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Efficacy of oral ketamine and oral midazolam as premedicants in the paediatric population undergoing elective surgical procedures

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Abstract
Background and Aim: Oral ketamine produces predictable satisfactory sedation and anxiolysis without significant side effects like respiratory depression or emergence delirium in children. this study is being carried out to compare Oral ketamine with oral midazolam to know the efficacy of both the drugs as premedicants in the paediatric population undergoing elective surgical procedures and ascertain the minimum interval required between premedication and parental separation.
Material and Methods: Present prospective, randomized study was conducted in 80 children in the age group of 4–12 years, of either sex or the American Society of Anesthesiologists (ASA) Physical status 1, posted for elective surgery. Patients were randomized by simple sealed envelope method into two groups of 40 each: Group A: received 0.5mg/kg midazolam and group B: received 5mg/kg ketamine orally. 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.
Results: At 10 minutes of premedication, 28 (70%) and 35(87.5%) patients had unsuccessful and 12(30%) and 5(12.5%) had successful sedation scores in midazolam and ketamine group respectively. At 20 minutes of premedication, 9(22.5%) and 28(70%) patients had unsuccessful and 31(77.5%) and 12(12%) had successful sedation scores in midazolam and ketamine group respectively. While at 30 minutes of premedication, 4(10%) and 17(42.5%) patients had unsuccessful and 36(90%) and 23(58.7%) had successful sedation scores in midazolam and ketamine group respectively. These results were statistically significant ($P \leq 0.05$)
Conclusion: Oral midazolam was superior to the ketamine for providing easy separation from parents and excellent mask acceptance in children. Oral midazolam had faster onset of sedation and provided higher sedation scores and lower anxiety scores as compared to ketamine.

Keywords: children, ketamine, midazolam, sedation

Introduction

Pediatric patients constitute a specific population of patients which are different from adults due to anatomical/physiological difference and difference in their pharmacodynamics and pharmacokinetics response. Most untoward response among the pediatric age group (preschool going children) is usually aggressive psychological response and reacts violently to parental separation [1-4]. Hence, the anesthesiologists involved in pediatric anesthesia have to be very careful in selecting a premedicant among the long list with emphasis to preoperative sedation, transfer to operating room, and subsequent smooth induction of anesthesia. Premedication causes sedation and reduction of anxiety during separation from parents. It also provides a calm and cooperative child for smooth induction of anesthesia.

Although many sedative agents such as hyoscine, phenothiazine, clonidine, midazolam, phencyclidine derivatives, and tramadol all have been used for the purpose of premedication with a view to have calm and quiet child for smooth induction of anesthesia, few of them can be given orally and can help in avoiding the pricks Midazolam, a benzodiazepine, has been routinely used orally for premedication in children scheduled for surgery [5]. 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 pharmacodynamic after oral administration and has been investigated as an alternate premedication [10-12]. It acts at the thalamoneocortical 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 [10, 13, 14].

Hence, this study is being carried out to compare Oral ketamine with oral midazolam to know the efficacy of both the drugs as premedicants in the paediatric population undergoing elective surgical procedures and ascertain the minimum interval required between premedication and parental separation.

Material and Methods

After due clearance from the Institutional Ethics Committee and after obtaining written informed consent from a parent or a legal guardian, this prospective, randomized study was conducted in 80 children in the age group of 4–12 years, of either sex and the American Society of Anesthesiologists (ASA) Physical status, posted for elective surgery.

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 40 each: Group A: received 0.5mg/kg midazolam and group B: received 5mg/kg ketamine orally.

Before administration of the premedication, the children were brought to the preoperative room along with their parents. 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.

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.

Statistical analysis

The data were analyzed using SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.

Results

The three groups were comparable with respect to age, gender, and weight [Table 1]. All 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, 28(70%) and 35(87.5%) patients had unsuccessful and 12(30%) and 5(12.5%) had successful sedation scores in midazolam and ketamine group respectively. At 20 minutes of premedication, 9(22.5%) and 28(70%) patients had unsuccessful and 31(77.5%) and 12(12%) had successful sedation scores in midazolam and ketamine group respectively. While at 30 minutes of premedication, 4(10%) and 17(42.5%) patients had unsuccessful and 36(90%) and 23(58.7%) had successful sedation scores in midazolam and ketamine group respectively. These results were statistically significant ($P \leq 0.05$) (Table 2).

Similarly, at 10 minutes of premedication 16(40%) and 33(82.5%) patients had unsuccessful and 24(60%) and 7(17.5%) had successful anxiolysis scores in midazolam and ketamine group respectively whereas at 20 minutes of premedication, 8(20%) and 16(40%) patients had unsuccessful and 32(80%) and 24(60%) had successful anxiolysis scores in midazolam and ketamine group respectively while at 30 minutes of premedication, 5(12.5%) and 20(50%) patients had unsuccessful and 35(87.5%) and 20(50%) had successful anxiolysis scores in midazolam and ketamine group respectively. Also these results were statistically significant ($P \leq 0.05$) (Table 3). At 35 minutes of premedication, results were also statistically significant (p=0.001).

Discussion

Psychological preparation of children before induction of anesthesia results in better perioperative outcome. Reduction of anxiety, calm, and sedated child in preanesthesia room has better postoperative emergence. Kain *et al.* [15] primary goal of premedicating the child is to produce amnesia, anxiolysis, and prevention of stress response during preinduction period. Although a drug given parenterally is more effective, in pediatric practice, needle pricks is feared most. Some studies [1, 6] suggest that oral midazolam is an ideal premedicant when compared with triclofos which is used as a second-line drug for insomnia in children while other drugs have failed.

Previous studies [16-20] has shown that both midazolam and ketamine are effective oral premedicants in children. Though several routes of administration of the pre-medicant have been studied, the oral route is the least traumatic for children [21-24]. 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 30% of patients and it was improved over time to 77.5% of patients at 20 minutes and 90% at 30 minutes. Similarly, at 10-minute ketamine produced sedation to 12.5% of patients and successful sedation was improved over time to 12% at 20 minutes and 58.7% 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. 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*.[24] 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 (80%) than ketamine group (60%).Our finding was corroborated with the finding of Funk *et al*, [24] At 30 minute, difference was statistically significant (P=0.001) for anxiolysis between group A and group B respectively. Our finding of anxiolysis score at 30 minutes was corroborated with the findings of Funk *et al.* [24] and Damle *et al.* [25] Successful venepuncture was obtained in 92.5% and 89.5% 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 [24, 25].

Table 1: Demographic data of study participants

Variable	Group A	Group B	P value
Age (months)	44.12±10.42	38.52±09.48	0.12
Gender (Male/female)	29 (72.5%) 11 (27.5%)	27 (67.5%) 13 (32.5%)	0.2
Weight (kg)	16.01±1.74	13.99±2.10	0.31

Statistically significance at p≤0.05

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

Groups	10 Minute		20 minute		30 minute	
	Unsuccessful	successful	Unsuccessful	successful	Unsuccessful	successful
Group A	28 (70%)	12(30%)	9(22.5%)	31(77.5%)	4(10%)	36(90%)
Group B	35(87.5%)	5(12.5%)	28(70%)	12(12%)	17(42.5%)	23(58.7%)
P value	0.02*		0.001*		0.05*	

* indicates statistically significance at p≤0.05

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

Groups	10 Minute		20 minute		30 minute	
	Unsuccessful	successful	Unsuccessful	successful	Unsuccessful	successful
Group A	16(40%)	24(60%)	8(20%)	32(80%)	5(12.5%)	35(87.5%)
Group B	33(82.5%)	7(17.5%)	16(40%)	24(60%)	20(50%)	20(50%)
P value	0.001*		0.03*		0.004*	

* indicates statistically significance at p≤0.05

Conclusion

Oral midazolam was superior to the ketamine for providing easy separation from parents and excellent mask acceptance in children. Oral midazolam had faster onset of sedation and provided higher sedation scores and lower anxiety scores as compared to ketamine. Hence, it has the potential to become a promising preanaesthetic drug in the paediatric age group in the near future.

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