

**Original Article**

# Oral Midazolam and Ketamine as Premedicants in Children- A Randomized Open Label Single Centre Study

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Email: [dr.pradnyabhalerao@gmail.com](mailto:dr.pradnyabhalerao@gmail.com), Tel.No.8806664773**Abstract**

Operation theatre and emergency room environment induces fears in a child which include those due to separation from parents, of pain, fear of the unknown and unfamiliar environment and fear due to loss of control and privacy. Pre-medication with anxiolysis and sedation may help to tide over these issues. We thus conducted this study to evaluate the effectiveness of oral midazolam and oral ketamine as premedicants in children. 100 children between the age group of 2-8 years undergoing surgery lasting 1-1.5 hours were considered for this study. The primary objective was to compare the two in terms of haemodynamic, anxiolysis, and onset and level of sedation. The secondary objective was to look into side effects if any. We found that the two groups were comparable in terms of demographics and haemodynamics. Onset of sedation was faster with midazolam. The sedation score, anxiolysis score, separation from parents score, anxiolysis on venepuncture were similar in both the groups. The side effects, though few, were more in the ketamine group.

**Keywords:** Oral premedication, midazolam, ketamine.**Introduction**

Surgery and anaesthesia can be a traumatic experience and cause a lot of stress in a child as well as parents. They induce fears in a child which include those due to separation from parents, of pain, fear of the unknown and unfamiliar environment and fear due to loss of control and privacy. These can be prevented by proper psychological preparation and use of appropriate

pharmacological adjuncts. An ideal premedicant would be the one which is atraumatic, well accepted, easily administered, acts rapidly, has minimal side effects and does not prolong emergence from anaesthesia. <sup>[1]</sup>

Midazolam is an imidazobenzodiazepine that is given in the oral dose of 0.5-0.75 mg/kg. It has a short half-life of 1-2 h, high potency, twice that of diazepam besides a rapid onset of action (within

10-30 min). It has sedative and anxiolytic activities, provides anterograde amnesia, and also has anticonvulsant properties. Ketamine, on the other hand, is a 2-(4-chlorophenyl)-2-methylamine cyclohexane hydrochloride that is given in the oral dose of 3-10 mg/kg. The onset of action is rapid, around 30 minutes. Ketamine provides well-documented anesthesia and analgesia. It has a wide margin of safety, as the protective reflexes are usually maintained. We thus compared the two drugs as premedicants in our study.<sup>[2]</sup>

The primary objective was to compare the two in terms of haemodynamics, anxiolysis, and onset and level of sedation. The secondary objective was to look into side effects if any.

### Material and Methods

This randomized, open labeled, single centre study was conducted in a tertiary care centre after ethical committee approval. A written informed consent from parents of the child was taken. Children with history of allergy to any of the drugs used in the study as well as children receiving anticonvulsants, sedatives or analgesics in the preoperative period were excluded from the study. 100 children belonging to ASA grade I – II, age 2 to 8 years, of either sex and posted for elective surgery lasting 1 to 1½ hrs were considered for the study. They were divided into two groups of 50 each by computerised randomization. Group I received oral midazolam 0.5mg/kg and group II received oral ketamine 5mg/kg body weight both mixed with orange fruit crush 45minutes prior to surgery. Pulse rate, blood pressure and respiratory rate were monitored prior premedication, at 15minutes and 45 minutes post premedication. Oxygen saturation was monitored throughout. Besides this onset of sedation, level of sedation (Sedation score), acceptance of premedication (Acceptance score), state of anxiolysis (Anxiolysis score) at separation from the parents score and venepuncture and side effects like vomiting, nystagmus, secretions and hallucinations were monitored. Both the groups were given general anaesthesia thereafter.

Statistical analysis was done using SPSS (SPSS 21st edition; IBM Corp, NY) computer program. Statistical calculations were performed by t-test or Mann–Whitney for continuous variables, and by Fisher exact test for discrete variables. P values <0.05 were considered statistically significant.

### Results

As far as the demographic data was concerned the two groups were comparable [Table1]. There was a fall in the pulse rate from before premedication values in group I but rise in Group II at 15 followed by some fall though not below pre-premedication values at 45minutes both [Figure1]. Similarly the systolic blood pressure was lower in Group II at 15 and 45 minutes both. There was significant change in the diastolic blood pressure pre and post medication [Figure2, 3]. The onset of sedation was 25 minutes in group I and 31 minutes in groupII [Figure6]. The sedation score was good in 60-70% children in group I and 70-80% in group II (TableI, Figure7). Sedation score of 3 was achieved in over 90% patients in both the groups [Figure7]. The anxiety on separation score was 1 in 62% patients in group I and 60% in group II [Table2, Figure8]. Successful separation was noted in 80% patients in group I and 76% in group 2 [Table4, Figure9]. The anxiety on venepuncture score was 1 in 56% in groupI and 52% in groupII (Table3, Figure10). 4% of children had vomiting in group I and 8% in groupII. 12% had secretions and 4% nystagmus in Group II.

**Table 1:** Sedation score<sup>[1]</sup>

1. Agitated (clinging to parents or crying)
2. Awake (alert but not clinging to the parents, may whimper but not cry, anxious)
3. Sleeping intermittently (relaxed, less responsive)
4. Asleep (response to minor stimulation, e.g. light touch, soft voice)
5. Barely arousable (arousable by persistent stimulation needs shaking or shouting to arouse)

**Table 2:** Anxiolysis score

1. Combative
2. Tearful / crying
3. Apprehensive
4. Calm

**Table 3:** Anxiolysis for venepuncture

1. Calm to venepuncture, no reaction, haemodynamically stable
2. Apprehensive venepuncture possible without much difficulty
- 3/4. Venepuncture difficult, anxious

**Table 4:** Separation from parents Score

- Score 1 : Excellent, happily separated  
 Score 2 : Good, separated without crying  
 Score 3 : Separated with crying  
 Score 4 : Need for restrain

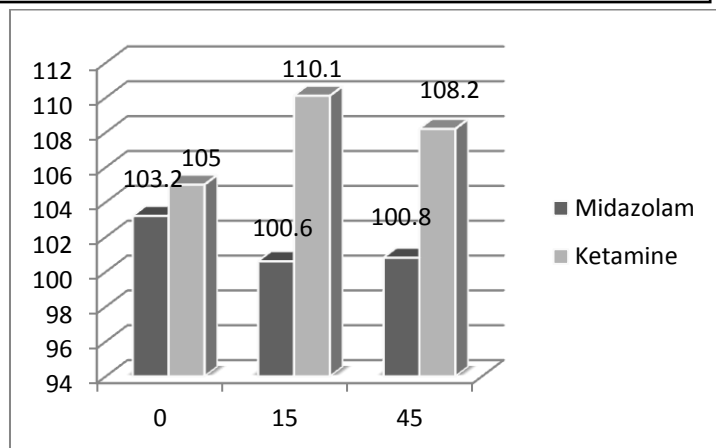
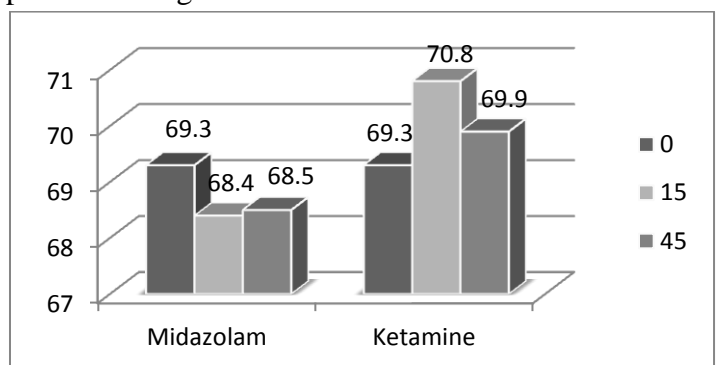
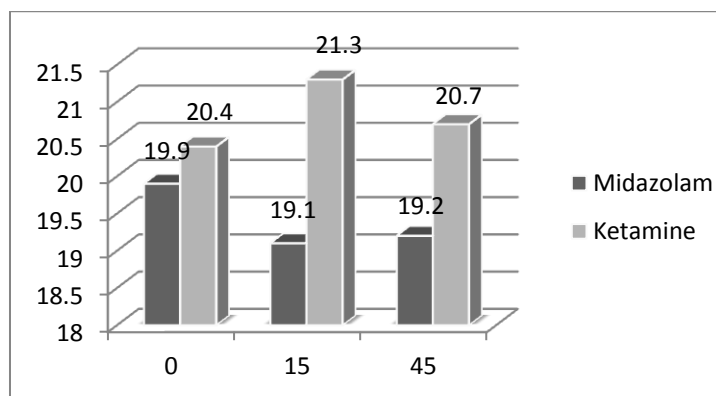
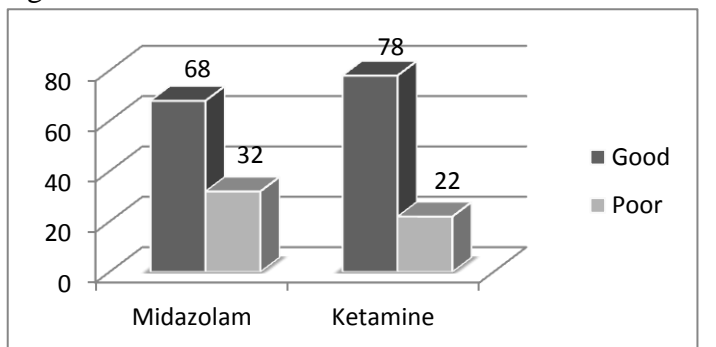
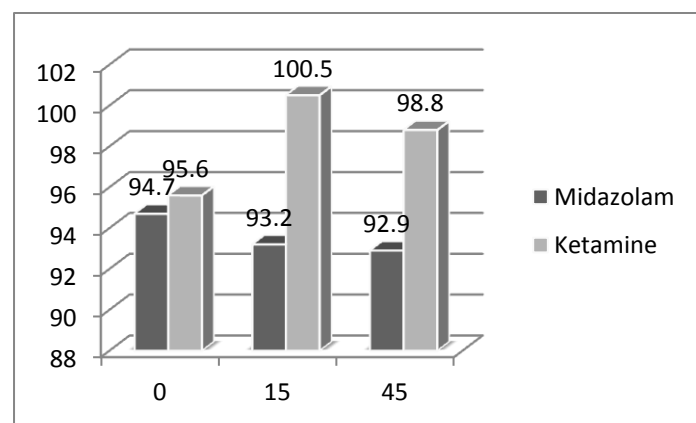
**Table 5:** Acceptance score

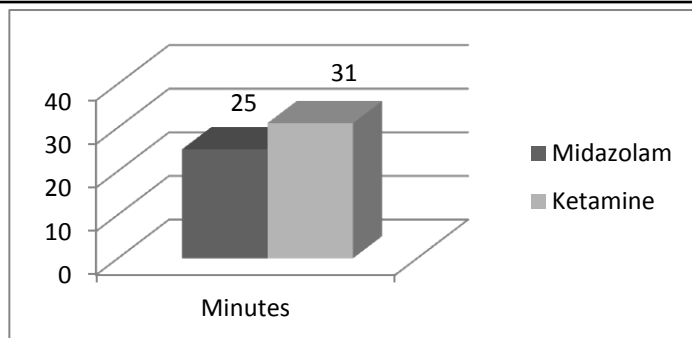
- 1 : Readily accepts  
 2 : Dislikes but accepts  
 3 : Head down / force to accept  
 4 : Refused to open mouth after tasting pre-medication

## Results

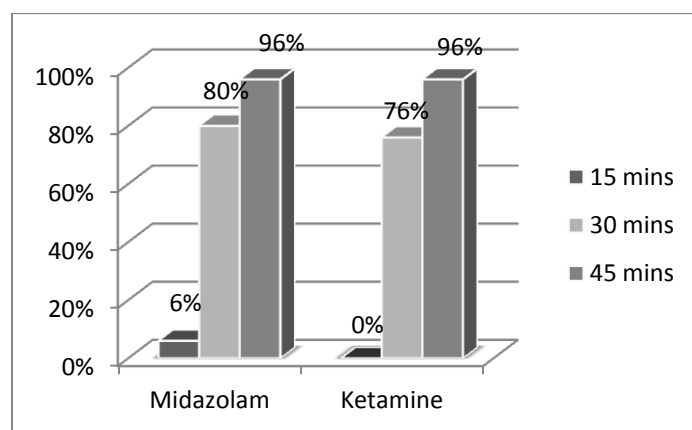
**Table 5 :** Demographic data

Ketamine	29	21	6.2±2.8	p>0.05
Drug	Sex		Age/years	p value
	Male	Female		
Midazolam	32	18	5.8±2.3	p>0.05
Ketamine	29	21	6.2±2.8	p>0.05

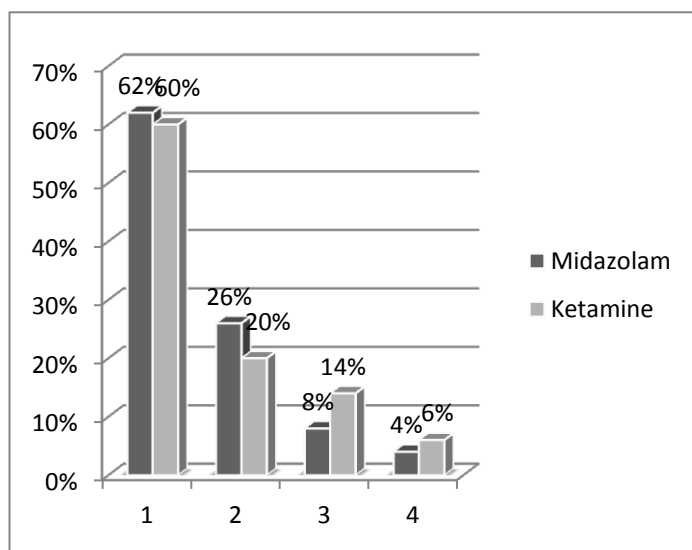
**Figure 2:** Systolic blood pressure( mm Hg), p<0.05-not significant**Figure 3:** Diastolic blood pressure ( mm Hg), p<0.05-not significant**Figure 4 :** Respiratory rate/minute, p<0.05-not significant**Figure 5:**Acceptance score**Figure 1 :** Pulse rate , p<0.05-not significant



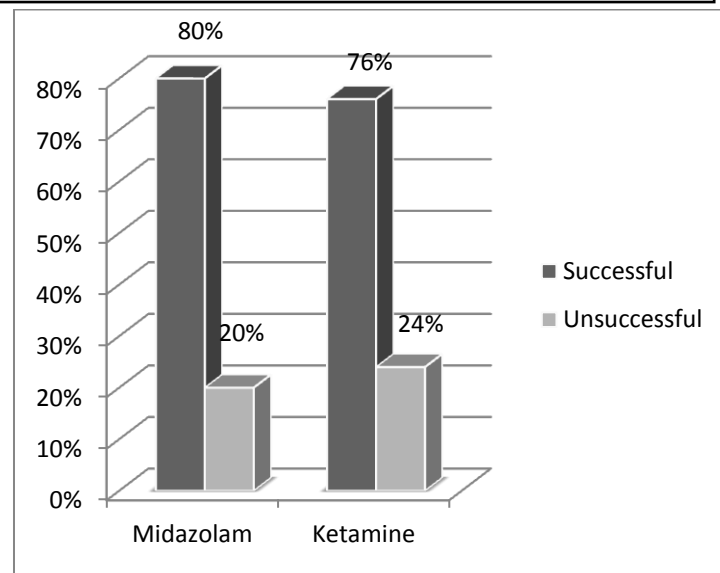
**Figure 6 : Onset of sedation**



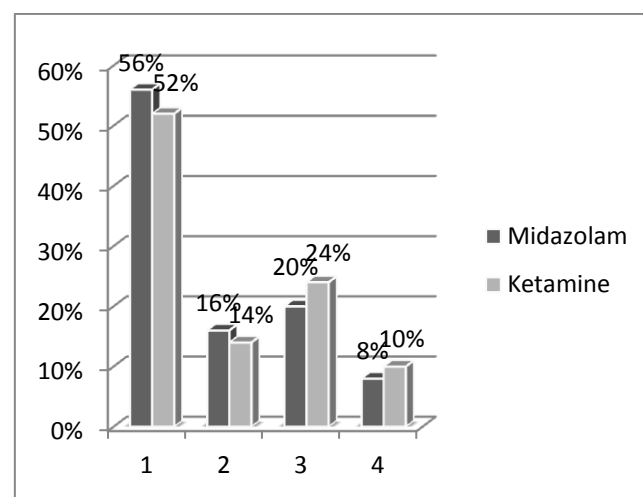
**Figure 7 : Level of sedation**



**Figure 8 :Anxiolysis on separation**



**Figure 9 : Separation from parents score**



**Figure 10 : Anxiolysis on venepuncture**

### Discussion

Premedicants can be given by various routes namely oral, intramuscular, intravenous, intranasal, and per-rectal. Injections cause screaming, struggling, bad memories in a child. <sup>[3]</sup>Intranasal drug can cause a burning sensation and bitter taste in the pharynx. The per-rectal route can be psychologically embarrassing, besides causing unreliable absorption. Therefore oral premedication in children is definitely a good alternative. The oral route causes the least anxiety in young children. Oral chloral hydrate has long been used for paediatric sedation for painless procedures, but the onset of sedation may be delayed and a prolonged recovery time is common.

The oral drug should be palatable. Since midazolam has a bitter taste fruit syrup was mixed with both to tide over this pitfall. Since the time to onset of sedation in both groups is about 30minutes the drug was given 45 minutes prior scheduled anesthesia induction.

A dose of 0.5mg/kg midazolam and 5mg/kg ketamine was used in our study. Higher doses of midazolam and ketamine have been used in other studies.<sup>[4, 5]</sup>

As far as the haemodynamic parameters were concerned in the midazolam group stability was better throughout. In the Ketamine group there was an initial rise in pulse rate and blood pressure at 15minutes followed by fall to normal basal values. This was however both statistically and clinically insignificant. The respiratory rate was not significantly altered in both groups [Figure 4]. Ketamine has been proven to be effective as an analgesic and amnesic when administered by the intravenous, intramuscular, and intranasal routes. Its efficacy upon oral administration was examined in various procedures, such as dental procedures, wound dressing in burns.<sup>[5]</sup> Onset of sedation was faster with midazolam in our study. The level of sedation score >3 was achieved similarly in both the groups at 45minutes. Studies have shown that achieving adequate sedation was more common in children treated with the combination of ketamine and midazolam rather than oral midazolam alone.<sup>[6,7,8]</sup> Procedural sedation was adequately achieved with fentanyl and midazolam combination in one study.<sup>[9]</sup> Separation from parents was equally good in both groups however anxiolysis on venepuncture was poor in 28% and 34% cases with midazolam and ketamine respectively. Rubinstein found that supplementation with intravenous drug was more in the ketamine group.<sup>[5]</sup>

The two drugs have been used safely in paediatric dental procedures in the doses similar to those on our study with apparently better outcomes with midazolam.<sup>[2, 10]</sup>

Thus both oral midazolam and ketamine were cardiorespiratory stable. Ketamine was better

accepted probably because the bitter taste of midazolam was not completely masked [Figure5]. Faster onset of sedation was seen with midazolam. Level of sedation and anxiolysis was comparable. Emesis and secretions was more with ketamine and was seen in a nystagmus in few with oral ketamine.

The limitation with use of these drugs orally is the decrease in bioavailability due to first pass effect with both the drugs, more so with midazolam.

### Conclusion

Oral midazolam and ketamine are good pre-medicants in children with adequacy in level of sedation and anxiolysis. The anterograde amnesia with midazolam could be an added advantage. Combining midazolam and ketamine could be an option.

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Conflicting Interest (If present, give more details): Nil

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