

Original Research Article

Placebo controlled comparative study of oral midazolam and oral ketamine as a premedication in paediatric age group

Somnath Longani¹, Krishna Pratap Mall^{2*}, Dipak Raval³

¹Department of Anaesthesia and Critical Care, Hind Institute of Medical Sciences, Barabanki, Uttar Pradesh, India

²Department of Anaesthesia, MRA Medical College, Ambedkarnagar, Uttar Pradesh, India

³Department of Anesthesia, M. P. Shah Medical College, G. G. Hospital, Jamnagar, Gujarat, India

Received: 07 November 2016

Revised: 10 November 2016

Accepted: 18 November 2016

*Correspondence:

Dr. Krishna Pratap Mall,

E-mail: kishnamall206@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Preanaesthetic medication can play an important part in the anaesthetic care of infants and children. It plays a vital role during induction and maintenance of anaesthesia as well as in post-operative period.

Methods: Ninety pediatric patients of ASA status I and II operated for routine surgical procedures at GGH, Jamnagar, Gujarat were studied for the comparison of oral midazolam and oral ketamine as a premedication. The paediatric patients were divided into 3 groups, group M oral midazolam, group K oral ketamine and group P placebo (honey) of 30 patients each.

Results: All the patients were given general anaesthesia with injection sodium thiopentone 4 to 5 mg/kg and inj. succinylcholine 1.5 mg/kg and maintained with inj. vecuronium and traces of halothane. Paracetamol rectal suppository 10 to 15 mg/kg was inserted before reversal for post-operative analgesia. All patients were reversed with inj. neostigmine 50 µg/kg and inj. glycopyrrolate 8 µg/kg given intravenously slowly. Intraoperative pulse rate, blood pressure, SPO₂ and ECG were recorded. Post operatively apart from vitals sedation score and anxiety score were recorded. The result analysed showed that sedation and anxiolysis was better in ketamine group both during separation from parents and I.V. cannulation. Recovery was smooth in ketamine group whereas recovery in midazolam group was associated with irritability and crying.

Conclusions: Oral ketamine is better premedication than oral midazolam in paediatric patients.

Keywords: Oral midazolam, Oral ketamine, Paracetamol rectal suppositories, Premedication

INTRODUCTION

The word “premedication” was first used by the American editor anaesthetist, Frank Horfer McMechan in 1920.¹ The same term was used by Sington in 1929 and Hewer in 1932 in his first edition of “Recent advances in anaesthesia”.^{2,3} Preanaesthetic medication can play an important part in the anaesthetic care of infants and children. Psychological preparation of the child for elective surgery can be facilitated by the use of educational booklet, movies, slide shows and by

reinforcement of the information by the anesthesiologist. Premedication drugs are used prior to anaesthesia. The ideal premedication should allay fear and anxiety without producing side effect and with minimal depression of respiratory system and cardiovascular system.⁴ It should be safe, simple and pleasant to taste and should act over a reasonable longer period of time. It plays a vital role during induction and maintenance of anaesthesia as well as in post-operative period, has an analgesic and an antiemetic property and has antispasmodic (antispasmodics) activity.

So, in present study we used oral Midazolam which is good sedative, anxiolytic, short acting without any major side effect and oral Ketamine having good sedative, analgesic and anxiolytic properties but both of them are bitter in taste so we added honey to make it palatable among children without hesitation.

METHODS

The present study was carried out in randomly selected ninety paediatric patients of both the sexes and of ASA physical status I and II from the routine surgical list of Guru Govind Singh Hospital, Jamnagar, Gujarat, India after taking permission from the Institutional ethical committee.

All the patients were thoroughly examined clinically on the previous day of operation. Vitals and routine investigations were recorded. Children having a history of convulsion, meningitis, neurological condition, having a congenital abnormality of the heart, respiratory tract infection and severe anemia were excluded.

Written consent was obtained from the parents for anaesthesia. All the children were divided equally into three groups of 30 patients each according to the premedication they received.

- *In group M:* Premedication in form of oral midazolam 0.5 mg/kg of body weight.
- *In group K:* Premedication in form of oral ketamine 6 mg/kg of body weight.
- *In group P:* Oral honey 3ml.

In all the groups along with the study drugs, 3ml of honey was mixed and given orally before 30 minutes of expected time of induction of anaesthesia. In the preanaesthesia room, dose time and acceptance of premedication were noted in all the cases.

Observations in preanesthetic room

Level of sedation: (3 point rating scale)⁵

- Score 1: Tearful /combative
- Score 2: Alert /aware, but not crying
- Score 3: Drowsy/sleeping.

Level of Anxiety: (3 point rating scale)⁵

- Score 1: Crying
- Score 2: Apprehensive but withdrawal from surrounding
- Score 3: Calm and sleepy.

Observations after thirty minutes premeditations

Response score⁵

Ocular response

- Score 1: No nystagmus
- Score 2: Nystagmus.

Response to voice

- Score 1: Coherent
- Score 2: In coherent
- Score 3: Not arousable.

Response to touch

- Score 1: Awake
- Score 2: Sleepy but arousable
- Score 3: Not arousable.

Special observations were done at the time of I.V. cannulation and at separation from their parents, the child's behavior was evaluated with a different 3 point rating scale.

Response to I.V. cannulations⁵

- Score 1: Crying
- Score 2: Apprehensive but withdrawal from surrounding
- Score 3: Calm and sleepy.

Separation score⁵

- Score 1: Crying
- Score 2: Apprehensive but withdrawal from surrounding
- Score 3: Calm and sleepy

Time of onset of sedation (when sedation score was 2) and maximum sedation (when sedation score was 3) was noted. Thirty minutes after premedication, patients were shifted to operation theater. All the patients were preoxygenated with paediatric face mask and response on putting mask was also scored in the form of quality of induction.

Quality induction⁵

- Score 1: (poor) afraid, combative, crying
- Score 2: (fair) moderate fear of mask, not easily calm
- Score 3: (good) slight fear of mask, easily calm
- Score 4: (excellent) unafraid, cooperative, accept mask, readily.

Anesthesia was induced with intra venous injection sodium thiopentone and suxamethonium.

RESULTS

Table 1: Sedation score at various intervals.

Time	Mean sedation score	Group M	Group K	Group P	P value		
					M versus P	K versus P	K versus M
10 min after premedication	Ranged	1to3	1to3	1to3	*p <0.05	*p <0.05	*p <0.05
	Mean±S.D.	1.60±0.814	1.70±0.47	1±0			
20 min after premedication	Ranged	1to3	1to3	1to3	*p <0.05	**p <0.001	*p <0.05
	Mean±S.D.	1.86±0.86	2.30±0.80	1±0			
30 min after premedication	Ranged	1to3	1to3	1to3	*p <0.05	**p <0.001	*p <0.05
	Mean±S.D.	1.90±0.88	2.30±0.80	1±0			
10 min after post op.	Ranged	1to3	1to3	1to3	*p <0.05	**p <0.001	*p <0.05
	Mean±S.D.	2.0±0.90	2.60±0.61	1±0			
20 min after post op.	Ranged	1to3	1to3	1to3	*P <0.05	**p <0.001	*p <0.05
	Mean±S.D.	2.0±1	2.30±0.80	1±0			
30 min after post op.	Ranged	1to3	1to3	1to3	*P <0.05	*p <0.05	****p >0.05
	Mean±S.D.	1.70±0.80	1.73±0.45	1±0			

= significant, p<0.05, ** = highly significant, p<0.001, *** = not significant, P > 0.05, paired students t – test

Table 2: Onset of sedation and maximum sedation (in minutes) in three groups.

Time		Group M	Group K	Group P	P value (K Vs M)
Onset of sedation	Ranged	9.2 to 11.6	8.4 to 12.5	No sedation	*p <0.05
	Mean±S.D.	9.46±1.01	10.38 ± 0.77		
Maximum Sedation	Ranged	17.5 to 21.5	17.4 to 21.5	No Sedation	**p >0.05
	Mean±S.D.	19.25±1.09	19.21 ± 2.47		

* = significant, ** = non-significant, Paired student t. test

Table 3: Response score (30 min after pre medication) in three groups.

Various response		Group M	Group K	Group P	P value		
					M versus P	K versus P	K versus M
Ocular response	Ranged	1 to 2	1 to 2	1 to 2	*p >0.05	**p <0.05	**p <0.05
	Mean±S.D.	1±0	1.43±0.50	1±0			
Response to touch	Ranged	1 to 3	1 to 3	1 to 3	**p <0.05	***p <0.001	**p <0.05
	Mean±S.D.	1.60±0.77	2.03±0.89	1±0			
Response to voice	Ranged	1 to 3	1 to 3	1 to 3	**p <0.05	***p <0.001	**p <0.05
	Mean±S.D.	1.63±0.76	2.16±0.83	1±0			

*=non significant, **=significant, ***=highly significant, paired student t. test

Table 4: Response to venepuncture (30 min after pre medication) in three groups.

Score	Group M	Group K	Group P	P value		
				M versus P	K versus P	K versus M
Ranged	1 to 3	1 to 3	1 to 3	*p <0.05	**p <0.001	*p <0.05
Mean ±S.D.	1.46±0.62	2.13±0.97	1±0			

* = significant, ** highly significant, paire student t test

Oral midazolam, oral ketamine and oral honey (placebo) were used as premedication successfully. Sedation score and anxiety score after premedication and postoperative was high in ketamine group as compared to oral midazolam or placebo. Oral midazolam took less time for onset of sedation as compared to oral ketamine but

maximum sedation was approximately equal in both the drugs but no sedation in control group. Oral ketamine gave better sedation and analgesia. With oral ketamine, majority of patients were calm and sleepy as compared to the oral midazolam and placebo during separation from parents. Group K response to venepuncture, separation

score and quality of induction is more as compared to group M and Group P. Only few complications like euphoria and hiccoughs were more in group M but

increased salivation and nystagmus were more common in group K.

Table 5: Separation score 30 min after premedication.

Score	Group M	Group K	Group P	P value		
				M versus P	K versus P	K versus M
Ranged	1 to 3	1 to 3	1 to 3			
Mean±S.D.	1.73±0.91	2.10±0.90	1±0	*p <0.05	**p <0.001	*p <0.05

* = significant, ** = highly significant, paired student t test

Table 6: Quality of induction in three groups.

Score	Group M	Group K	Group P	'P' Value		
				M versus P	K versus P	K versus M
Ranged	1 to 4	1 to 4	1 to 4			
Mean ±S.D.	2.26±0.98	2.83±1.23	1.23±0.43	**p <0.001	**p <0.001	*p <0.05

* = significant, ** non significant, paired student t test

DISCUSSION

Role of anesthesiologists in premedicating a patient before induction of anaesthesia is of vital importance. There is almost universal agreement on the need for some premedication which forms an integral part of anesthetic management. But surprisingly there are only few established facts regarding anxiousness and apprehensiveness developed among patients before anaesthesia in anaesthetic literature.⁶ Premedication in children form a separate entity and differs from methods employed for adults due to the many reasons such as physiological and psychological makeup of the child, emotion, fear of injections, excitement and apprehension.^{7,8} Physiologically child is unstable than adults; so there is marked fluctuation of pulse, blood pressure, respiration and secretion during anaesthesia, even if the dose is altered slightly.⁹ In an un-cooperative child, drug dosage if accidentally increased or decreased may make the child unsuitable for anaesthesia.¹⁰ A palatable oral preparation is usually acceptable to child and fluctuation of dosage being minimum; this cannot produce unpredictable side effects.

Opioids are frequently used as premedication. They have good analgesic effects and have ability to calm the patient but lack the ability to tranquilize with some side effects namely nausea, vomiting, and giddiness, cardiovascular and respiratory depression which may make anaesthesia difficult and hazardous. With opioids as premedication, there is delayed post-operative recovery with prolonged depression of laryngeal reflexes and under ventilation, which leads to pulmonary complications.^{11,12} Even newer opioids like fentanyl and sufentanil are not free from side effects like respiratory depression. In a study by Karl et al, it was found that sufentanil although being a very

good premedication, had serious side effects like oxygen desaturation (SPO₂ < 96%) in as many as 55% of patients, difficulty in ventilation of patients in 37% of patients and requiring reversal by naloxone in some patients.¹³

Nowadays benzodiazepines like diazepam, lorazepam, triazolam and midazolam have been used as premedication in children through various routes.¹¹ Premedication drugs like diazepam, trimeprazine have been used in children. Diazepam has a good anxiolytic properties, with poor anti-emetic effect, has a longer duration of action and a more profound respiratory depressant effect. Trimeprazine also provides good sedation and had a mild anti-sialogogue effect but it is associated with more post-operative restlessness.

In various studies comparing midazolam, with other drugs like diazepam, morphine, fentanyl, sufentanil, scopolamine, promethazine and pethidine, it was found to be very effective, short acting, having profound amnesic properties, hemodynamic stability, lesser respiratory depression and safe.¹⁴

Use of ketamine in children has renewal interest in search of an ideal premedicant, as it includes a state of analgesia, sedation and anxiolytic without depressing either cardiovascular or respiratory system.

In this study, in group M and K, majority (90% and 80% respectively) of patients had a good response to drug administration while in group P, all the patients had the good response to the drug administration.

Oral midazolam, oral ketamine and oral honey (placebo) were used as premedication successfully, sedation score

and Anxiety score after premedication and postoperative was high in ketamine group as compare to oral midazolam or placebo in this study. Oral midazolam took less time for onset of sedation as compared to oral ketamine but maximum sedation was approximately equal in both the drugs but no sedation in control group. oral ketamine gave better sedation and analgesia.

Suranjit et al evaluated that 80% of patients were calm at intravenous cannulation after oral ketamine and 33% were calm of intravenous cannulation after oral midazolam.¹⁵ This is similar to this study where majority of patients were calm and sleepy with oral ketamine as compared to oral midazolam and placebo during separation from parents.

Funk et al evaluated that success rate for anxiolysis and behavior at separation was 70% with oral ketamine and of 51% with oral midazolam. Quality of Induction was also found better in oral ketamine group as compared to oral midazolam in this study.¹⁶

Kulkarni et al concluded that 94% patients were well sedated and accepted the face mask prior to induction of anaesthesia after administration of oral ketamine before operation. Similar results were observed in our study.¹⁷

Midazolam causes anterograde and ketamine causes retrograde amnesia. Patients in midazolam group have more post-operative irritability and crying as compared to oral ketamine group but oral Ketamine causes more secretion and emergence phenomenon as compare to oral midazolam.

CONCLUSION

Ketamine is a very safe drug when used by oral route as a premedication in children as compared to midazolam or placebo.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Aasim SA, Zubair SI. Comparative study of oral ketamine and oral midazolam as premedication in paediatric patients. J Chalmeda Anand Rao Institute Med Sci. 2012;5(1):20-2.
2. Sington H. Discussion on medication in Anaesthesia. Proc Roy Soc Med. 1929;22:653.
3. Trivedi V. A comparative clinical study of tramadol versus pentazocine for sedation and analgesia as

- premedication a study of 60 cases. Inter J Anesthesiol. 2009;26(1):1-8.
4. Eckenhoff JE. Relationship of anesthesia to postoperative personality changes in children. Am J Dis Child. 1953;86:587-91.
5. Raman TSR, Deshmukh J. Pain less invasive procedure. Indian Paedia. 1999;36:1023-8.
6. Eckenhoff JE. Preanaesthetic sedation of children analysis of the effects for tonsillectomy and adenoidectomy. Arch Otolaryngol. 1953;57:411.
7. Beeby DG. Behavior of unsedated children in anaesthetic room. British J Anaesthesia. 1980;52:279.
8. Steward DJ. Psychological preparation and premedication, In: Gregory GA., editor. Pediatric anesthesia. New York: Churchill Livingstone, 1983.
9. Korsch BM. The child and the operating room. Anaesthesiology. 1975;43:1251-7.
10. Reitan JA, Soliman IE. A comparison of midazolam and diazepam for induction of anaesthesia in high risk patients. Anaesth Intensive Care. 1987;15(2):175-8.
11. Feld LH, Negus JB, White PF. Oral midazolam pre anaesthetic medication in paediatric out patients. Anaesthesia. 1990;73:831-4.
12. White PF, Vasconez LO, Mathes SA. Comparison of midazolam and diazepam for sedation during plastic surgery. Plast Reconstr Surg. 1988;81(5):703-12.
13. Karl HW, Rosenberger JL, Larach MG. Transmucosal administration of midazolam for premedication of pediatric patients. Anaesthesiology. 1993;78:885-9.
14. Debnath S, Pande Y. A comparative study of oral premedication in children with ketamine and midazolam. Indian J Anaesthesia. 2003;47:45-7.
15. Loepke AW, Soriano SG. An Assessment of the effects of general anesthetics on developing brain structure and neurocognitive function: anesthesia and the developing brain. Anesthesia Analgesia. 2008;106(6):1681-707.
16. Funk W, Jakob W, Riedl T, Toeger K. Oral preanaesthetic medication for children: double blind randomized study of a combination of mizazolam and ketamine vs midazolam or ketamine alone. British J Anaesthesia. 2000;84:335-40.
17. Kulkarni JA. Oral Ketamine for premedication in children. Paediatric Anaesthesia. 2003;45:315-7.

Cite this article as: Longani S, Mall KP, Raval D. Placebo controlled comparative study of oral midazolam and oral ketamine as a premedication in paediatric age group. Int J Adv Med 2017;4:66-70.