in their study, but most children above 6 years can be convinced for mask induction, so do not require premedication.

In this study age group is 1-6 years. A study done by Ghai B *et al.*<sup>[6]</sup> in 2005 at PGIMER, Chandigarh, India, they found, in group MK (18.36%, n =9) lesser children were asleep than in group M (39%, n = 19) and greater children 46.93% (n = 23) in MK group were calm, quiet The difference was statistically significant. The reason may be due to higher doses of drugs in combination group than that of this study. In Horiuchi T *et al.*<sup>[12]</sup> study, group K (26%) had significantly lower incidence of 'effective' sedation (scores 2 or 3) than group M (39%). In addition, group K (37%) had higher incidence of score 5 (agitated) than group M (7%).

They have used 50 mg ketamine lollipop to all children between 2 to 6 years of age, it may be attractive and acceptable for children and easy to prepare but the dose might be inappropriate. Dose must be calculated in respect to weight. This might be the reason for more agitated children in Group K (37%) than in Group M (7%), where dose was given in accordance to weight (0.5 mg/kg of syrup Midazolam). Funk *et al.*<sup>[5]</sup> in 2000 at university of Rogensberg, Germany, compared oral ketamine 6 mg/kg with oral midazolam 0.5 mg/kg alone or a combination of oral midazolam 0.5 mg/kg and ketamine 3 mg/kg. Success rate observed was low in all groups. The reason for low success rate may be due to definition of success as asleep (score 4) and awake as no success. In our study we defined success as awake, calm and quite child.

In this study, the parental separation score was relatively better in MK group. Forty children (80%) in group B and 36 children (72%) in group A have good separation, awake and calm. In Ghai B *et al.*<sup>[6]</sup> study, they found that for separation score, 23 children (47%) in M group than 10 children (20.4%) in MK group were asleep (score 1). For score 2 (awake, calm children with good separation),

percentage was lesser in group M (41%, n=20) than in group MK (73.46%, n=36). The reason may be due to higher doses of drugs in combination group than that of this study. Horiuchi T *et al.* [11] found group K had significantly higher incidence of ‘poor’ (score 3) separation than group M (18.5% vs 0%, P = 0.017). The reason might be inappropriate dose, 50 mg ketamine lollipop to all children between 2-6 years irrespective of weight. Funk *et al.* [5] found success rate for behavior at separation were only 51% in ketamine group, approximately 70% in midazolam group and >90% in combination group. In our study also success was more with combination group in this study, the mask acceptance was also relatively better in B group. Forty children (80%) in B group and 24 children (48%) in group A were calm, awake, cooperative, accepting mask. This difference was also statistically significance. Darlong V *et al.* [11], they found no statistically significant difference in the responses to induction and mask acceptance, > 90% of children in all three groups had good scores. i.e. for Mask acceptance in Group M 26 (89.6%), in Group MKL 27 (93.1%), in Group MKH 27 (93.1%) and for response to induction in Group M 21 (72.4%), in Group MKL 21 (72.4%), in Group MKH 24 (82.8%). The differences were not statistically significance. In Ghai B *et al.* [6] group M has 52.08% (n=25) of score 1 (Excellent, asleep, calm, awake, cooperative, accepting the mask) than in group MK 57.14% (28), comparable induction score. Horiuchi T *et al.* [12] found in mask cooperation scores no statistical differences between the two groups. However, the incidence of ‘poor’ (score 3) for mask cooperation was significantly higher in group K than group M (26% vs 7%). The reason might be inappropriate dose, 50 mg ketamine lollipop to all children between 2-6 years irrespective of weight. In this study, the time of recovery in both groups were comparable. In group A was 18.12 ± 5.98 min whereas in group B was 18.10 ± 4.22 min. Darlong V *et al.* [11] found that Recovery was faster in Group MKL (22.2 ± 5.7 min) as compared to Groups M (36.4 ± 12.1 min) and MKH (52.2 ± 21.9 min). Ghai B *et al.* [6] found comparable score of mean postanesthesia recovery time between the two groups (120 ± 24 min in group MK and 128 ± 35 min in group M).

The study done by Thakur JP *et al.* [13] also showed almost similar results comparable to our study.

**Table 1:** Evaluation scores [6].

<b>A</b>	<b>Sedation scores</b>
1	Asleep
2	Drowsy, responds to verbal commands /gentle stimulation
3	Awake, calm, quiet
4	Anxious, depressed/agitated/crying
<b>B.</b>	<b>Parental separation score</b>
1.	Asleep
2.	Good separation, awake, calm
3	Awake, anxious, can be easily reassured 4
4	Crying, cannot be reassured
<b>C.</b>	<b>Mask-acceptance score</b>
1	Excellent, asleep, calm, awake, cooperative, accepting the mask
2	Slight fear but can be reassured easily
3	Moderate fear and reassured with difficulty
4	Crying, needs restraint

**Table 2:** Modified Aldrete Recovery Score [9].

<b>1</b>	<b>Oxygenation</b>	
	SpO <sub>2</sub> > 92% on room air	2
	SpO <sub>2</sub> > 90% on oxygen	1
	SpO <sub>2</sub> < 90% on oxygen	0
<b>2</b>	<b>Respiration</b>	
	Breathes deeply and coughs freely	2
	Dyspneic, shallow or limited breathing	1
	Apnea	0
<b>3</b>	<b>Circulation</b>	
	Blood pressure ± 20 mm Hg of normal	2
	Blood pressure ± 20–50 mm Hg of normal	1
	Blood pressure more than ± 50 mm Hg of normal	0
<b>4</b>	<b>Consciousness Fully awake</b>	2
	Arousable on calling	1
	Not responsive	0
<b>5</b>	<b>Activity</b>	
	Moves all extremities	2
	Moves two extremities	1
	No movement	0

As the two groups were identical regarding age, sex, weight, and ASA status, both the groups were comparable.

**Table 3:** Demographic Distribution

<b>Group</b>	<b>Group A</b>	<b>Group B</b>
Age in years (mean ± SD)	3.50± 1.82	3.68 ± 1.78
Sex (M/F)	28/22	26/24
ASA I	50	50
Weight in kg	11.98 ± 4.32	12.86 ± 3.76
Interval between premedication to induction (min)	25.72 ± 2.96	26.12 ± 2.64
Duration of surgery (min)	33.72 ± 24.97	32.94 ± 26.34

**Table 4:** Data showing sedation, parental separation, mask acceptance scores and average recovery time.

	<b>Groups</b>	
	<b>A</b>	<b>B</b>
<b>Sedation scores</b>		
1	6(12%)	5(10%)
2	2 (4%)	1(2%)
3	38 (76%)	42(84%)
4	4(8%)	2 (4%)
<b>Parental separation scores</b>		
1	2 (4%)	3 (6%)
2	36 (72%)	40 (80%)
3	8(16%)	4(8%)
4	4 (8%)	3 (6%)

Mask-acceptance Scores		
1	24 (48%)	40 (80%)
2	3 (6%)	5 (10%)
3	5 (10%)	2(4%)
4	18 (36%)	3 (6%)
Average recovery time (min)	18.12 ± 5.98	18.10 ± 4.22

### Conclusion

Our study concluded that both Ketamine and Ketamine with Midazolam are safe and equally effective for sedation, separation from parents, mask acceptance and recovery status.

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