



## A Comparative Study of Combination of Low-Dose Ketamine And Midazolam Versus Ketamine and Midazolam Alone as Oral Premedication in Paediatric Population

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### ABSTRACT

**Background:** Oral premedication is an easily acceptable alternate route of achieving a calm, sedated child for smooth induction of anaesthesia. Oral premedication has a good patient compliance and is very easy to administer. A calm child entering the operation theatre also provides parental satisfaction, removing fears from their minds too. Oral Ketamine and oral Midazolam have been tried for the last 20 years as good premedicants with varying results.

A combination of low-dose oral Midazolam and Ketamine has been used in this study to find out whether there is advantage in terms of minimal side-effects, sedation onset when compared to individual drugs. An ideal atraumatic premedicant can provide effective analgesia and also minimize separation anxiety, improve induction by mask-acceptance, minimize emotional trauma and have decreased occurrence of negative behavioral issues.

**The combination of oral low dose Ketamine at 3 mg/kg and Midazolam at 0.25 mg/kg is more efficacious when compared to individual oral Midazolam at 0.5 mg/kg and individual oral Ketamine at 6 mg/kg in terms of better onset of sedation, adequate depth of sedation, anxiolysis, hemodynamic stability and good, smooth post-operative recovery.**

**KEYWORDS :** Premedication, Ketamine, Midazolam, analgesic, premedicant

### Introduction:

Preparing the paediatric patients for surgery can be a complex process because of many individuals and factors involved. A hospitalized child has the fear of separation, fear of pain, physical trauma and fear of stranger(s) or unknown. A child can predict and anticipate pain based on the past experiences but cannot reason out or accept explanations from doctors and nurses. The child cannot communicate the fear and anxiety, but can only cry. The fear can be so severe that it can manifest as various forms of regressive behaviors after hospitalization. Hence traumatic experiences in the tender minds of children can be effectively prevented by a very good premedication. Further, parenteral premedication aggravates the fear and anxiety of paediatric patients.

An ideal atraumatic premedicant can decrease separation anxiety, improve induction by mask-acceptance, minimizing emotional trauma. Decreased occurrence of negative behavioral problems<sup>2</sup> after surgery have been observed with Midazolam as a premedicant<sup>1</sup>.

A combination of low-dose oral Ketamine and Midazolam has been used in this study to determine the efficacy of the premedicant in terms of sedation scores, anxiolysis and post-operative recovery.

### Materials and Methods:

Seventy five children aged between 1 and 12 years, ASA Grades I and II, undergoing elective surgery were included in this randomized study.

Approval from the Hospital Ethical Committee and consent from the parents were duly obtained.

The children were randomly allocated into 3 groups of 25 each.

### Drugs used:

Ketamine (50 mg/ml vial), Midazolam syrup (2 mg/ml)

### Grouping:

Group KM: Children of this group were given a combination of Ketamine in a dose of 3 mg/kg and Midazolam in a dose of 0.25 mg/kg orally, 30 minutes before the surgery.

Group K: Children of this group were given Ketamine in a dose of 6 mg/kg orally, 30 minutes before surgery

Group M: Children of this group were given Midazolam syrup in a dose of 0.5 mg/kg orally, 30 minutes before surgery.

### Monitoring:

All the children were constantly monitored. The heart-rate, blood pressure, Oxygen saturation were recorded every 10 minutes upto 30 minutes before induction

They were constantly observed for changes in the mood, behavior, appearance, onset of sedation time when sedation score was less than or equal to 3.

Sedation level at 30 minutes after premedication, anxiety level at the time of parental separation, at the time of I.V. cannulation and mask acceptance were noted. The children were observed for side effects like hiccough, salivation, euphoria, nausea, vomiting preoperatively.

**To assess the level of sedation, a 5-point Sedation scale was used – Table-1**

SCORE	SEDATION LEVEL
1	Barely Arousable (full sleep)
2	Eyes closed (light sleep)
3	Eyes open but drowsy
4	Awake
5	Agitated

Table 1: THE 5 – POINT SEDATION SCALE

**To assess the level of anxiety, a 4-point Anxiety scale was used – Table-2**

SCORE	ANXIETY LEVEL
1	Calm, sleepy
2	Apprehensive, but withdrawn from surroundings
3	Crying
4	Agitated, difficult to control

Table 2: THE 4 – POINT ANXIETY SCALE

Intravenous Cannulation with appropriate I.V. cannula was done. In crying, agitated children, Sevoflurane with Oxygen was administered by mask to calm the children and I.V. line secured. Isolyte P was started at appropriate rate.

Intraoperative monitoring included precordial stethoscope, pulse oximetry, ECG, and NIBP.

- All the surgeries were proceeded under General Anaesthesia with controlled ventilation using Mapleson F Circuit.
- All children were preoxygenated with 100% Oxygen and induced with Inj. Thiopentone Sodium 5 mg/kg I.V. and Inj. Succinylcholine 2 mg/kg I.V.

Intubation was done with appropriate Endotracheal tube

Increased secretions during laryngoscopy and intubation, if present, were noted.

Anaesthesia was maintained with Nitrous Oxide (66%), Oxygen (33%) and Sevoflurane (1%). Inj. Vecuronium (0.08 mg/kg) I.V. was used as muscle relaxant.

At the end of surgery, Inj. Neostigmine (50 µg/kg) I.V. and Inj. Atropine (20 µg/kg) I.V. were used for reversal and patient extubated after recovery of reflexes.

Post-operatively, Oxygen saturation, continuous heart rate monitoring were done and blood pressure recorded every 10 minutes.

Recovery was assessed by Aldrete Score – Table 3. Crying, Irritability, nausea, vomiting, hallucinations and any other side effects up to 6 hours were noted during the post-operative period.

SL. NO.	PARAMETER	OBSERVATION	ALDRETE SCORE
1	COLOUR	Pink	2
		Pale or dusky	1
		Cyanotic	0
2	RESPIRATION	Can breathe deeply and cough	2
		Shallow but adequate exchange	1
		Apnea or obstruction	0
3	CIRCULATION	BP within 20% of normal	2
		BP within 20 – 50% of normal	1
		BP deviating > 50% from normal	0
4	CONSCIOUSNESS	Awake, alert, oriented	2
		Arousable, but readily drifts to sleep	1
		No movement	0
5	ACTIVITY	Moves all extremities	2
		Moves 2 extremities	1
		No movement	0

Table 3: ALDRETE SCORE

**Results:**

All the seventy five children accepted the drug and no vomiting was reported after swallowing.

The results are summarized in Table - 4

The onset time and post-operative recovery time were statistically analyzed using student's unpaired 't' test.

The sedation scores, anxiolysis scores, pre-operative and post-operative side effects were analyzed with Chi-square test.

SL. NO.	PARAMETER	Group KM	Group K	Group M	STATISTICAL SIGNIFICANCE P = 0.05
1	SEDATION TIME in Minutes	9.92 ± 0.64	15.16 ± 3.8	12.08 ± 3.83	P < 0.05 (Significant)
2	SEDATION SCORE < 3 within 30 min.	100 %	88 %	40 %	P < 0.05 (Significant)

3	ANXIOLYSIS SCORE				
	Calm at Parental separation	100 %	80 %	80 %	P < 0.05 (Significant)
	Cried at Parental separation	0 %	20 %	20 %	P > 0.05 (Not Significant)
	Calm at I.V. Cannulation	100 %	80 %	28 %	P < 0.05 (Significant)
	Cried at I.V. Cannulation	0 %	12 %	60 %	P < 0.05 (Significant)
	Non-cooperative at I.V. Cannulation	0 %	8 %	12 %	P > 0.05 (Not Significant)
4	POST-OPERATIVE RECOVERY TIME in Minutes	18.24 ± 9.27	29.0 ± 8.72	36.92 ± 5.82	P < 0.05 (Significant)
5	SIDE EFFECTS				
	PRE-OPERATIVE FACTORS				
	Euphoria (crying and laughing)	0 %	0 %	60 %	P < 0.05 (Significant)
	Hiccough	0 %	0 %	8 %	P > 0.05 (Not Significant)
	Increased salivation	4 %	12 %	0 %	P > 0.05 (Not Significant)
	POST-OPERATIVE FACTORS				
	Crying	0 %	0 %	52 %	P < 0.05 (Significant)
	Irritability	0 %	0 %	68 %	P < 0.05 (Significant)
	Nausea	0 %	16 %	0 %	P < 0.05 (Significant)
	Vomiting	0 %	8 %	0 %	P > 0.05 (Not Significant)
	Hallucination	0 %	12 %	0 %	P < 0.05 (Significant)

Table 4: RESULTS

The combination of oral low dose Ketamine at 3 mg/kg and Midazolam at 0.25 mg/kg was more efficacious when compared to individual oral Midazolam at 0.5 mg/kg and individual oral Ketamine at 6 mg/kg.

This was considering better onset of sedation, adequate depth of sedation, anxiolysis, hemodynamic stability and good, smooth post-operative recovery.

**Discussion:**

Lin YC et al3 showed that 6 mg/kg of Ketamine made for better sedation and anxiolysis than 0.5 mg/kg of Midazolam.

Feld et al4 and Alderson et al5 observed that 0.5 mg/kg of Midazolam could not produce sleep in children even after 30 min. The optimum dose of Midazolam as recommended by Kothari et al6 and Kain ZN et al8 for satisfactory sedation and anxiolysis is 0.75 mg/kg.

It was proved in our study that when oral Midazolam of 0.5 mg/kg alone was used as a premedicant,

only 40% of the patients included in the study achieved a sedation score of less than 3

60% of the patients were euphoric  
 20% cried at parental separation  
 60% cried at I.V. Cannulation  
 12% were non-cooperative  
 Post-operative crying and irritability were observed in more than 60% of the patients.

Further, when oral Ketamine of 6 mg/kg alone was used as a premedicant in our study,

88% of the patients included in the study achieved a sedation score of less than 3

80% were calm at parental separation and I.V. cannulation

Although there was a 12% incidence of increased salivation, recovery was smooth except for occurrence of emesis (8%)

This proved conclusively that increasing the dosage of Ketamine is associated with increased dosage-related side effects<sup>2</sup>.

Many studies have proved that combined oral Ketamine and oral Midazolam is better in terms of sedation, anxiolysis and smooth recovery.

Addition of Midazolam to Ketamine in low doses have proved that the combination has Synergistic Effects.

Studies by Funk et al<sup>7</sup> and Trabold et al<sup>9</sup> proved that the combination of oral Ketamine 3 mg/kg and oral Midazolam 0.5 mg/kg improved the depth of sedation and did not prolong emergence or discharge from PACU.

The side effects of Ketamine like hallucination are nullified with Midazolam. Smooth recovery with stable hemodynamics is observed.

### Conclusion:

In our study also, minimal side effects were observed and incidents of salivation was less than 10% (not significant)

Hemodynamic stability was well maintained and the post-operative recovery was smooth and without any side effects in our study.

Hence this study concludes that oral premedication with a combination of low dose Ketamine 3 mg/kg and oral Midazolam 0.25 mg/kg given 15 to 30 minutes before is efficacious in terms of quicker onset (onset time – 9.92 min) and results in better sedation scores (100% sedated within 30 min; sedation score < 3).

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