

Oral premedication in children: Comparison of combination of midazolam-ketamine and oral midazolam- A Randomised trial

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Abstract

Introduction: Premedication with sedative drugs is often used in paediatric practice as one of the modalities to reduce preoperative anxiety in children undergoing surgery. It reduces both patient and parental anxiety and improves overall satisfaction. Also, provides anterograde amnesia and reduces postoperative behavioral changes and adverse outcomes in children. The ideal premedication in children should be readily acceptable and should have speedy and reliable onset with negligible side effects.

Materials and Methods: After obtaining institutional medical ethics committee approval, sixty ASA physical status I or II children, aged 1-8 years scheduled for elective surgery were randomly allocated into one of the two groups. Group M (n=30): received preservative free oral midazolam 0.5mg/kg (1ml=5mg) + acetaminophen based syrup (5ml=120mg) upto maximum value of 0.4ml/kg. Group MK (n=30): received preservative free oral midazolam 0.25 mg/kg (1ml=5mg) with 3mg/kg oral ketamine (1ml=50mg) + acetaminophen based syrup (5ml=120mg) upto maximum value of 0.4ml/kg.

Results: Combination of midazolam 0.25mg/kg and ketamine 3mg/kg provided faster onset and higher degree of sedation, comparable incidence of satisfactory parental separation and mask acceptance without any added side effects in comparison to midazolam 0.5mg/kg.

Conclusion: Addition of low dose ketamine to midazolam as a premedication provides adequate sedation.

Keywords: Premedication, Midazolam, Ketamine, Pediatric patients, Sedation.

Introduction

The preoperative period is a stressful event for the majority of individuals undergoing surgery. This is especially true in the pediatric patients and is related to a limited understanding of the nature of the illness and the need of surgery by young children. Among the different results that may be achieved with premedication such as amnesia, optimization of preoperative conditions and prevention of physiological stress, the primary aim in children is anxiolysis. Almost 50% of children show signs of significant preoperative fear and anxiety.¹ An atraumatic premedication can help minimize these problems when a calm separation from parents and a smooth induction of anaesthesia is achieved. Children getting premedication show fewer signs of postoperative depressing behavioral changes including regressive conduct, aggressive behavior, eating and sleep disorders, and weakening of toilet teaching.²

A number of techniques are often utilized in preoperative setting to decrease the nervousness of pediatric patients and out of which use of pharmacological premedication has shown to be most beneficial and lucrative when compared with other approaches. The ideal premedication in children should be readily tolerable and acceptable as well as should have rapid and reliable onset with minimal or no adverse effects and should also reduce both patient and

parental anxiety and improve overall satisfaction along with reduction in postoperative behavioral changes and adverse outcome in children.

Oral midazolam fulfills all these qualities such as sedative and anxiolytic activities, provides anterograde amnesia, and has anticonvulsant properties too.³ However, data from various studies report that good or exceptional outcome are observed in only 60-80% of cases.⁴⁻⁶ Whereas, ketamine, NMDA receptor antagonist, has similar pharmacodynamics to midazolam still, it provides well documented anesthesia and analgesia. Also, ketamine has wider margin of safety, as the protective reflexes usually remain intact with its use. The main aim of our study was to evaluate the safety and efficacy of oral midazolam and low dose combination of midazolam-ketamine as premedication in pediatric patients undergoing surgery.

Materials and Methods

This was prospective, randomised, double blind study that was carried out at Kasturba Medical College, Manipal in the year 2010 after obtaining institutional medical ethics committee approval and written informed consent from parents or guardians of each child. 60 children with American Society of Anesthesiologists (ASA) physical status I or II, aged 1-8 years scheduled for elective surgery with expected duration of surgery <3hours were enrolled randomly

using computer-generated slips into two separate groups that were scheduled for surgeries under general anaesthesia in the Kasturba Medical College, Manipal. Group M (n=30): received preservative free oral midazolam 0.5mg/kg (1ml=5mg) + acetaminophen based syrup (5ml=120mg) up to maximum value of 0.4ml/kg. Group MK (n=30): received preservative free oral midazolam 0.25 mg/kg (1ml=5mg) with 3mg/kg oral ketamine(1ml=50mg) + acetaminophen based syrup (5ml=120mg) upto maximum volume of 0.4ml/kg. Acetaminophen was added to improve the palatability of premedicants and also for its additional analgesic properties.

Children with compromised upper airway associated upper respiratory tract infections, severe mental retardation, raised intracranial pressure, previous history of convulsions, a documented or well-known allergy or sensitivity in response to anyone of the two study drugs, having organ dysfunction, arrhythmias or any congenital heart disease, obese children with history of obstructive sleep apnoea and those already on sedatives or antiepileptics were excluded from the study design.

Oral premedication, in both the groups, was given thirty minutes prior to anticipated time of induction of

anaesthesia. The oral administration for both the groups was preferred as it is the most acceptable, tolerable and well-known approach of giving any drug. All the study drugs were prepared by an independent investigator who was not involved in the observation or administration of anaesthesia for the children. Also, observers and attending anaesthetists evaluating preoperative sedation and emergence were blinded to the study groups.

After the administration of drugs, the response to drug, level of sedation, parental separation score, mask acceptance score and emergence score were assessed. Onset of sedation was defined as the minimum time interval required for the child to fall asleep and become drowsy or somnolent. Sedation status was assessed at 15 minutes and 30 minutes with a four point scale. A score of one or two was considered unsatisfactory and three or four satisfactory. In addition, parental separation score was also marked on a four-point scale. Score of three or four was considered satisfactory. Similarly, mask acceptance and emergence score were evaluated based on four-point scale and score of three or four was considered satisfactory in both.

Scoring system

Score	Sedation	Parental separation score	Mask acceptance score	Emergence score
1	Agitated	Poor (crying, clinging)	Poor (terrified, crying with mask)	Excellent(crying, thrashing, need for restraint)
2	Awake, calm	Fair (crying, not clinging, not quiet with reassurance)	Fair (fear of mask, not reassured)	Good (constant crying)
3	Drowsy, readily responds to verbal commands	Good (whimpers, easily reassured)	Good (slight fear of mask, reassured)	Fair(occasional crying)
4	Asleep, slowly responds to verbal commands	Excellent (unafraid, easy separation)	Excellent (unafraid, accepts face mask)	Poor (quiet)

If it was not possible to separate the child from the parents after 30mins, rescue medication with ketamine 5mg/kg and glycopyrrolate 10 microgram/kg was given intramuscularly.

The child was then shifted to operating room for the scheduled procedure. After noting the mask acceptance score, children were induced using a standardized anesthesia technique with halothane in a mixture of 50% nitrous oxide and 50% oxygen. Monitoring was continuous throughout the procedure and consisted of three lead electrocardiogram, blood pressure, respiratory rate and arterial oxygen saturation. Intravenous access was established after induction and vecuronium 0.1mg/kg was used to facilitate endotracheal intubation. During laryngoscopy, oral secretions were graded as 1-normal and 2-increased.

Intraoperative analgesia was given with pethidine 0.5mg/kg. At the end of the surgery, halothane and nitrous was switched off and neuromuscular blockade was reversed using neostigmine with glycopyrrolate and the child was extubated once adequate reversal and return of pharyngeal reflexes achieved.

After extubation, emergence score was calculated using emergence criteria and then the children were kept in the recovery room (PACU) under observation until discharge. In the postoperative care unit, undesirable side effects were noted if any.

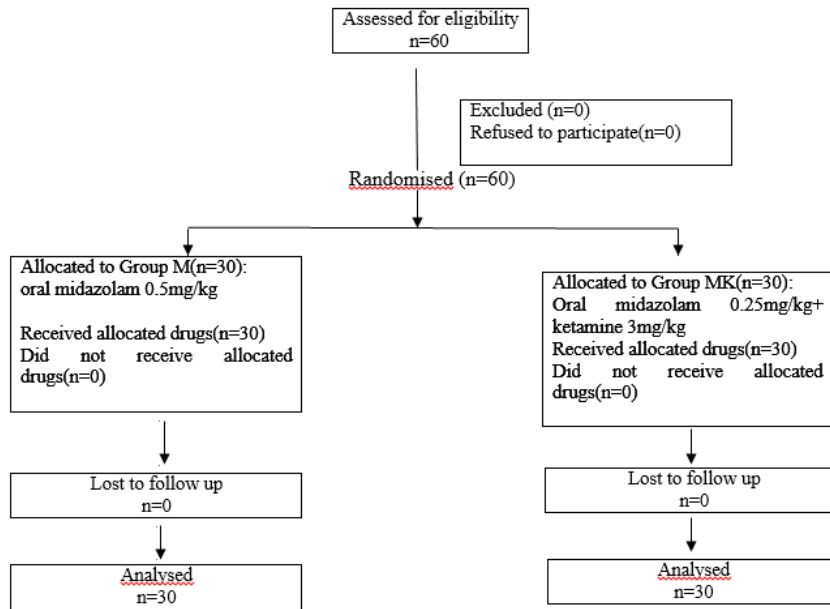
Statistical Analysis

Statistical analysis was done by means of SPSS version 17. All values were reported as mean ± SD and range. For numerical data, analysis was done by

unpaired Student's t-test to detect the differences between the groups for age, weight and level of sedation. Similarly, for categorical data, Fisher's exact test was used to detect differences for the scores. Further, data was expressed as mean ± SD or frequency (%). A P value < 0.05 was considered statistically significant.

Result

60 participants were enrolled. The demographic profile of both the groups were comparable with respect to age, gender, weight, and ASA I/II status (p>0.05) (table 1). Baseline pulse rate, MAP and SpO₂ were comparable in both the groups.



Consort flow diagram of study

Sedation was assessed after 15 minutes and 30 minutes of premedication using sedation score on 4 point scale mentioned above in which scale 1 and 2 were considered to be non sedated and 3 and 4 as sedated. Though in both the groups children were sedated but more number of children in MK group were sedated as compared to group M and this difference between the two groups was very highly significant statistically (p<0.008)(Table 2).

Evaluation of behavior at the time of separation from parents and at the time of mask application was recorded using separation score and mask acceptance score. The comparison of both the scores between the two groups was done using Chi-square test with continuity correction and found the difference was statistically not significant. (p<0.684 and 0.758 respectively)(Table3).

Rescue medication was given with ketamine 5mg/kg and glycopyrrolate 10 microgram/kg IM in 6/30 and 5/30 in group M and group MK respectively.

The mean number of doses of rescue medication used in both the groups were comparable and hence were not significant statistically (p< 0.05)

There were no other complications seen in both the groups following premedication. Incidence of adverse effects such as nausea, vomiting, nystagmus, inadequacy of breathing, were assessed and only one case of nystagmus was observed in MK group which was found to be statistically insignificant.

At the end of the surgery, emergence score was noted. Both the groups were comparable in terms of behavior at the time of emergence and this difference between the groups was statistical insignificant. (p<0.396) (Table 4).

Postoperatively, one child in MK group had nausea and vomiting compared to two children in group M. on the contrary, 2 children in MK group had increased secretions compared to one in group M. None of the children in both the groups showed any abnormal behavior postoperatively. (p=1;NS).

Table 1: Demographic data

	Group M	Group MK	P Value
Age(years)	4.61±1.95	4.36±3.35	0.752 NS
Weight(kg)	14.20±3.27	12.53±3.02	0.066 NS
Gender(M/F)	17/13	16/14	NS
ASA I/II	28/2	27/3	NS

Mean±SD, p<0.05% is significant

Table 2: Comparison of sedation score At 15 and 30 mins.

	Group M		Group MK		P Value
	Unsedated (1&2)	Sedated (3&4)	Unsedated (1&2)	Sedated (3&4)	
Sedation score at 15 mins	23	7	18	12	P<0.001(HS)
Sedation score at 30 mins	12	18	5	25	P<0.001(HS)

HS Highly significant

Table 3: Comparison of separation scores

Separation score	Group M	Group MK	P value
Unsatisfactory(1,2)	6	4	P >0.05(NS)
Satisfactory(3,4)	24	26	

NS- non significant

Table 4: Comparison of emergence score

Emergence score	Group M	Group MK	P value
Satisfactory(1,2)	20	23	P >0.05(NS)
Unsatisfactory(3,4)	10	7	

NS- non significant

Discussion

Oral premedication is used extensively in children as it is palatable and easily acceptable to children.⁷ Oral midazolam is readily used premedication in our hospital. With the objective of maintaining anxiety free period provided by midazolam, and addition of the calming and pain-relieving properties of ketamine whilst reducing the unwanted adverse effects, we evaluated in a prospective randomized double blind trial, whether the combination of midazolam 0.25mg/kg and ketamine 3mg/kg proves beneficial premedication with comparison of midazolam 0.5mg/kg alone in children planned for elective procedures.

We, in our study, did not come across any incidence of nausea, vomiting or breathing inadequacy in either of the two groups. Nystagmus was observed in only one child that too in the combination group and no incidence of nystagmus was documented in the oral midazolam group.

In a similar study, Darlong et al used a combination of oral midazolam 0.25mg/kg and ketamine 3mg/kg and compared it with oral midazolam 0.5mg/kg and oral ketamine 6mg/kg alone and did not note any difference in change in the pre-operative parameters like SpO₂, blood pressure, respiratory rate or heart rate and after pre medication. They did not observe any nausea, vomiting or nystagmus in their study.⁸ Lin et al, compared a combination of oral midazolam 0.5mg/kg and ketamine 3mg/kg with oral midazolam 0.75mg/kg and ketamine 6mg/kg alone. They concluded that the tolerability of oral midazolam and ketamine combination to be good or excellent in 75% of the children under study, but they did not illustrate the criterion for good or excellent acceptability of oral midazolam and ketamine.⁹

In our study, we found the incidence of sedation at 15 minutes to be high in the combination group (56%) as compared to midazolam group (20%). We found this to be statistically and clinically significant. These results are comparable to the former results concluded by Darlong⁸ et al (54.1% vs 20.83%).

At 30 minutes, following premedication, the rate of sedation was again noted to be significantly higher in the MK group as compared to M group (92% vs 60%). Darlong et al⁸ did not find any difference to a great extent in sedation score at 30 minutes (70.8% vs 66.6%). Similarly, Lin et al also reported the onset of utmost sedation to be quicker in the combination group as compared to midazolam group. However, the dose of study drugs used by both the observers was higher than what we used in our study groups. They used a mixture of combination of midazolam 0.5mg/kg and ketamine 3mg/kg.⁹

Our study results were in contrast with the results of Funk et al. They in their study observed that 60% of children were adequately sedated irrespective of the study drug being used. Again, the dose used by them, of the study drugs was higher than what we used. They used a combination of midazolam 0.5mg/kg and ketamine 3mg/kg.

While separating the children from their parents, we found that majority of the children were able to get separated satisfactorily according to the criteria used in both the groups (88% in MK group vs 84% in group M). The such marked incidence of satisfactory separation was also witnessed by Funk et al (90% and 70% in two groups)¹⁰ and Darlong et al (83.3% of children in both the groups). Similarly, Beebe and colleagues¹¹ in 1992 and Lin et al⁹ in 1993 premedicated their study group children using

combination of oral midazolam in a dose of 0.5mg/kg and ketamine 3mg/kg. Beebe's study noted that, the satisfactory level of separation with midazolam was in 92% cases and it was 100% when combination of both oral premedicants was used, and only 60% when alone ketamine was given. Lin et al did not experience any change in the conduct on partition and induction following administration of ketamine 6mg/kg and midazolam 0.75mg/kg and this 100% acceptable partition in these studies might be attributed to higher dosages used in both the groups as compared to our study results.

In our study, we found satisfactory acceptance of the face mask to be 68% in the combination group and 72% in the midazolam. These children were either not afraid of the face mask at all or only had slight fear. These results are again in agreement with earlier studies^{8,9} (79.1% vs 75% Darlong et al and 73.3% vs 66.6% Lin et al)

We also assessed the incidence of oral secretions at laryngoscopy. Only 2 children in the combination group found to be having increased secretions at the time of laryngoscopy. We did not find any literature where the author studied the incidence of secretions at laryngoscopy. Even though ketamine is known to increase oral secretions, but we did not find this as a major drawback when it given in combination with midazolam.

During emergence, we found only 1 child in combination group and 4 in midazolam group to be crying excessively. All other children were either quiet or occasionally crying. We cannot conclude much from the emergence results because in our study, the types of surgery varied from less painful herniotomies to very painful osteotomies. Also, we did not record the total requirement of pethidine during surgery. The length of the surgery and therefore the time during which the child was under anesthesia also varied from 1-3hours.

In our study, we decided to give rescue medication to those children who could not be separated from the parents even after reassurance. The incidence of requirement of rescue medication was found to be low in both the groups (12% in MK and 16% in group M)

In the postoperative period we found a very low incidence of nausea, vomiting or increased secretions. Since we know that ketamine produces emergence delirium but in our study, we did not witness any signs or symptoms related to this phenomenon in any child in combination group where ketamine was used along with midazolam. Hence, this can completely be attributed to the combination of midazolam with ketamine as midazolam being benzodiazepine is known to reduce this emergence phenomenon of ketamine. Such psychedelic adverse events were not observed by Beebe et al and Lin et al whereas, in contrast, 100 children were studied who were posted for oral surgical procedures and hallucinations were reported in approximately 20% cases in which ketamine 5mg/kg-

midazolam 0.35mg/kg combination was used and this might be owed to combination of doses.^{9,11} However, it is astounding that studies where only ketamine was in action, did not find these adverse reactions.

Although the onset of sedation was faster in combination group and although we had a greater percentage of children who were sedated in the combination group, there was no significant difference in the separation score and the mask acceptance score between the two groups. Also, we did not find any significant untoward adverse effects in either of the two groups.

Conclusion

In conclusion, combination of midazolam 0.25mg/kg and ketamine 3mg/kg as premedication in children undergoing surgery is equally safe and efficacious as midazolam 0.5 mg/kg in terms of sedation, parental separation and mask acceptance. However, the combination provides faster onset and higher incidence of sedation without any added side effects in comparison to midazolam 0.5mg/kg alone.

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