

# Comparison of Midazolam and Ketamine as Oral premedicants in pediatric patients

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## Abstract

Background: Preanesthetic medication plays an important role in the anesthetic care of children by allaying anxiety, decreasing vagal stimulation and preventing postoperative psychological sequelae. Midazolam and Ketamine are used by oral route as premedicants in pediatric anesthesia. This study was undertaken to compare the two drugs. Methods: Fifty children in the age group of 1 to 7 years posted for elective surgical procedures were randomly allocated to one of two groups – 'Group K' and 'Group M'. Group K received Ketamine 6 mg.kg<sup>-1</sup> p.o. and Group M received Midazolam 0.5 mg.kg<sup>-1</sup> p.o. Drug acceptance was noted. Heart rate, arterial pressure, respiratory rate, sedation score, anxiolysis score were noted before drug administration, 15 min and 30 min after drug administration. Parental separation score at 30 min and mask acceptance score were also noted. Sedation scores and anxiolysis scores between the groups were compared by Mann-Whitney test; Parental separation, drug acceptance and mask tolerance were analysed by Fisher's exact test. A 'p value' of < 0.05 was considered statically significant. Results: Sedation score, anxiolysis score and mask acceptance score were significantly higher in Group-K than in Group-M (p<.05). Hemodynamic parameters, parental separation and drug acceptance were similar in both groups. Conclusion: Ketamine 6 mg.kg<sup>-1</sup> p.o. is a better premedicant than Midazolam 0.5 mg.kg<sup>-1</sup> p.o. in pediatric patients. Optimum time interval for parental separation is 30 minutes after administration of preanesthetic medication.

## BACKGROUND

Preanesthetic medication in pediatric patients is a challenge for anesthesiologists. It plays an important role in the anesthetic care of infants and children by allaying anxiety, decreasing vagal stimulation and preventing postoperative psychological sequelae. A peaceful separation of the parent and the child is the definition of successful premedication. The ideal premedication in children should possess the following attributes:

- An acceptable preparation (readily accepted by children)
- Rapid and reliable onset (with sufficient duration of action to accommodate delays in operating room schedules)
- Provide anxiolysis with sedative effects
- Minimal side effects (less nursing supervision)

- Rapid elimination / rapid recovery (early discharge)

Earlier studies have indicated that both oral Midazolam and oral Ketamine fulfil many of these characteristics, and both may be useful premedicants in pediatric anesthesia. Feld and co-workers<sup>1</sup> suggested that Midazolam 0.5 mg.kg<sup>-1</sup> p.o. 30 min prior to induction was as effective as Midazolam 0.2 mg.kg<sup>-1</sup> i.m. for preanesthetic medication. They also suggested that administration of small amounts of fluid to children prior to induction of anesthesia does not pose a significant risk. Levine and co-workers<sup>2</sup> concluded that children may be separated from their parents as early as ten minutes after receiving oral Midazolam 0.5 mg.kg<sup>-1</sup>. Gutstein and co-workers<sup>3</sup> had found that Ketamine 6 mg.kg<sup>-1</sup> provides predictable, satisfactory premedication without significant side effects. We therefore designed this study to compare Midazolam and Ketamine as oral premedicants in pediatric anesthesia.

**METHODS**

The study was conducted after obtaining approval from institute ethics committee. All patients were examined preoperatively and informed parental consent was obtained for inclusion in this study. Fifty children in the age group of 1 to 7 years posted for elective surgical procedures were included in the study. 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. Those included in the study were randomly allocated to one of two groups – ‘Group K’ and ‘Group M’. Group K received Ketamine 6 mg.kg<sup>-1</sup> p.o. and Group M received Midazolam 0.5 mg.kg<sup>-1</sup> p.o.; both drugs were mixed with a flavoring agent and Atropine 40 µgkg<sup>-1</sup>.

Acceptance of the premedication was noted. The following parameters were assessed before premedication and at 15 and 30 minutes after administering premedication.

a)Heart rate

b)Respiratory rate

c)Sedation score – using a five point scale

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)

d)Anxiolysis score

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

e)Quality of induction score (mask tolerance assessed before induction of anaesthesia)

1. Poor (combative / crying)

2. Fear (fear to mask)
3. Good (easily calmed)
4. Excellent (co-operative)

f)Arterial pressure before premedication and 30 min after premedication.

g)Parental separation 30 min after premedication

1. successful
2. failed.

Data were analyzed with SPSS (ver 11.0) statistical software. Changes in heart rate and respiratory rate in a particular group over time was analyzed using repeated measures ANOVA test. Variations in arterial pressure was analyzed using paired-t test. Changes in the above variables over time between the two groups were analyzed by two way ANOVA test. Sedation scores and anxiolysis scores between the groups were compared by Mann-Whitney test. Difference in sedation and anxiolysis score over different time intervals in a particular group was compared by Friedman test. Parental separation, drug acceptance and mask tolerance were analysed by Fisher’s exact test. A ‘p value’ of < 0.05 was considered statically significant.

**RESULTS**

Patients were comparable in both groups with respect to age, sex, and weight (Table 1).

**Figure 1**

Table 1: Patient Characteristics

|           | <i>Group K<br/>(Mean ± S.D)</i> | <i>Group M<br/>(Mean ± S.D)</i> |
|-----------|---------------------------------|---------------------------------|
| Age       | 4.4 ± 1.84                      | 4.08 ± 2.1                      |
| Weight    | 14.68 ± 3.88                    | 13.34 ± 3.76                    |
| Sex (M/F) | 18 / 7                          | 20 / 5                          |

Basal heart rate was comparable between the groups (Table 2). The mean basal heart rate varied from 118.28±15.21 in Group K and 123.28±15.55 in Group M. There was no significant difference in heart rate between groups (f = 2.01, p value > 0.13) after administration of premedication.

Basal respiratory rate was comparable between the groups. The mean basal respiratory rate was 25.60±5.13 in Group K and 27.28±7.73 in Group M. There was no significant change in respiratory rate between groups (f = 0.57, p =

0.564) after administration of premedication.

Arterial pressure was comparable between the groups. The mean basal mean arterial pressure in Group K was  $72.72 \pm 7.89$  and in Group M it was  $74.90 \pm 8.62$ . There was no significant change in arterial pressure between groups with progression of time after administration of the premedication. In Group K there was significant change in diastolic pressure ( $t = 2.83, p = 0.01$ ) and mean arterial pressure ( $t = 2.51, p = 0.02$ ) over time. In Group M there was no such significant change ( $p > 0.25$ ).

Figure 2

Table 2: Hemodynamic parameters

|                           | Time            | Group K<br>(Mean ± S.D) | Group M<br>(Mean ± S.D) |
|---------------------------|-----------------|-------------------------|-------------------------|
| Heart Rate                | 0 min           | 118.28±15.21            | 123.28±15.55            |
|                           | 15 min          | 121.24±11.25            | 125.44±16.39            |
|                           | 30 min          | 124.92±11.86            | 128.36±17.20            |
| Respiratory Rate          | 0 min           | 25.60±5.13              | 27.28±7.73              |
|                           | 15 min          | 24.80±4.97              | 27.36±7.96              |
|                           | 30 min          | 23.16±5.21              | 26.88±8.10              |
| Arterial pressure (mm Hg) | Systole 0 min   | 96.40±12.03             | 100.72±11.85            |
|                           | Systole 30 min  | 96.80±9.73              | 99.84±7.98              |
|                           | Diastole 0 min  | 60.88±6.93              | 62.00±9.16              |
|                           | Diastole 30 min | 64.88±7.85              | 62.40±11.18             |
|                           | Mean BP 0 min   | 72.72±7.89              | 74.90±8.62              |
|                           | Mean BP 30 min  | 75.52±7.04              | 74.88±8.68              |

Basal sedation score was comparable between the groups with median of 2 in both groups and mean of  $1.60 \pm 0.50$  in Group K and  $1.76 \pm 0.43$  in Group M (Table 3). With progression of time each group (Group K; chi square = 46.26,  $p = 0.000$  and Group M; chi square = 43.62,  $p = 0.000$ ) had statistically significant change in the sedation score. There was a statistically significant increase in sedation score at 30 minutes interval in Group K compared to Group M ( $U = 204.00; p = 0.012$ ). The median sedation score observed was 4 in Group K while it was 3 in Group M at 30 minutes interval.

Figure 3

Table 3: Details of sedation and anxiolysis scores

|            | Score | Number of patients |         |             |         |             |         |
|------------|-------|--------------------|---------|-------------|---------|-------------|---------|
|            |       | Time 0             |         | Time 15 min |         | Time 30 min |         |
|            |       | Group K            | Group M | Group K     | Group M | Group K     | Group M |
| Sedation   | 1     | 10                 | 6       | 0           | 0       | 0           | 0       |
|            | 2     | 15                 | 19      | 0           | 7       | 0           | 2       |
|            | 3     | 0                  | 0       | 6           | 17      | 5           | 12      |
|            | 4     | 0                  | 0       | 14          | 1       | 18          | 9       |
|            | 5     | 0                  | 0       | 5           | 0       | 0           | 2       |
| Anxiolysis | 1     | 5                  | 4       | 0           | 0       | 0           | 0       |
|            | 2     | 16                 | 14      | 2           | 9       | 1           | 1       |
|            | 3     | 4                  | 7       | 13          | 9       | 3           | 10      |
|            | 4     | 0                  | 0       | 10          | 7       | 21          | 14      |

Basal anxiolysis score was comparable between the groups with median of 2 in both groups and mean of  $1.96 \pm 0.61$  in Group K and  $2.12 \pm 0.66$  in Group M (Table 3). With progression of time, the median anxiolysis score observed in both groups were similar (median at 15 and 30 minutes interval was 3 and 4 respectively in each group) but with progression of time each group had statistically significant change in anxiolysis score (Group K: chi square = 45.51,  $p = 0.000$ ; Group M: chi square = 38.52,  $p = 0.000$ ). There was statistically significant increase in anxiolysis score in Group K compared to Group M at 30 minutes interval ( $U = 228.50, p = 0.04$ ).

The acceptance to drugs was statistically insignificant between the groups ( $p > 0.05$ ), 96% of children in Group K and 92% of children in Group M accepted the premedication well (Table 4). Separation was successful in 96% of children in Group K and 84% in Group M. The values were statistically insignificant between the groups. Application of anaesthetic facemask was excellent in 52% of children in Group K and 24% in Group M while it was good in 44% of children in Group K and 48% in Group M. Acceptance to facemask was statistically significant between the groups ( $p < 0.05$ ).

**Figure 4**

Table 4: Details of Drug Acceptance, Parental separation and Mask tolerance

|                      | Score | Group K  | Group M  |
|----------------------|-------|----------|----------|
| Drug acceptance      | Good  | 24 (96%) | 23 (92%) |
|                      | Poor  | 1 (4%)   | 2 (8%)   |
| Parental separation  | Good  | 24 (96%) | 21 (84%) |
|                      | Poor  | 1 (4%)   | 4 (16%)  |
| Mask tolerance score | 1     | 1 (4%)   | 2 (8%)   |
|                      | 2     | 0        | 5 (20%)  |
|                      | 3     | 11 (44%) | 12 (48%) |
|                      | 4     | 13 (52%) | 6 (24%)  |

**DISCUSSION**

Providing conscious sedation to facilitate parental separation in young children is often problematic. Many sedative analgesic agents and routes of delivery for facilitation of painful procedures have been studied, with varying degrees of patient acceptance, efficacy and safety<sup>4</sup>. The inhaled route appears effective primarily in children over eight years of age and requires specialized equipment and significant safety precautions<sup>5</sup>. The intravenous and intramuscular routes are traumatic. The disadvantages of intramuscular medications are that they are painful to administer and threatening to child, a sterile abscess may form and often the child remembers the shot they received. The rectal route is marked by variable absorption, difficulty in predicting depth of sedation, and is often not well accepted by children over three years of age<sup>7</sup>. The absorption of drug through rectal route depends on the amount of faecal material present, the pH of medication administered, whether the child expels some of the drug at the time of administration and where in the rectum the drug is administered (as drug administered high in the rectum undergo first pass metabolism via superior haemorrhoidal vein which drains into portal circulation where as drugs administered low in the rectum bypass first pass hepatic metabolism as the venous drainage is by inferior haemorrhoidal vein)<sup>6</sup>. The intranasal route is similarly marked by variable absorption, may be irritating to nasal mucosa and drugs administered may traverse directly into the central nervous system through the cribriform plate by traveling along the olfactory nerves<sup>6</sup>. Transmucosal absorption of potent synthetic opiates, although more consistent in producing sedation, carries a significant risk of

major adverse effects like hemoglobin desaturation, itching and increased nausea and vomiting.

The oral route provokes 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. Feld and co-workers<sup>1</sup> observed that even with a high dose of oral midazolam(0.75 mg.kg<sup>-1</sup>), some children (28%) remained anxious or combative when separating from parents. Postoperative amnesia was not evaluated in this study. However, neither chloral hydrate nor midazolam produce an analgesic effect. Brzustowicz and co-workers<sup>8</sup> administered a solution of meperidine (1.5 mg.kg<sup>-1</sup>), diazepam (0.02 mg.kg<sup>-1</sup>) and atropine (0.02 mg.kg<sup>-1</sup>) to children older than six months. The only statistically significant difference observed between control and premedicated patients were that premedicated patients had fewer oral secretions and cried less on arrival in the operating room. Cetina had found that rectal or oral Preanaesthetic medication with ketamine 15mg.kg<sup>-1</sup> combined with droperidol was superior to i.m. or i.v. premedication. Gutstein and co-workers<sup>3</sup> observed that after oral ketamine administration sedation occurred in 15 – 20 minutes, which is comparable to other oral premedication regimens. The bioavailability of oral ketamine and oral midazolam are 10% - 16% and 40% - 50% respectively due to extensive first pass hepatic extraction. Stewart and co-workers<sup>9</sup> compared the efficacy of oral ketamine 10mg.kg<sup>-1</sup> to intramuscular morphine 0.1 mg.kg<sup>-1</sup>, both in combination with trimeperazine 3 mg.kg<sup>-1</sup>, as anaesthetic premedicant for 40 children presenting for cardiac surgery. No significant differences in patient arousal or cooperation with induction of anaesthesia were found. No adverse effects of ketamine were noted, although the authors commented that the concomitant use of sedating agent and the prolonged surgical time might explain this finding.

Our study evaluated the efficacy of oral ketamine and oral midazolam as premedicant in pediatric patients. We did not include placebo group as the effectiveness of both oral ketamine and midazolam were compared with placebo and were found to be superior to placebo in the previous studies.

Baseline sedation and anxiolysis of children in both groups were comparable with median score of 2. Sedation and anxiolysis scores increased in each group with progression of time, which was both statistically and clinically significant. The scores peaked at the time of parental

separation. At 30 minutes the sedation and anxiolysis scores were better in ketamine group compared to midazolam group. In ketamine Group 18 (72%) children were asleep (sedation score 4) and 21 (84%) were calm (anxiolysis score 4) while in midazolam group it was 9 (36%) and 14 (56%) respectively at 30 minutes. Tobias and co-workers<sup>10</sup> observed that ketamine possesses both analgesic and amnesic properties whereas more commonly used agents such as benzodiazepines produce only amnesia. There was excellent anxiolysis at the time of parental separation and mask application in both the groups. However, mask tolerance was better (statistically and clinically significant) in ketamine group.

Our study showed that there were statistically significant changes in heart rate, respiratory rate and blood pressure in each group over time, however it was clinically insignificant. There was increase in heart rate in both groups from baseline. Probably it could be due to use of oral atropine as its action starts within 30 minutes, peaks at one hour and lasts for two hours. Ketamine group showed decrease in respiratory rate with progression of time especially at 30 minutes possibly due to its peak action at the time as the majority of children were well sedated (asleep but could be woken up on light touch) and had good anxiolysis. There was no statistically significant change in cardio respiratory variables between groups with progression of time. Gutstein and co-workers<sup>3</sup> and McMillan<sup>11</sup> also observed the benign effects of oral ketamine and oral midazolam on cardio respiratory system respectively. Lerman and co-workers<sup>12</sup> compared the clinical characteristics of oral ketamine and oral midazolam and found that no important side effects were attributable to either premedication. Gringrich<sup>13</sup> aborted his study after undesirable side effects, including increased secretions, laryngospasm, hallucination and dysphoria from oral ketamine 6 mg.kg<sup>-1</sup>.

Even though not evaluated, we noticed the safety of oral ketamine and midazolam. There were no important circulatory, respiratory or neurological effects. In the ketamine group, some side effects like nystagmus (15 cases), vomiting (3 cases), and vertigo (2 cases) were noticed. In the midazolam group, 3 patients had vomiting. McMillan<sup>11</sup> observed untoward effects like loss of balance, blurred vision and dysphoria in children with midazolam 0.75mg.kg<sup>-1</sup> and 1mg.kg<sup>-1</sup>. In both groups, most of the patients had repeated, unpurposeful movements of the upper limb. There was no emergence phenomena or delayed recovery in the ketamine group; While Tobias<sup>10</sup> who used oral ketamine 10

mg.kg<sup>-1</sup> in 34 children found emergence phenomena in 9% of children, but none required any pharmacological intervention. Increased nor-ketamine levels could explain the absence of emergence phenomena after oral administration, as compared to parenteral route. Serum ketamine levels necessary for analgesia is 150 ng/ml. However, the peak serum ketamine level after ketamine is taken orally ranges from 35-55 ng/ml<sup>14</sup>. Nor-ketamine is the primary active metabolite of ketamine. It is one third as potent as ketamine. Due to high first pass hepatic metabolism, serum nor-ketamine levels after oral ketamine are two to three times greater than those after parenteral ketamine. The peak analgesic effect of oral ketamine corresponds to the peak serum levels of nor-ketamine not ketamine. This suggests that nor-ketamine contributes significantly to the analgesic effects of oral ketamine. These increased amounts of nor-ketamine relative to oral ketamine may account for part of the sedative effects observed and possibly the reduced incidence of side effects with oral administration. Thus oral ketamine appears to be better premedicant than oral midazolam in paediatric patients.

A deficiency of our study design was that we did not quantify the effects of preanaesthetic medication on oxyhemoglobin saturation, CO<sub>2</sub> level as well as residual gastric volume during immediate preinduction period, parental response regarding child's preoperative experience and anterograde amnesic effect of midazolam. Use of atropine in both the groups could have masked the difference in hemodynamics between the groups. We also did not assess the influence of these drugs on recovery from anaesthesia.

### CONCLUSION

Ketamine 6 mg.kg<sup>-1</sup> p.o. is a better premedicant than Midazolam 0.5 mg.kg<sup>-1</sup> p.o. in pediatric patients. Optimum time interval for excellent anxiolysis and sedation from administration of oral premedication, both ketamine and midazolam, to parental separation is 30 minutes.

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