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ORIGINAL ARTICLE

Comparison of Oral Midazolam and Oral Ketamine as Premedicants for Parent–Child Separation in Paediatric Elective Surgery

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Abstract

Introduction: Preoperative anxiety in children undergoing surgery can adversely affect parent–child separation, induction of anaesthesia, and postoperative behavioural outcomes. Oral premedication is widely used in paediatric anaesthesia as it is non-invasive and well accepted. Midazolam and ketamine are the commonly employed oral premedicants, each with distinct pharmacological profiles. **Materials and Methods:** This prospective randomized double-blinded comparative study was conducted in a tertiary care hospital and included 66 children aged 1– 6 years belonging to ASA physical status I and II, scheduled for elective surgical procedures. Children were randomly allocated into two equal groups: Group M received oral midazolam 0.5 mg/kg and Group K received oral ketamine 5 mg/kg, both mixed with paracetamol syrup for palatability. Sedation scores, heart rate, and oxygen saturation were recorded at baseline and at 0, 5, 10, 15, and 20 minutes after premedication. **Results:** Baseline demographic data such as weight and age were comparable between the two study groups. Oxygen saturation and Heart rate remained stable throughout the observation period at any point of time, in both the groups with no statistically significant differences. **Conclusion:** Both the oral ketamine and oral midazolam provided good sedation and maintained the expected hemodynamic stability in the paediatric patients. However, oral midazolam had better behavioural outcomes during parent–child separation and lesser adverse effects, suggesting that it may be the preferred oral premedicant for elective surgical procedures in children.

Keywords: Paediatric premedication, Oral midazolam, Oral ketamine, Parent–child separation, Sedation

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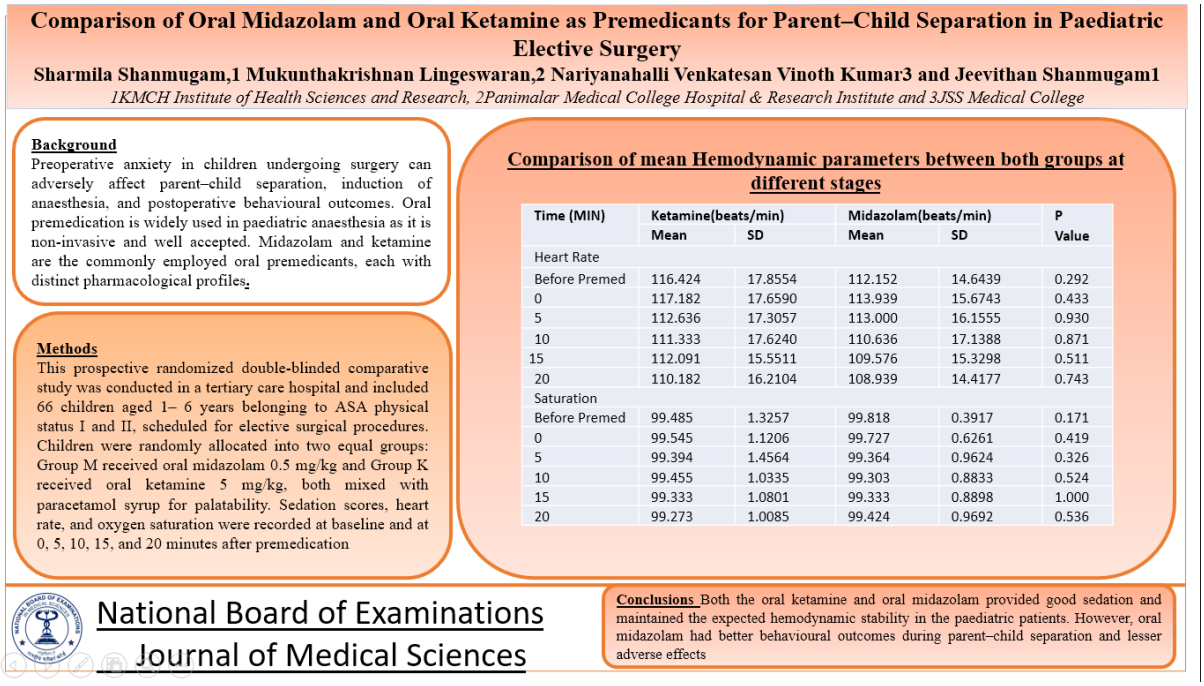
Graphical Abstract



Introduction

Preparing paediatric patients for surgery is a challenging process, as children often experience significant anxiety related to separation from parents, unfamiliar hospital environments, and anaesthesia induction. Children are frequently unable to articulate their fears, yet experience levels of anxiety comparable to adults [1]. Surgical procedures and anaesthesia induction are known to cause considerable emotional stress in children, and pre-anaesthetic medications are commonly administered to reduce anxiety, facilitate child–parent separation, and promote smooth induction of anaesthesia [2].

Preoperative anxiety typically develops at around 7–8 months of age and peaks at approximately one year of age [3]. Children between one and five years of age, those with anxious temperaments, previous unpleasant medical experiences, or whose parents demonstrate poor coping skills are particularly vulnerable to heightened anxiety [4]. Without appropriate intervention, young children may develop post-hospitalisation behavioural changes such as separation anxiety, sleep disturbances, feeding difficulties, nightmares, bedwetting, and regression of toilet training [5]. Pre-anaesthetic medication plays an essential role in alleviating these psychological effects, decreasing the vagal responses, and preventing the expected postoperative behavioural sequelae [6].

An ideal paediatric premedicant should be cost effective, easily available, palatable, faster in onset, reliable, and free from adverse effects during induction, recovery, and discharge [7]. Despite the various pharmacological premedicant, no single drug has achieved the acceptance worldwide, highlighting the need for continued evaluation of commonly used premedicants.

The most frequently used oral premedicants in paediatric anaesthesia are Ketamine and Midazolam [1,5]. Due to its anxiolytic, sedative, and amnestic

properties, Midazolam, a short-acting benzodiazepine, is widely used. However, its variability in oral bioavailability and bitter taste remain disadvantages [8]. Different strategies, including the mixing intravenous midazolam with flavoured syrups or juices, have been used successfully to improve palatability [9,10].

Ketamine, a phencyclidine derivative and NMDA receptor antagonist, produces dissociative anaesthesia (sedation) with preservation of airway reflexes and respiratory drive [8]. Oral ketamine usually provides an effective analgesia and sedation. Typical sedation is achieved within 10–15 minutes at the doses of 5–6 mg/kg [8]. The drug, ketamine may be associated with adverse effects such as increased postoperative emesis [3] and nystagmus. Paracetamol syrup, widely used in paediatric practice because of its safety, analgesic, and antipyretic properties, has been employed as a palatable vehicle for oral administration of premedicants [11].

The previous research papers demonstrated the efficacy of oral midazolam and ketamine, when administered with flavoured syrups [6,11] and the present study was designed to compare oral ketamine and oral midazolam, both mixed with paracetamol syrup, as premedicants during the elective surgery of paediatric patients. The current research aimed to assess their effects on sedation, child–parent separation, hemodynamic stability, the behaviour during induction of anaesthesia, and the perioperative adverse effects.

Materials and Methods

This prospective randomized double-blinded comparative study was conducted in the Theatre Complex of the Department of Anaesthesiology at a tertiary care teaching hospital. Prior to commencement of the study, approval was obtained from the Institutional Ethical and Scientific Committee. Parents or legal guardians of all eligible children were approached during the preoperative assessment period and were explained in detail about the nature, purpose, and usefulness of premedication. It was clearly communicated that the study was observational in nature, non-invasive. The informed consent in the written format was obtained from the parents or guardians in accordance with ethical principles justified in the Declaration of Helsinki. Confidentiality of patient information was strictly maintained, and participation was entirely voluntary in nature, with the option to withdraw at any stage without affecting the standard of care.

A total of 66 paediatric patients scheduled for elective surgical procedures under general anaesthesia were included in the study. Children aged between 1 and 6 years, weighing less than 20 kg, and belonging to American Society of Anaesthesiologists (ASA) physical status I and II were enrolled. Children with known allergy to midazolam or ketamine, risk of aspiration, weight more than 20 kg, anatomical airway abnormalities, systemic illnesses affecting drug absorption, renal disease, developmental delay, congenital syndromes, seizure disorders, or other central nervous system disorders were excluded. Emergency procedures, ASA grade more than II, and surgeries expected to last more than two hours were also excluded.

The study followed a double-blinded randomised design. Eligible patients were randomly allocated into two equal groups of 33 each using a sealed opaque envelope method. Sixty-six cards

marked either “K” (ketamine) or “M” (midazolam) were prepared, shuffled, sealed in opaque envelopes, and sequentially numbered. For each patient, an envelope was opened by the consultant anaesthesiologist, who prepared the study drug accordingly. The study drug was administered by a trainee anaesthesiologist who was blinded to the drug allocation and was responsible for data collection. The nature of the drug administered was revealed to the investigator only after completion of data collection for all patients.

Children in Group K received oral ketamine at a dose of 5 mg/kg, while those in Group M received oral midazolam at a dose of 0.5 mg/kg. Intravenous formulations of ketamine (50 mg/mL) and midazolam (5 mg/mL) were used and mixed with commercially available flavoured paracetamol syrup (15 mg/kg; 250 mg/5 mL) to improve palatability. Adequate care was given to ensure that the total volume of the administered agents must not exceed 0.5 mL/kg. Both the drugs were odourless and colourless, also, for maintaining the blinding, the same brand of paracetamol syrup was used in both the drug groups.

Following premedication, the pulse oximetry was used to monitor the oxygen saturation of arterial blood (SpO2) continuously and direct clinical observation was also made. At 0, 5, 10, 15, and 20 minutes after administration of the study drug, the heart rate, oxygen saturation (SpO_2), and sedation scores were recorded at the baseline. The Sedation was evaluated using a four-point sedation scale as follows. Score 1: Alert and active; Score 2: Awake but calm; Score 3: Drowsy but arousable; Score 4: Asleep and not easily arousable.

Twenty minutes after the premedication, the participants were separated from their parents and transferred to the operation theatre room. Behaviour during parent–child separation was evaluated using the *Parental Separation Anxiety Scale*, and behaviour during induction was assessed using a *four-point mask acceptance scale.* Scores of 1 and 2 were considered acceptable for both separation and mask acceptance.

In the operating room, standard monitors including electrocardiogram, non-invasive blood pressure, and pulse oximetry were applied. Anaesthesia was induced using sevoflurane in a 50:50 mixture of oxygen and nitrous oxide. Airway management with laryngeal mask airway or endotracheal tube and the use of caudal analgesia were performed as appropriate for the surgical procedure. Any perioperative adverse effects such as airway obstruction, desaturation, nystagmus, hiccups, bradycardia, nausea, or vomiting were noted and recorded.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 27.0 for Windows. Descriptive statistics such as mean, standard deviation, frequency, and percentage were used to summarise demographic and clinical variables. Continuous variables including heart rate and oxygen saturation were analysed using the independent samples t-test. Sedation and behaviour scores, being ordinal data, were analysed using the Mann–Whitney U test. A P value of less than 0.05 was considered statistically significant, and all analyses were performed at a 95% confidence interval.

Results

The baseline demographic characteristics were comparable between the ketamine and midazolam groups. The mean age of children in the ketamine group was 3.00 ± 1.63 years, while it was 3.32 ± 1.48 years in the midazolam group, with no statistically significant difference (P = 0.42). Similarly, the mean body weight did not differ significantly between the two groups (13.22 ± 3.71 kg vs. 13.95 ± 3.54 kg; P = 0.43). However, a statistically significant difference was observed in sex distribution, with males constituting a higher proportion in the ketamine group (78.8%) compared to the midazolam group (42.4%) (P = 0.003) (Table 1).

Table 1. Baseline Demographic Characteristics of the Study Population

Variable	**Ketamine (n = 33)**	**Midazolam (n = 33)**	**P value**
Age (years), mean ± SD	3.00 ± 1.63	3.32 ± 1.48	0.42
Weight (kg), mean ± SD	13.22 ± 3.71	13.95 ± 3.54	0.43
Sex – Male, n (%)	26 (78.8%)	14 (42.4%)	0.003
Sex – Female, n (%)	7 (21.2%)	19 (57.6%)	

Table 2 compares the hemodynamic parameters and oxygen saturation between the ketamine and midazolam groups at different time intervals from baseline to 20 minutes after premedication. The mean heart rate was marginally higher in the ketamine group before premedication (116.42 ± 17.86 beats/min) compared to the midazolam group (112.15 ± 14.64 beats/min), but this difference was not statistically significant (P = 0.292). At subsequent intervals, including 10 minutes (111.33 ± 17.62 vs. 110.64 ± 17.14 beats/min) and 20 minutes (110.18 ± 16.21 vs. 108.94 ± 14.42 beats/min), heart rates remained comparable between the two groups (P > 0.05).

Table 2. Comparison of mean Hemodynamic parameters between both groups at different stages

Time (MIN)	**Ketamine(beats/min)**		**Midazolam(beats/min)**		**P Value**
	Mean	**SD**	**Mean**	**SD**	
Heart Rate					
Before Premed	116.424	17.8554	112.152	14.6439	0.292
0	117.182	17.6590	113.939	15.6743	0.433
5	112.636	17.3057	113.000	16.1555	0.930

10	111.333	17.6240	110.636	17.1388	0.871
15	112.091	15.5511	109.576	15.3298	0.511
20	110.182	16.2104	108.939	14.4177	0.743
Saturation					
Before Premed	99.485	1.3257	99.818	0.3917	0.171
0	99.545	1.1206	99.727	0.6261	0.419
5	99.394	1.4564	99.364	0.9624	0.326
10	99.455	1.0335	99.303	0.8833	0.524
15	99.333	1.0801	99.333	0.8898	1.000
20	99.273	1.0085	99.424	0.9692	0.536

In both the groups, oxygen saturation values were consistently maintained above 99% throughout the observation period. At 20 minutes, the mean SpO_2 was 99.42 ± 0.97% in the midazolam group and 99.27 ± 1.01% in the ketamine group, with no statistically significant difference seen between the study groups (P = 0.536). Overall, there was no significant difference in oxygen saturation or heart rate between the study groups at any time point, as shown in Table 2.

The mean sedation scores compared at different time intervals between the midazolam and ketamine groups are presented in Table 3. Before premedication, the mean sedation score was slightly higher in the ketamine group (3.36 ± 0.55) compared to the midazolam group (3.09 ± 0.58), though this difference did not reach statistical significance (P = 0.059). Following administration of the study drugs, sedation scores decreased progressively over time in both groups. At 10 minutes, the mean sedation scores were 2.36 ± 0.60 in the ketamine group and 2.55 ± 0.67 in the midazolam group (P = 0.316). By 20 minutes, both groups achieved comparable levels of sedation (1.91 ± 0.77 vs. 1.94 ± 0.61; P = 0.810), indicating no statistically significant difference in sedation between the two groups at any observed time point (Table 3).

Table 3. Comparison of mean Sedation score at different times

Time(min)	Ketamine		Midazolam		Mann-Whitney U Value	P Value
	Mean score	SD	Mean score	SD		
Before Pre-med	3.364	0.5488	3.091	0.5790	418.500	0.059
0	3.333	0.5401	3.152	0.5658	459.500	0.197
5	2.818	0.4647	2.848	0.6185	537.500	0.913
10	2.364	0.6030	2.545	0.6657	474.500	0.316
15	2.000	0.6614	2.152	0.6185	479.500	0.344
20	1.909	0.7650	1.939	0.6093	527.500	0.810

The comparison of behaviour scores at induction and parent–child separation between the ketamine and midazolam groups is shown in Table 4. At induction, the mean behaviour score was comparable between the ketamine group (2.12 ± 0.89) and the midazolam group (1.94 ± 0.70), with no statistically significant difference observed (P = 0.400). However, at the time of parent–child separation, a statistically significant difference was noted between the two groups. The mean behaviour score was higher in the ketamine group (2.49 ± 0.80) compared to the midazolam group (2.09 ± 0.72), and this difference was statistically significant (P = 0.037), as shown in Table 4. In ketamine group nearly one fourth (24.24%) experienced complications (1 child had vomiting and 7 children had nystagmus). In midazolam group no one had any complications.

Table 4. Comparison of Behaviour score between both groups at induction and separation

Time (min)	**Ketamine**		**Midazolam**		**Mann-Whitney U Value**	**P Value**
	Mean score	**SD**	**Mean score**	**SD**		
At induction	2.121	0.8929	1.939	0.7044	484.000	0.400
At separation	2.485	0.7953	2.091	0.7230	395.000	**0.037**

Discussion

Preoperative anxiety in children remains a significant concern in paediatric anaesthesia and has been shown to negatively influence parent–child separation, induction of anaesthesia, and postoperative behavioural outcomes [1,2]. Oral premedication is widely preferred in paediatric practice due to its non-invasive nature and better acceptance by children compared to parenteral routes [8]. The present study compared oral midazolam and oral ketamine, both administered with paracetamol syrup, with respect to sedation, behavioural response, hemodynamic stability, and adverse effects in children undergoing elective surgical procedures.

In the present study, baseline demographic variables such as age and weight were comparable between the two groups, although a statistically significant difference was observed in sex distribution (Table 1). This imbalance is unlikely to have influenced the primary outcomes, as previous studies have not demonstrated a consistent association between sex and preoperative anxiety levels or response to sedative premedication in young children [6,12]. Hence, the observed differences in behavioural response and adverse effects can reasonably be attributed to the pharmacological properties of the study drugs rather than demographic variation.

Hemodynamic parameters remained stable in both groups throughout the observation period. There were no statistically significant differences in heart rate or oxygen saturation between the ketamine and midazolam groups from baseline to 20 minutes following premedication (Table 2). Oxygen saturation was consistently maintained above 99% in both groups, indicating preserved respiratory function. These findings are consistent with earlier studies reporting stable cardiovascular and respiratory parameters with oral ketamine and oral midazolam when used in appropriate doses for paediatric premedication [6,7,11].

Sedation scores highlight a progressive and gradual decline over time in both groups, showcasing an increased depth of sedation after the administration of the drugs. Though the onset of sedation appeared little earlier in the ketamine group, this difference did not reach significant level at any time point (Table 3). At 20 minutes, both the groups have achieved comparable sedation scores, showing the equivalent and effective sedation during the time of parent–child separation. These results are in par with the previous studies demonstrating the similar sedative effectiveness of oral ketamine and oral midazolam in paediatric age group [6,7,13].

The critical determinant of effective paediatric anaesthetic management is the behavioural response during parent–child separation and the induction of anaesthesia. In the current study, induction period, behaviour scores were comparable between the study groups, showing the similar acceptance of face mask and further cooperation. (Table 4). However, at the time of parent–child separation, the midazolam group showed significantly better behaviour scores when, compared to the ketamine group ($P = 0.037$). These results spotted the superior anxiolytic effect of midazolam during the separation period. This can be attributed to its benzodiazepine-mediated anxiolysis and amnestic properties [1,5,12].

The drug Ketamine was associated with a higher incidence of adverse effects in the current study. In the ketamine group, 24.24% of the children gone through the

adverse effects, with seven children exhibiting nystagmus and one child developing vomiting, whereas nil complications were observed in the midazolam group. These findings are similar with the previous studies highlighting the increased incidence of emesis and nystagmus, after the oral ketamine administration [12]. Although these adverse effects were transient and did not require medical intervention, their occurrence may be clinically relevant, particularly in the paediatric population. Nystagmus can be alarming to parents and caregivers, and vomiting may increase perioperative discomfort and anxiety, thereby negatively influencing parental satisfaction and acceptance of premedication. Similar findings have been reported in previous studies, which have documented a higher incidence of minor but noticeable adverse effects such as nystagmus and emesis following oral ketamine administration [3,11]. These observations suggest that, despite its sedative efficacy, ketamine may be associated with reduced overall tolerability when compared to midazolam, especially in settings where parental perception and child comfort are critical components of perioperative care.

The use of oral paracetamol syrup was well tolerated in both groups and positively contributed to the improved palatability and acceptance of the two agents. This approach has been shown to be efficient in the previous studies without altering the pharmacodynamic effects of midazolam or ketamine [11]. The judicious use of a flavoured syrup as a diluent denotes an easy, simple, and practical strategy to improve compliance in paediatric patients.

Limitations

This study was conducted at a single centre with a relatively small sample size and short preoperative observation period. A statistically significant imbalance in sex distribution was observed between groups, although this is unlikely to have influenced primary outcomes. Larger multicentre trials with extended follow-up are recommended.

Conclusion

The current study highlights that both the oral ketamine and oral midazolam offer comparable hemodynamic stability and sedation, but the oral midazolam provides better behavioural outcomes during the parent–child separation and is associated with fewer adverse effects. The above observations from the study, emphasize the preferential use of oral midazolam as a premedicant in the paediatric patients undergoing elective surgical procedures.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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