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ORIGINAL ARTICLE

Comparative Effectiveness of Oral Midazolam vs. Oral Ketamine as Pre-Anesthetic Medication in Paediatric Cardiac Patients at Bangladesh Shishu Hospital & Institute

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Abstract

Background*: Pediatric anesthesia for cardiac surgery presents unique challenges, requiring effective pre-anesthetic medications to manage preoperative anxiety and sedation.*

Objective: *This study aims to compare the effectiveness and safety of oral midazolam and oral ketamine as pre-anesthetic medications in pediatric cardiac patients at Bangladesh Shishu Hospital & Institute.*

Methods*: This prospective randomized double-blind clinical trial included 50 pediatric patients scheduled for elective cardiac surgery, randomly assigned to receive either oral midazolam (0.5 mg/kg) or oral ketamine (5 mg/kg) 30 minutes before anesthesia induction. Sedation levels were assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale. Secondary outcomes included ease of parental separation, mask acceptance, and the occurrence of adverse effects evaluated by a blinded observer. Data were analyzed using SPSS version 26.*

Results*: The mean age of patients was 7.5 years (SD 2.4), with no significant differences between the groups in demographic or clinical characteristics. Deep sedation (score 1) was achieved by 8% of the midazolam group and 4% of the ketamine group (p=0.34). Excellent mask acceptance was observed in 64% of the midazolam group and 56% of the ketamine group (p=0.55). Nausea occurred in 4% of the midazolam group and 12% of the ketamine group (p=0.29), with no significant differences in other adverse effects.*

Conclusion*: Both oral midazolam and oral ketamine are effective and safe for pre-anesthetic medication in pediatric cardiac patients, with no significant differences in sedation levels, parental separation, mask acceptance, or adverse effects. These findings support the use of both medications in clinical practice, allowing for flexible patient management based on individual needs.*

Keywords*: Cardiac surgery, ketamine, midazolam, paediatric anesthesia, pre-anesthetic medication.*

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Introduction

Pediatric anesthesia particularly for cardiac patients, presents a unique set of challenges that require meticulous management to ensure patient safety and optimal outcomes. One of the primary concerns in pediatric anesthesia is managing preoperative anxiety and providing effective sedation which are crucial for smooth induction and overall patient cooperation. The preoperative period can be particularly distressing for both pediatric patients and their parents, often leading to increased anxiety that can complicate the induction process. Studies have shown that behavioral interventions using technologies such as smartphone applications can significantly reduce preoperative anxiety in children and their parents, enhancing the overall experience and cooperation during anesthesia induction.[1] Additionally, proper communication and parental presence have been highlighted as critical factors in reducing preoperative anxiety and improving the overall perioperative experience for pediatric patients.[2,3] Oral midazolam and ketamine are two commonly used pre-anesthetic medications in pediatric anesthesia each with its unique pharmacological properties and clinical applications. Oral midazolam, a benzodiazepine, is widely recognized for its anxiolytic, sedative, and amnesic properties. It acts by enhancing the inhibitory effects of gamma-aminobutyric acid (GABA) in the central nervous system, leading to sedation and anxiolysis. Typical dosages for pediatric patients range from 0.5 to 0.75 mg/kg, with studies demonstrating its effectiveness in reducing anxiety and facilitating smoother induction of anesthesia.[4,5] Midazolam is well-tolerated with a relatively short onset of action and minimal side effects, making it a preferred choice for pediatric premedication.[6]

On the other hand, oral ketamine, an NMDA receptor antagonist is known for its dissociative anesthetic properties, providing profound analgesia and sedation. Ketamine's unique mechanism of action and its ability to maintain cardiovascular stability make it an attractive option for certain pediatric patients, especially those undergoing painful procedures. Typical dosages range from 3 to 6 mg/kg, and it has been shown to be effective in providing sedation and anxiolysis, although with a different side effect profile compared to midazolam.[7,8] However, ketamine is associated with a higher incidence of adverse effects such as nausea, vomiting, and emergence phenomena, which can complicate its use in pediatric anesthesia.[9]

Comparative studies between oral midazolam and ketamine have provided valuable insights into their relative effectiveness in terms of sedation quality, anxiolysis and patient cooperation. A randomized study comparing midazolam (0.5 mg/kg) and ketamine (5 mg/kg) demonstrated that midazolam provided better sedation and anxiolysis, resulting in easier separation from parents and smoother induction of anesthesia.[10] Another study comparing the two drugs found that the combination of midazolam and ketamine resulted in superior anxiolysis and behavior during parental separation and venipuncture compared to either drug alone, with midazolam showing better results when used individually.[11] Additionally, a review of various premedication regimens concluded that midazolam is generally associated with fewer adverse effects such as nausea and vomiting, making it a safer option for pediatric patients.[12] Safety profiles of these medications are critical considerations in pediatric anesthesia. Midazolam has been associated with fewer adverse effects compared to ketamine which has a higher incidence of complications such as oxygen desaturation requiring supplemental oxygen. For instance, a study evaluating the combination of midazolam and ketamine for sedation in children found that the addition of midazolam led to an increased incidence of oxygen desaturation events but a decreased incidence of vomiting compared to ketamine alone.[13] Another study reported that midazolam provided better anxiolysis and had fewer side effects such as tachycardia and secretions compared to ketamine, highlighting its favorable safety profile.[14] The need for effective premedication strategies in paediatric cardiac patients is particularly pressing at Bangladesh Shishu Hospital & Institute, where optimizing patient outcomes is paramount. This study aims to compare the effectiveness, safety and patient outcomes associated with oral midazolam and oral ketamine as pre-anesthetic medications in paediatric cardiac patients. By leveraging insights from previous research, this study seeks to identify the optimal premedication regimen that can enhance patient safety, reduce preoperative anxiety and improve overall perioperative outcomes for this vulnerable population.

Materials and Methods

The study was a prospective randomized double-blind clinical trial conducted over the period from January 2023 to November 2023 at the paediatric cardiac patients at Bangladesh Shishu Hospital & Institute. The study included a sample size of 50 paediatric patients scheduled for elective cardiac surgery with patients randomly assigned to one of two groups: Group A receiving oral midazolam and Group B receiving oral ketamine as pre-anaesthetic medication. Inclusion criteria were children aged 3-12 years, undergoing elective cardiac surgery and having no known allergies to the study drugs. Patients with neurological disorders, significant hepatic or renal impairment, and those who had received pre-anesthetic medication within 24 hours before surgery were excluded. Both medications were administered orally 30 minutes before anaesthesia induction with dosages determined based on body weight: 0.5 mg/kg for midazolam and 5 mg/kg for ketamine. The primary outcome measure was the level of sedation, assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale. Secondary outcomes included ease of parental separation, mask acceptance and occurrence of adverse effects, assessed by a blinded observer. Data was analysed in SPSS version 26. Informed consent was secured from the parents or guardians of all participants.

Results

The study included 50 pediatric patients scheduled for elective cardiac surgery, equally distributed between Group A (midazolam) and Group B (ketamine). The mean age of patients in Group A was 7.4 ±2.5 years, while Group B had a mean age of 7.6±2.3 years, with both groups ranging from 3 to 12 years. The gender distribution was fairly balanced with 56% males and 44% females in Group A and 52% males and 48% females in Group B, resulting in an overall distribution of 54% males and 46% females. Regarding weight, the mean weight for Group A was 22.3±5.4 kg and for Group B was 21.8±5.1 kg, with the combined mean weight of the study population being 22.1±5.2 kg. The American Society of Anesthesiologists (ASA) physical status classification indicated that 72% of patients in Group A were classified as ASA I compared to 68% in Group B. Conversely, 28% of Group A and 32% of Group B were classified as ASA II leading to an overall distribution of 70% ASA I and 30% ASA II across the study population (Table I).

Table I

Distribution of study population based on demographic and clinical characteristics of study participants (N: 50)

Characteristic	Group A (Midazolam)	Group B (Ketamine)	Total
Number of Patients	25	25	50
Age (years)			
Mean±SD	7.4±2.5	7.6±2.3	7.5±2.4
Range	3-12	3-12	3-12
Gender			
Male n (%)	14(56)	13(52)	27(54)
Female n (%)	11(44)	12(48)	23(46)
Weight (kg)			
Mean ±SD	22.3±5.4	21.8±5.1	22.1±5.2
ASA Physical Status			
I n (%)	18(72)	17(68)	35(70)
II n (%)	7(28)	8(32)	15(30)

The sedation levels of the study population, assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale, were distributed as follows. In Group A (midazolam), 2 patients (8%) achieved deep sedation (score 1), compared to 1 patient (4%) in Group B (ketamine), with a P-value of 0.34 indicating no significant difference. Moderate sedation (score 2) was observed in 5 patients (20%) in Group A and 4 patients (16%) in Group B, with a P-value of 0.71, showing no significant difference between the groups. Mild sedation (score 3) was reported in 10 patients (40%) in Group A and 8 patients (32%) in Group B, with a P-value of 0.52. Minimal sedation (score 4) was noted in 6 patients (24%) in Group A and 7 patients (28%) in Group B, with a P-value of 0.76, indicating no significant difference. Finally, 2 patients (8%) in Group A and 5 patients (20%) in Group B were alert (score 5), with a P-value of 0.21. These results suggest that both midazolam and ketamine provided comparable levels

of sedation in pediatric cardiac patients with no statistically significant differences observed in any of the sedation levels assessed by the MOAA/S scale (Table II).

Table II
Distribution of study population based on sedation levels using MOAA/S scale (N: 50)

MOAA/S scale Score	Group A (Midazolam) n=25	Group B (Ketamine) n=25	p value
1 (Deep Sedation)	2	1	0.34
2 (Moderate)	5	4	0.71
3 (Mild)	10	8	0.52
4 (Minimal)	6	7	0.76
5 (Alert)	2	5	0.21

The ease of parental separation among the study population was evaluated, revealing the following distributions. In Group A (midazolam), 18 patients (72%) experienced easy separation from their parents, compared to 15 patients (60%) in Group B (ketamine), with a P-value of 0.43, indicating no significant difference. Moderate ease of separation was reported in 5 patients (20%) in Group A and 6 patients (24%) in Group B, with a P-value of 0.73. Difficult parental separation occurred in 2 patients (8%) in Group A and 4 patients (16%) in Group B, with a p value of 0.38 (Table III).

Table III
Distribution of study population based on ease of parental separation (N: 50)

Ease of separation	Group A (Midazolam) n=25	Group B (Ketamine) n=25	p value
Easy	18	15	0.43
Moderate	5	6	0.73
Difficult	2	4	0.38

The distribution of mask acceptance among the study population was as follows. In Group A (midazolam), 16 patients (64%) had excellent mask acceptance, compared to 14 patients (56%) in Group B (ketamine), with a P-value of 0.55, indicating no significant difference. Good mask acceptance was observed in 6 patients (24%) in Group A and 7 patients (28%) in Group B, with a P-value of 0.74. Fair mask acceptance was reported in 2 patients (8%) in Group A and 3 patients (12%) in Group B, with a p value of 0.64. Poor mask acceptance occurred in 1 patient (4%) in both groups, resulting in a p value of 1.00 (Table IV).

Table IV
Distribution of study population based on mask acceptance (N: 50)

Mask acceptance	Group A (Midazolam) n=25	Group B (Ketamine) n=25	p value
Excellent	16	14	0.55
Good	6	7	0.74
Fair	2	3	0.64
Poor	1	1	1.00

The occurrence of adverse effects among the study population was assessed, revealing the following distributions. In Group A (midazolam), 1 patient (4%) experienced nausea, compared to 3 patients (12%) in Group B (ketamine), with a P-value of 0.29, indicating no significant difference. Vomiting was reported in 2 patients (8%) in Group A and 4 patients (16%) in Group B, with a P-value of 0.38. Agitation was observed in 3 patients (12%) in Group A and 5 patients (20%) in Group B, with a P-value of 0.44. Respiratory depression occurred in 1 patient (4%) in Group B, while no patients in Group A experienced this adverse effect, resulting in a p value of 0.31. Other adverse effects were noted in 1 patient (4%) in Group A and 2 patients (8%) in Group B, with a p value of 0.55 (Table V).

Table V
Distribution of study population based on adverse effects (N: 50)

Adverse effect	Group A (Midazolam) n=25	Group B (Ketamine) n=25	p value
Nausea n (%)	1 (4)	3 (12)	0.29
Vomiting n (%)	2 (8)	4 (16)	0.38
Agitation n (%)	3 (12)	5 (20)	0.44
Respiratory Depression n (%)	0 (0)	1 (4)	0.31
Other n (%)	1 (4)	2 (8)	0.55

Discussion

The primary objective of this study was to compare the effectiveness and safety profiles of oral midazolam and oral ketamine as pre-anesthetic medications in paediatric cardiac patients at Bangladesh Shishu Hospital & Institute. Our findings demonstrate that both medications provide comparable sedation levels and ease of parental separation, with no statistically significant differences in mask acceptance and adverse effects, corroborating the results of several previous studies. In our study, the mean age, gender distribution, and ASA physical status of the two groups were well-matched, ensuring a balanced comparison. The sedation levels, assessed using the MOAA/S scale, revealed that deep sedation (score 1) was achieved by 8% of patients in the midazolam group and 4% in the ketamine group, with no significant difference (p=0.34). Moderate sedation (score 2) was observed in 20% of the midazolam group and 16% of the ketamine group (p=0.71), while mild sedation (score 3) was reported in 40% and 32% of the midazolam and ketamine groups, respectively (p=0.52). Minimal sedation (score 4) occurred in 24% of the midazolam group and 28% of the ketamine group (p=0.76). These results are consistent with previous studies that reported similar sedation profiles for both medications, indicating their effectiveness in achieving the desired sedation levels for pediatric patients.[13,15] Parental separation, an important factor in pediatric anesthesia, was easy for 72% of the midazolam group and 60% of the ketamine group, with no significant difference (p=0.43). Moderate ease of separation was reported in 20% of the midazolam group and 24% of the ketamine group (p=0.73), while difficult separation occurred in 8% and 16% of the midazolam and ketamine groups, respectively (p=0.38). These findings are in line with the study by Zarei et al[16], which found that midazolam and dexmedetomidine were more effective in easing parental separation compared to ketamine. Mask acceptance, a critical aspect of anesthesia induction, was excellent in 64% of the midazolam group and 56% of the ketamine group (p=0.55), good in 24% and 28% of the midazolam and ketamine groups, respectively (p=0.74), fair in 8% and 12% (p=0.64), and poor in 4% of both groups (p=1.00). These results are comparable to those reported by Oliveira Filho et al[17], who found no significant differences in mask acceptance between midazolam and ketamine. Regarding adverse effects, nausea occurred in 4% of the midazolam group and 12% of the ketamine group (p=0.29), vomiting in 8% and 16% (p=0.38), agitation in 12% and 20% (P=0.44), respiratory depression in 0% and 4% (p=0.31) and other adverse effects in 4% and 8% (p=0.55). These findings suggest that both medications are generally well-tolerated with ketamine associated with a higher, though not significant, incidence of nausea, vomiting and agitation. Wathen et al[13] and Agarwal et al[18] reported similar findings, noting that ketamine alone had a higher incidence of vomiting, whereas the addition of midazolam increased oxygen desaturation events. Our study's results are consistent with previous research, such as the studies by Cheuk et al[19] and Erk et al[20] which reported similar adverse effect profiles for midazolam and ketamine, including tachycardia, increased secretions, and hallucinations. Furthermore, the study by Ren[21] highlighted the safety of combining midazolam with ketamine, reporting lower incidences of postoperative dysphoria, nausea and vomiting compared to ketamine alone. These findings support the continued use of both medications in clinical practice allowing anesthesiologists to choose the most appropriate premedication based on individual patient needs and clinical scenarios.

Conclusion

This study demonstrates that both oral midazolam and oral ketamine are effective and safe pre-anesthetic medications for pediatric cardiac patients. Our findings reveal no significant differences in sedation levels, parental separation ease, mask acceptance or the incidence of adverse effects between the two groups. While both medications were generally well-tolerated, ketamine was associated with a higher though not statistically significant, incidence of nausea, vomiting and agitation.

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