

Comparative study between oral midazolam and oral ketamine as preanaesthetic medication in paediatric patients undergoing elective surgery: a randomized double blind study

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Abstract

Introduction: Prime objective of anaesthesiologist is to minimize adverse psychological and physiological effects of anaesthetic technique. Premedication causes sedation and reduction of anxiety during separation from parents. It also provides a calm and cooperative child for smooth induction of anesthesia. We evaluated the differences in quality of premedication with orally administered midazolam and ketamine in the paediatric population undergoing elective surgical procedures and tried to ascertain the minimum interval required between premedication and parental separation. Objective: This study was undertaken to compare the efficacy and safety of oral midazolam and oral ketamine as a preanaesthetic medication for paediatric patients undergoing elective surgery. Materials and

Materials and Methods: In this prospective, randomized, double blind study a total of 60 children aged 1-6 years, belonging to ASA grade 1 and 2, scheduled for elective surgery were randomized into two groups of 30 each to receive either midazolam 0.5 mg/kg (Group A) or ketamine 5 mg/kg (Group B) orally. Parameters to be assessed were quality of sedation and anxiolysis, ease of parent-child separation and ease of venepuncture.

Results: Overall success rate of midazolam for sedation and anxiolysis was higher than ketamine in all the time frames. Successful separation from parents was easy in 25 patients (83.33%) in group A and 13 patients (43.33%) in group B. Successful venepuncture was obtained in 93.33% and 90% of patients in group A and group B respectively. This higher rate of success during venepuncture was probably due to use of EMLA cream prior to venepuncture.

Conclusion: We concluded that premedication with oral midazolam 0.5mg/kg provides better sedation and anxiolysis, easy parent child separation than oral ketamine 5mg/kg.

Keywords: Midazolam, Ketamine, Preanaesthetic, Anxiolysis, Venepuncture.

Introduction

Depending about the age, developmental maturity and past surgical experiences, children suffer from varying degrees of terror while facing the prospects of surgery. Also surgery and anesthesia may cause considerable stress for both parents and children. The anticipation of pain, separation from family, and fear of surgery are few of the factors that trigger perioperative anxiety in children.^{1,2,3} Prime objective of anaesthesiologist is to minimize adverse psychological and physiological effects of anaesthetic technique.⁴ Premedication causes sedation and reduction of anxiety during separation from parents. It also provides a calm and cooperative child for smooth induction of anesthesia.

Midazolam is a water-soluble benzodiazepine with greater amnestic than sedative potential⁵ and has been routinely used orally for premedication in children scheduled for surgery. It has a rapid onset and short duration of action. It is reliable in achieving sedation and anxiolysis.^{6,7} However, search for a better alternative continues due to concerns such as bitter taste, cognitive impairment, long-term behavioral

disturbances, paradoxical reactions, hiccups, and respiratory depression.^{8,9} Oral ketamine has similar pharmacodynamic¹⁰ after oral administration and has been investigated as an alternate premedication.^{6,11,12} It acts at the thalamocortical projection to produce dose-dependent sedation and dissociative anesthesia. Oral ketamine produces predictable satisfactory sedation and anxiolysis without significant side effects like respiratory depression or emergence delirium in children.^{1,2,6}

The aim of this study was to evaluate the differences in quality of premedication with orally administered midazolam and ketamine in the paediatric population undergoing elective surgical procedures and ascertain the minimum interval required between premedication and parental separation.

Materials and Methods

After obtaining institutional ethical committee approval and parent's written informed consent, the study was conducted in sixty (60) paediatric patients, aged 1-6 years of ASA grade 1 and 2, scheduled for elective surgical procedures. This prospective,

randomized, double blind study was carried out in the Department of Anaesthesiology and Department of Surgery at B.S. Medical College and Hospital, Bankura, for a period of one year. Patients with known history of allergies to benzodiazepines and ketamine, central nervous system dysfunction –epilepsy or raised intracranial tension, cardiovascular malformation, respiratory dysfunctions such as COPD, asthma, chronic bronchitis, prolonged therapy with hepatic enzyme – inducing drugs, children refusing to take the whole dose of premedication were excluded from the study. Patients were randomized by simple sealed envelope method into two groups of thirty (30) each: Group A: received 0.5mg/kg midazolam and group B: received 5mg/kg ketamine orally.

One hour before surgery, a mixture of local anaesthetics (EMLA) was applied for surface anaesthesia at the probable site of venepuncture. Patient received the premedication around 45 minutes before surgery in the preanaesthetic waiting room. Since oral preparations of both the drugs were not available, parenteral formulations in the concentrations of 5mg/ml for midazolam and 50mg/ml for ketamine were used. The drugs were mixed with freshly prepared sugar solution to make the volume 5ml and to ensure palatability of the preparation. Now Anaesthesiologist No.1 fed the drug either midazolam or ketamine according to the group of the child. Where Anaesthesiologist No.2 received the patient, and recorded the parameters, unaware of patient group allocation. Then Anaesthesiologist No.2 handed patient's case record form to Anaesthesiologist No.1, who entered the data into Microsoft excel sheet.

Before and after premedication sedation and anxiolysis score were assessed, after premedication it was assessed at 10, 20, and 30 minutes. Thirty five minutes after oral premedication, children were separated from parents. During parental separation, parent child separation score was assessed and recorded. Children were then transferred to the operating room. In the operating room, routine monitoring with ECG, non-invasive arterial pressure and pulse oximetry was commenced. Venepuncture was done approximately 5 minutes later in the induction room. After venepuncture, patients were induced with inhalational agent through face mask and the remaining part of the anaesthesia was conducted with standard anaesthesia protocol.

Sample size calculation and statistical analysis

The calculated sample size was 30 patients for each group based on a study by Darlong et al¹³ with significance level (α) of 0.05 and power of the test (β) of 0.8. Data was first plotted in Microsoft excel sheet, calculated in absolute numbers and presented in

percentage scale. For statistical evaluation, the scores were condensed to a dichotomous variable consisting of successful (scores 3 and 4) or un- successful (scores 1 and 2) for sedation, anxiolysis, easy parent child separation and easy venepuncture. Chi square test and student's unpaired t test were used for statistical analysis. P value ≤ 0.05 was considered as significant. INSTAT software (Graphpad prism software, Inc, La Zolla, CA. USA) was used for statistical analysis.

Observation and Results

The descriptive statistics of age, weight, sex and ASA physical status distribution were comparable between two groups and difference was found to be statistically insignificant, (Table 1). Before premedication, all the patients belonged to unsuccessful sedation score category and baseline sedation and anxiolysis score was comparable between two groups.

At 10 minutes of premedication, 20(66.67%) and 27(90%) patients had unsuccessful and 10(33.33%) and 3(10%) had successful sedation scores in midazolam and ketamine group respectively. At 20 minutes of premedication, 7(23.33%) and 22(73.33%) patients had unsuccessful and 23(76.67%) and 8(26.67%) had successful sedation scores in midazolam and ketamine group respectively. While at 30 minutes of premedication, 2(6.67%) and 12(40%) patients had unsuccessful and 28(93.33%) and 18(60%) had successful sedation scores in midazolam and ketamine group respectively. These results were statistically significant (Table 2).

Similarly, at 10 minutes of premedication, 12(40%) and 24(80%) patients had unsuccessful and 18(60%) and 6(20%) had successful anxiolysis scores in midazolam and ketamine group respectively whereas at 20 minutes of premedication, 5(16.67%) and 19(63.33%) patients had unsuccessful and 25(83.33%) and 11(36.67%) had successful anxiolysis scores in midazolam and ketamine group respectively while at 30 minutes of premedication, 3(10%) and 15(50%) patients had unsuccessful and 27(90%) and 15(50%) had successful anxiolysis scores in midazolam and ketamine group respectively. Also these results were statistically significant (Table 3).

At 35 minutes of premedication, 5(16.7%) and 17(56.67%) patients had unsuccessful and 25(83.33%) and 13(43.33%) had successful easy parent child separation scores in midazolam and ketamine group respectively and the results were statistically significant ($p=0.001$) (Figure 1). During venepuncture, 2 (6.67%) and 3(10%) patients had unsuccessful and 28(93.33%) and 27(90%) had successful easy venepuncture scores in midazolam and ketamine group.

Table 1: Demographic data of the patients

Variables	Group A	Group B	P value
Age (months)	45.133±12.23	39.533±12.59	0.730
Weight (kg)	15.33±1.86	14.76±1.99	0.947
Sex (M:F)	22 (73.33%): 8 (26.67%)	23 (76.67%): 7(23.33%)	0.766
ASA (grade I:II)	22 (73.33%): 8 (26.67%)	23 (76.67%): 7 (23.33%)	0.766

Table 2: Unsuccessful and successful sedation between two groups at 10, 20 and 30 minute

Groups	Time- 10 minute		Time - 20 minute		Time- 30 minute	
	Unsuccessful	Successful	Unsuccessful	Successful	Unsuccessful	Successful
Group A	20(66.67%)	10(33.33%)	7(23.33%)	23(76.67%)	2(6.67%)	28(93.33%)
Group B	27(90%)	3(10%)	22(73.33%)	8(26.67%)	12(40%)	18(60%)
P value	0.028		0.000		0.002	

Table 3: Unsuccessful and successful anxiolysis between two groups at 10, 20 and 30 minute

Groups	Time- 10 minute		Time - 20 minute		Time- 30 minute	
	Unsuccessful	Successful	Unsuccessful	Successful	Unsuccessful	Successful
Group A	12 (40%)	18(60%)	5 (16.67%)	25(83.33%)	3(10%)	27(90%)
Group B	24(80%)	6 (20%)	19(63.33%)	11(36.67%)	15(50%)	15(50%)
P value	0.002		0.000		0.001	

Discussion

A number of studies have demonstrated the beneficial effects of good pre-anaesthetic medication in children.¹⁴⁻¹⁶ Previous studies^{3,4,14,17,18} have shown that both midazolam and ketamine are effective oral pre-medicants in children. Though several routes of administration of the pre-medicant have been studied, the oral route is the least traumatic for children.^{5-7,19-21} Nicholson et al²² suggested that oral preanaesthetic medication may be as efficacious as intramuscular preanaesthetic medication in paediatric patients. Hence, the oral route of administration of the drugs was used in our study as it is the most acceptable route, especially in children. Children of age group 1 to 6 years were chosen for the study, as this is the most vulnerable group for stress response. The demographic data of the patients were comparable between two groups and seem that it has no influence on outcome of the study.

Both the drugs (midazolam and ketamine) produced sedation and anxiolysis with variable percentage of success over different time course. Overall success rate for midazolam was higher in all the time frame. At 10 minute, midazolam produced sedation in 33.33% of patients and it was improved over time to 76.67% of patients at 20 minutes and 93.33% at 30 minutes. Similarly, at 10-minute ketamine produced sedation to 10% of patients and successful sedation was improved over time to 26.67% at 20 minutes and 60% at 30 minutes. We have documented that at 30 minutes, the number of successfully sedated patient was increased in both the groups over progression of time, the increment was significantly higher in group A compared to group B. Among the different time frames at 10 minute, effect of ketamine

was negligible but this effect was improved over time. This may be due to longer onset of action of ketamine compared to midazolam.

Similarly, the success rate of midazolam for anxiolysis was improved over time. Initially, at 10 minutes, the success rate for anxiolysis was higher than the sedation and rate of improvement of sedation was higher than anxiolysis. This may be due to the concentration of midazolam required for anxiolysis was much less than the concentration required for sedation, so anxiolysis has been achieved earlier than sedation and there was not much increase after 20 minute. At 10 minute, there was an increase in the number of patients with successful sedation and anxiolysis that was supported by the study of Funk et al.¹⁷ Comparison of sedation and anxiolysis produced by midazolam and ketamine at 10 minutes revealed that midazolam produced a higher percentage of successful sedation and anxiolysis and that was statistically significant but the difference of success rate at 20 minutes was statistically highly significant (0.000). Also, on the same time frame (20 minutes), the success rate of anxiolysis was significantly higher in midazolam group (83.33%) than ketamine group (36.67%). Our finding was corroborated with the finding of Funk et al,¹⁷ the success rate in ketamine group was lower in our study compared to their study; this may be due to the use of a lower dose of ketamine (5mg/kg) in our study. At 30 minute, 27 and 15 number of patients achieved successful anxiolysis in group A and group B respectively. Here, again the difference was statistically significant (P=0.001). Our finding of anxiolysis score at 30 minutes was corroborated with the findings of Funk et al¹⁷ and Damle et al.¹⁸ The contrary results of Damle

et al¹⁸ study from ours can be explained by use of a higher dose of ketamine in their study (6 mg/kg).

In present study, at 35 minutes after premedication, we attempted to separate the patients from their parents. It was able to achieve successful easy separation in 25 patients (83.33%) in group A and successful easy separation in 13 patients (43.33%) in group B. Our findings can be supported by the findings of^{14,17,18} Successful venepuncture was obtained in 93.33% and 90% of patients in group A and group B respectively. This higher rate of success during venepuncture was probably due to the use of EMLA cream prior to venepuncture. Our findings were correlated with previous studies.^{17,18}

Conclusion

In present study, children suffer from varying degrees of anxiety while facing the prospects of surgery. Under the conditions of this study, oral midazolam 0.5mg/kg has better efficacy in terms of preoperative sedation, anxiolysis, easy parent child separation than oral ketamine 5mg/kg. Hence, it has the potential to become a promising preanaesthetic drug in the paediatric age group in the near future.

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References

1. Nasser Kaviani , Mina Shahtusi , Maryam Haj Norousali Tehrani , Sara Nazari. Effect of Oral Midazolam Premedication on Children's Co-operation Before General Anesthesia in Pediatric Dentistry. J Dent Shiraz Univ Med Sci., September 2014;15(3):123-8
2. Oyedepo OO, Nasir AA, Abdur-Rahman LO, Kolawole IK, Bolaji BO, Ige OA. Efficacy and safety of oral ketamine premedication in children undergoing day case surgery. West Afr Coll Surg. 2016;6(1):1
3. Egan KJ, Ready LB, Nessly M, Greer BE. Self-administration of midazolam for postoperative anxiety: A double blinded study. Pain. 1992;49:3-8.
4. Kain ZN. Committee on Pediatric Anaesthesia. Preoperative psychological issues in children. ASA Newsletter 2000;64(8).
5. Stoelting RK, Hillier SC, editors. Pharmacology and physiology in anesthetic practice. 4th ed. Philadelphia (PA): Lippincott Williams and Wilkins; 2006. Benzodiazepines; pp. 142-7.
6. Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic medication in children. Anesthesiology. 1992;76:28-33.
7. Kain ZN, Hofstadter MB, Mayes LC, Krivutza DM, Alexander G et al. Midazolam: Effects on amnesia and anxiety in children. Anesthesiology. 2000;93:676-84.
8. Bergendahl H, Lönnqvist PA, Eksborg S. Clonidine in paediatric anaesthesia: Review of the literature and comparison with benzodiazepines for premedication. Acta Anaesthesiol Scand. 2006;50:135-43.
9. Bergendahl H, Lönnqvist PA, Eksborg S. Clonidine: An alternative to benzodiazepines for premedication in children. Curr Opin Anaesthesiol. 2005;18:608-13.
10. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effect of i.m and oral ketamine . Br J Anaesth 1981;53:805-9.
11. Cioaca R, Canavea I. Oral transmucosal ketamine :an effective premedication in children.Paediatr Anaesth 1996;6:361-5.
12. Sekerci S, Doenmez A, Ates Y, Oekten F . Oral ketamine in children (placebo controlled double-blind study). Europe J Anaesthesiology 1996;13:606-11.
13. Darlong V, Shende D, Subramanyam MS, Sunder R, Naik A. Oral ketamine or midazolam or low dose combination for premedication in children. Anaesthesia and Intensive Care. 2004;32(2):246-49.
14. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine. Can J Anaesth. 1994;41(3):221-6.
15. Desjardins R, Ansara S, Charest J. Pre-anaesthetic medication in paediatric day-care surgery. Can Anaesth Soc J. 1981;28(2):141-8.
16. Jones RD, Visram AR, Kornberg JP, Irwin MG, Gunawardene WM. Premedication with oral midazolam in children an assessment of psychomotor function, anxiolysis, sedation and pharmacokinetics. Anaesth Intensive Care. 1994;22(5):539-44.
17. Funk W et al. Oral preanaesthetic medication for children; double blind randomized study of a combination of midazolam and ketamine vrs midazolam or ketamine alone. Br J Anaesth 2000;84:335-40.
18. Dalmes S G et al. Comparison of oral ketamine and oral midazolam as sedative agenyis in pediatric dentistry. J Indian Soc Pedod Prevent Dent 2008
19. Khalil S, Philbrook L, Rabb M, Wagner K, Jennings C, Chuang AZ. Sublingual midazolam premedication in children: a dose response study. Paediatric Anaesth. 1998;8:461-5.
20. American academy of paediatrics. Committee on drugs. Alternative routes of drug administration- advantages and disadvantages (subject review). Paediatrics. 1997;100:143-52.
21. Feld LH, Urquhart ML. Premedication in children: oral vs. intramuscular midazolam. Anesthesiology 1998;69:A745.
22. Nicholson SC, Betts EK, Jokes DR, Christianson, Walters JW, Mayes KR, et al. Comparison of oral and intramuscular preanaesthetic medication for paediatric inpatient surgery. Anaesthesiology 1989;71:8-10.