Original Research Article

Indian Journal of Anesthesia and Analgesia
January – February 2020; 7(1) (Part -II): 284-290
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.7120.39

Efficacy of Addition of Low Dose Oral Ketamine to Oral Midazolam Results in Better Premedication Than Either Drugs Given Alone in Children

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Abstract

Context: When we never induce anesthesia in a struggling adult patient, fearing hypertensive response, we never bother to properly sedate the pediatric patient before bringing the child to operation theatre. *Aims:* To Compare combination of midazolam and ketamine with midazolam or ketamine alone as oral preanesthetic medication in children undergoing elective surgeries. *Settings and Designs:* Hospital based comparative study was carried out at Department of Anesthesiology, SVS Medical College, Mahabubnagar *Methods:* 150 children of ASA Grade I and II in the age group of 2–10 years were included in the study and were randomly divided into three groups of 50 each. Group A received 0.5 mg/kg Midazolam in 5 ml orange syrup, Group B received Ketamine 6 mg/kg while Group C received a combination of oral Midazolam 0.5 mg/kg and oral Ketamine 3 mg/kg in 5 ml orange syrup. *Statistical Analysis:* The statistical analysis done by Chi-square test. *Results:* In Group A, 58% children were adequately sedated and 72% children were having an acceptable anxiolysis and parental separation scores. In Group B, acceptable sedation, anxiolysis and behavior at parental separation was obtained in 52% children. Group C shows an acceptable sedation in 68% children. Acceptable anxiolysis was observed in 82% of children. 80% children were calm with parental separation. Side effects were mainly seen in Ketamine group with 14% children showing nystagmus and 10% of children had excessive salivation. 8% children in Ketamine Group also developed hallucination. *Conclusion:* The present study showed that oral premedication with Midazolam 0.5 mg/kg alone produces as good results as the combination of Midazolam 0.5 mg/kg and Ketamine 3 mg/kg in children.

Keywords: Midazolam; Ketamine; Preanesthetic; Medication; Children; Elective surgeries.

How to cite this article:
Pujala Umapathy, Juluri Vamshi Krishna, Md Ayathullah. Efficacy of Addition of Low Dose Oral Ketamine to Oral Midazolam Results in Better Premedication Than Either Drugs Given Alone in Children. India J Anesth Analg. 2020;7(1 Part -II):284-290.

Introduction

Anesthesia and surgery represent an enormous time of stress for the child. The reasons for stress include primarily (a) separation from parents (ii) strange surroundings (iii) painful procedures (iv) frightening procedures and (v) survival.[1]

They are unable to understand the necessity for their surgery, nor arethey likely to be amenable to reasoned explanation. Eckenhoff demonstrated that stormy anesthetic induction in children leads to an increased incidence of postoperative behavioral problems. These problems can be diminished by psychologic preparation; however,

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Received on 14.11.2019, **Accepted on** 03.01.2020

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a pharmacologic adjunct may be more reliable and better suited for efficient use of operating room time than psychologic preparation.[2]

Of the various aspects of pediatric anesthesia, the most neglected part is premedication. In most of the busy pediatric surgical theatres, it is very common to find children in waiting area in various stages of anxiety and distress emitting various tones of crying. Most of the time, the anesthetist will struggle with the child to start the intravenous line or induce inhalationally. When we never induce anesthesia in a struggling adult patient, fearing hypertensive response, we never bother to properly sedate the pediatric patient before bringing the child to operation theatre.[3]

A variety of premedications administered *via* various routes have been introduced. Route of administration is another important factor, for those patients who do not already have established venous access since, starting intravenous access to administer sedation may be as traumatic as the procedure itself. Therefore, an orally active agent could be especially preferable.[4]

Recent reports suggest that both oral Midazolamand oral Ketaminemay fulfil many of these criteria. The parenteral formulation of both Midazolam and Ketamineare effective as oral premedication in children. Ketamine has well-characterized sedative, anesthetic and analgesic properties. It also has advantages over other sedative anesthetic drugs, because it stimulates the cardiovascular system, usually associated with an unobstructed airway with preserved upper airway reflexes and causes minimal respiratory depression.[5]

Ketamine has been tried with a high overall success rate, without significant side effects. However, it is widely acknowledged that Ketamine IV or IM causes hallucinations in many patients. Even subanesthetic concentration of Ketamine produces psychedelic effects, when given IV.[6]

The combination of oral Ketamine 4–6 mg/kg, oral Midazolam 0.5 mg/kg and oral atropine 0.02 mg/kg provides a well-sedated patient. Studies have shown that a combination of Midazolam plus Ketamine provides better premedication than Midazolam or Ketamine alone. Benzodiazepines augment the action of Ketamine effects and attenuate emergence sequela.[7]

In the present study, an attempt is made to evaluate the scope of oral Midazolam 0.5 mg/kg, oral Ketamine 6 mg/kg and combination of Midazolam 0.5 mg/kg + Ketamine 3 mg/kg orally as a premedicant in pediatric age group.

Materials and Methods

This study was conducted on patients admitted to SVS Medical College, Mahabubnagar, during the period from December 2016 to September 2018, with cooperation from residents from Departments of General Surgery, ENT and Orthopedics. 150 patients of ASA Grade I and II, of either sex, aged between 2 and 10 years were included in this study. Children undergoing surgical procedure between 20 minutes and 2 hours duration were selected for the study. The children were divided into three groups of 50 each randomly.

Children of Group A received Midazolam 0.5 mg/kg orally Group B received Ketamine 6 mg/kg orally and Group C received Midazolam 0.5 mg/kg + Ketamine 3 mg/kg Orally. The premedication was prepared using orange syrup as a carrier 0.5 ml/kg up to a maximum of 10 ml. This was administered to children 30 minutes before induction. Those children who refused to take the whole dose we reexcluded from the study.

The child's condition was evaluated just before induction by the surgical resident with a scale assigning a score of 1 to 4 to the quality of sedation, anxiolysis and behavior at parental separation, while side effects were assessed by the anesthesiology resident conducting the case. All observers including anesthesiology residents, surgical residents and nurses were blinded about the contents of the oral premedicate.

Inclusion criteria

Patients coming for elective major or minor surgeries under general or regional anesthesia;

Age 2–10 years;

ASA Grade I and II.

Exclusion criteria

ASA Grade III and IV;

History of prematurity and chronic illness;

History of developmental delay;

Increased intracranial pressure;

Increased intraocular pressure;

Valvular heart disease;

Psychiatric disturbances.

The study was approved by the ethical committee of SVS Medical college, Mahabubnagar. Written, informed consent was obtained from parents for conducting study on their children.

Drugs and Dosages

In the preoperative room, baseline recordings of heart rate, respiratoryrate, systolic blood pressure and activity of child were noted.150 cases were divided into three groups of 50 each. Group A received Midazolam 0.5 mg/kg oral. Group B received Ketamine 6 mg/kg orally and Group C received a combination of Midazolam 0.5 mg/kg and Ketamine 3 mg/kg orally. This was given with orange syrup 0.5 ml/kg to mask the bitter taste of the drug, 30 minutes before induction of anesthesia.

The children were evaluated for quality of sedation, anxiolysis and behavior at parenteral separation, 30 minutes after administration of the premedicant by the concerned surgical resident and side effects such as tachycardia, bradycardia, hypertension, hypotension, hypertonia, nystagmus, vomiting, in voluntary movements, respiratory depression, apnoea, excitement, salivation, sweating and lacrimation were noted by the Anesthesiology resident. Children were observed for any signs of upper airway obstruction, respiratory depression, apnoea and oxygen desaturation.

Preanesthetic assessment

All patients were visited and evaluated for fitness for the intended procedure and anesthesia on the day prior to the surgery. During this visit, the procedure of the study planned was explained to the parents. An attempt was made to alleviate the anxiety of the patients. Parents were also instructed on the nil per oral guidelines. General clinical examination of the patient was performed including a general physical and systemic examination.

Laboratory investigations

The following laboratory investigations were performed on all the patients in the study:

Blood: Hb%, Blood Grouping and Typing, bleeding time, Clotting time, HIV and HBs Ag.

Urine: Albumin, Sugar, and Microscopy.

Chest *X*-ray: If required.

Preoperative fasting: No oral liquids up to 2 hours before the procedure;

Avoidance of milk/solids for 6 hours prior to the procedure.

Sedation was graded as follows:

Score 1: Alert

Score 2: Awake

Score 3: Drowsy

Score 4: Asleep

Anxiolysis was graded as follows:

Score 1: Panicky

Score 2: Moaning

Score 3: Composed

Score 4: Asleep, friendly

Behavior at parenteral separation was graded as follows:

Score 1: Combative, clinging to parents

Score 2: Anxious, consolable

Score 3: Calm

Score 4: Asleep

All monitors attached in operation theatre: The aesthetic agents administered were standardized Inj. Glycopyrrolate 0.04 mg/kg, Inj. Ondansetron 0.1 mg/kg and Inj. Fentanyl 1 mcg/kg was given.

General anesthesia was induced with Sevoflurane 6% and air & Oxygen (60:40), Trachea was intubated by appropriate size endotracheal tube after intravenous (IV) Atracurium 0.5 mg/kg. Intraoperative sedation was not given and analgesic was provided by caudal block with Inj. Bupivacaine 0.25% 1 ml/kg for intraoperative anesthesia. The neuromuscular blockade was reversed with Inj. Neostigmine (0.05 mg/kg), with Inj. Glycopyrrolate (0.01 mg/kg) Reversal and extubation was uneventful in all patients. Sedation score was estimated by single observer according to sedation scale.

Parameters observed were:

Level of sedation and score of sedation;

Emotional reaction: crying, apprehension and calm;

Separation reaction: crying, apprehension and good;

Acceptance reaction to face mask;

Side effects and recovery time.

Sedation, anxiolysis, cooperation was recorded immediately after giving oral drug at following intervals: 5 min, 10 min, 20 min, 30 min, 40 min. Heart rate and oxygen saturation were monitored throughout the procedure. The statistical analysis done by chi square test.

Results

Table 1 shows comparison of various parameters in three groups. All the three groups were comparable in terms of age, sex, mean weight and ASA Grade ($p > 0.05$).

Table 2 shows surgical procedures carried out in three groups. All the groups were almost similar in terms of surgical procedures carried out. The total number of children undergoing a particular surgery was similar in all the groups.

Table 3 shows comparison of sedation between the groups. Sedation was assessed on a 4-point scale. Acceptability was defined as a Score of III and IV. In Group A, an acceptable sedation was obtained in 58% (29 of 50) children. In Group B, an acceptable sedation was obtained in 52% (26 out of 50) childrens. In Group C, an acceptable sedation was obtained in 68% (34 out of 50) children. However, there is no significant difference between the Three Groups ($p > 0.05$).

Table 4 shows comparison of anxiolysis between the groups. Anxiolysis was similarly assessed on a 4-point scale. Acceptability was defined as a Score of III and IV. In Group A, acceptable anxiolysis was obtained in 72% (36 out of 50) children. In Group B, acceptable anxiolysis was obtained in 52% (26 out of 50) children. In group C, acceptable anxiolysis was seen in 82% (41 out of 50) children. Statistical studies show a significant difference between the study groups as a whole and between Groups B and C.

Table 5 shows comparison of behavior at parental separation between the Three Groups. Behavior at parental separation was also assessed by a 4-point scale. Acceptability was defined as a Score of III and IV. In Group A, an acceptable score for behavior at parental separation was seen in 36 (72%) out of 50 children. In Group B, an acceptable score for behavior at parental separation was seen in 26 (52%) children. In Group C, an overall acceptable score for behavior at parental separation was obtained in 40 (80%) children. Significant difference on statistical analysis is seen between study groups as a whole and between Groups B & C.

Table 1: Comparison of various parameters in three groups

Parameters Number		Group A		Group B		Group C	
		%	Number	%	Number	%	
Age (years)	2–5	20	40	21	42	14	28
	5–7	17	34	16	32	17	34
	8–10	13	26	13	26	19	38
	Mean ± SD	5.7 ± 2.6		5.4 ± 2.5		6.2 ± 2.6	
Sex	Male	39	78	37	74	35	70
	Female	11	22	13	26	15	30
Weight (kg)	Mean ± SD	18.22 ± 6.3		19.92 ± 5.69		19.22 ± 5.75	
ASA grade	I	42	84	44	88	45	90
	II	8	16	6	12	5	10

Table 2: Surgical procedures carried out in three groups

Surgical procedures	Group A		Group B		Group C	
	Number	%	Number	%	Number	%
Tonsillectomy	9	18	8	16	6	12
Circumcision	8	16	7	14	6	12
Orthopedic	6	12	5	10	11	22
Herniotomy	4	8	10	20	4	8
Tongue tie release	4	8	6	12	1	2
Other ENT	10	20	8	16	5	10
Others	9	18	6	12	17	34
Total	50	100	50	100	50	100

Table 3: Comparison of sedation between the groups

Sedation score	Group A		Group B		Group C	
	Number	%	Number	%	Number	%
I (Alert)	9	18	6	12	3	6
II (Awake)	12	24	18	36	13	26
III (Drowsy)	23	46	18	36	24	48
IV (Asleep)	6	12	8	16	10	20
Total	50	100	50	100	50	100

Table 4: Comparison of anxiolysis between the groups

Score	Group A		Group B		Group C	
	Number	%	Number	%	Number	%
I (Panicky)	6	12	10	20	1	2
II (Moaning)	8	16	14	28	8	16
III (Composed)	31	62	20	40	30	60
IV (Asleep, friendly)	5	10	6	12	11	22
Total	50	100	50	100	50	100

Table 5: Comparison of behavior at parental separation between the three groups

Score	Group A		Group B		Group C	
	Number	%	Number	%	Number	%
I (Combative clinging)	4	8	12	24	2	4
II (Anxious, consolable)	10	20	12	24	8	16
III (calm)	34	68	20	40	34	62
IV (Asleep)	2	4	6	12	9	18
Total	50	100	50	100	50	100

Table 6: Adverse effects between the groups

Adverse effects	Group A		Group B		Group C	
	Number	%	Number	%	Number	%
Vomiting	0	0	3	6	0	0
Nystagmus	2	4	7	14	2	4
Salivation	2	4	5	10	3	6
Tachycardia	2	4	1	2	4	8
Bradycardia	1	2	0	0	0	0
Excitement	0	0	4	8	0	0
Involuntary movements	2	4	1	2	0	0
Respiratory depression	1	2	0	0	0	0
Total	50	100	50	100	50	100

Table 6 shows adverse effects between the groups. The side effects with Midazolam, Ketamine and the combination are shown in Table 6. Vomiting was observed in 3 children in Ketamine Group (Group B) while it did not occur in either of other groups. Nystagmus was seen in 7 children in Group B while 2 children each in the other groups showed nystagmus. Group B also showed more incidence of salivation in 5 children, salivation was also observed in 3 children in Group C and 2 children in Group A. Tachycardia occurred in 4 children in Group C while Group A showed 2 and Group B had 1 child with tachycardia. One child in Midazolam group had bradycardia.

Discussion

In the present study, children in the three groups were of 2–10 years of age with mean age of 5.7 ± 2.6 years, weight of a mean of 19.12 kg with a male preponderance of 74%. This is in comparison; with studies conducted by Funk W et al.[8] who studied children in the age group of 2–10 years with a mean age of 5–7 years.

Prior studies have documented the effectiveness of 0.5 mg/kg oral Midazolam.[3,9]

Unfortunately, gastric absorption of Midazolam is variable and results in large difference in the time it takes for different patients to become adequately sedated. The sedative effect of Midazolam was found to be maximal at 30 minutes after oral administration in a study by Weldon BC et al.[10], Kazak Z et al.[4], observed that oral Midazolam 0.5 mg/kg promotes smooth and satisfactory induction of anesthesia and reduces the psychological effects of hospitalization in children.

Satisfactory sedation we got in our study was 58% which corresponded well with that obtained by Funk W et al.[8] (58%) when 0.5 mg/kg Midazolam was given. Funk W et al.[8] in their study with 0.5 mg/kg Midazolam found to obtainan acceptable anxiolysis in 75% of children. Similarly, studies by Feld LH[3] et al. and Warner DL et al.[11] showed that 69% and 65% of children were asleep or awake

and calm at induction of anesthesia after receiving Midazolam 0.5 mg/kg orally. We had a success rate of 72% which corresponds to the above studies.

Midazolam in the dose of 0.5 mg/kg provided an acceptable behavior at parental separation score in 72% of children in our study. Funk W et al.[8] in their study got a score of 68% for acceptable parental separation and Alderson PJ et al.[12] also got a score of 70%.

Funk W et al.[8] in their study got an acceptable sedation score in 47% children who were given Ketamine in dose of 6 mg/kg. This corresponds well with our study in which we got an acceptable sedation score in 52% of children. Studies by Warner DL et al.[11] showed an acceptable anxiolysis score in 42% of children, Masamaddi GS et al.[13] showed an acceptable anxiolysis score in 80% of children while Funk W et al.[8] had an acceptable score of 54% when 6 mg/kg Ketamine was given orally. This corresponds well with our result which showed an acceptable score in 52% of children with 6 mg/kg Ketamineorally.

Our studies showed an acceptable score for parental separation in 52% of children who were premedicated with 6 mg/kg Ketamine orally. This corresponds well with the studies by Funk W et al.[8] and Alderson PJ et al.[12] who got acceptable scores in 50% and 65% of children respectively.

Lin YC et al.[14] reported no difference in separation with Midazolam 0.75 mg/kg, Ketamine 6 mg/kg or the combination of 0.5 mg/kg and 3 mg/kg respectively. Their success rate with combination were about 80% at separation, and the incidence of oral secretions and nystagmus was lesser as compared to Ketamine. Warner DL et al.[11] found the combination of Midazolam 0.4 mg/kg and Ketamine 4 mg/kg to be significantly more effective than Midazolam 0.5 mg/kg or Ketamine 6 mg/kg alone. No psychological disturbances were noted in the immediate postoperative period. The success rate for anxiolysis and separation was found to be > 90% and only 70% for sedation with a combination of Midazolam 0.5 mg/kg and Ketamine 3 mg/kg by Funk W et al.[8]

We got an acceptable sedation score in 68% children with a combination of Midazolam 0.5 mg/kg with Ketamine 3 mg/kg. This corresponds well with the studies of Funk W et al.[8] who got an acceptable score in 70% children. Lin YC et al.[14] in their study got an acceptable anxiolysis score in 73% of children while Warner DL et al.[11] got an acceptable score in 85% ofchildren. This corresponds well with our results (82%) when the combination of 0.5 mg/kg Midazolam was given with 3 mg/kg Ketamine.

We got an acceptable score for parental separation in 80% of children who were premedicated with the combination. This corresponds well with the studies of Ghai B et al.[15] who got an acceptable behavior at parental separation score in 73% of children.

Lin YC et al.[14] also got similar results in 80% of children. In our study, there was no significant difference in sedation in the 3 groups, 30 minutes after receiving the study agents ($p > 0.05$). This corresponds to the results obtained by Pan AK et al.[16] and Funk W et al.[8] in their studies.

Also, both anxiolysis and behavior at parental separation scores were significantly better in Midazolam alone. These results are similar to the results obtained by Funk Wet al.[8] and Warner DL et al.[11]

The incidence of preoperative nystagmus was 14% with Ketamine and 4% each with Midazolam alone and with the combination. However, none of the children seemed distressed by the nystagmus. The reported incidence of nystagmus with Ketamine ranged from 26% to 60%. 9,22. An incidence of 13% for nystagmus with orally administered Midazolam was mentioned by Lin YC et al.[14]

The side effects noted in the present study were similar to the results obtained by Pan AK et al.[16] and were not clinically significant.

Conclusion

The present study showed that oral premedication with Midazolam 0.5 mg/kg alone produces as good results as the combination of Midazolam 0.5 mg/kg and Ketamine 3 mg/kg in children. Although, Midazolam 0.5 mg/kg produced lesser sedation than the combination, it was no disadvantage as separation from parents was successful and coincided with good anxiolysis.

The incidence of side effects was highest with Ketamine 6 mg/kg, especially nystagmus. The combination increased the cost factor, made preparation of premedication more complex and produced higher incidence of tachycardia as compared to Midazolam alone. Even though, the combination did not produce statistically better sedation, anxiolysis or behavior at parental separation than Midazolam, the combination did produce distinctly better premedication characteristics than either Midazolam or Ketamine alone when given through oral route.

Key Messages

Oral premedication with Midazolam 0.5 mg/kg alone can be used in children undergoing elective surgeries.

Source(s) of support: Nil

Presentation at a meeting: Nil

Conflicting Interest: None

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