Original Article

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Comparison of Intranasal Ketamine with Midazolam as Premedication in Children

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Author`s Contribution

[1,4]Substantial contributions to the conception or design of the work; or the acquisition, Active participation in active methodology, [2]analysis, or interpretation of data for the work, [3,5,6]Drafting the work or revising it critically for important intellectual content

Funding Source: None
Conflict of Interest: None

Received: June 28, 2024
Accepted: Nov 09, 2024

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ABSTRACT

Objective: To compare the efficacy of Ketamine and Midazolam in terms of early sedation, with better five-point sedation scores, easy intravenous access, recovery time, and safety in terms of hemodynamic stability, and minimum complications rate when administered intranasal for pediatric premedication.

Methodology: This randomized clinical trial was conducted in Department of Anesthesia, Sahiwal Teaching Hospital form March 2023 to February 2024. Total 132 patients aged 2-10 years with ASA physical statuses I or II scheduled for elective surgery under general anesthesia. They were randomly assigned to Group K (n=66) receiving 3mg/kg of ketamine and Group M (n=66) receiving 0.1mg/kg of midazolam 30 minutes before anesthesia induction, administered intranasally.

Results: Most patients in both groups had an alert five-point sedation scale, 22 (33.3%) and 22 (33.3%). (p=0.644). The mean onset of sedation for the ketamine and midazolam groups was 14.72±2.01 and 11.43±1.34, respectively, (p<0.001). The most common venipuncture score in the ketamine and midazolam group was grade II, 27 (40.9%) and 39 (59.1%), respectively. (p=0.012). In the ketamine and midazolam groups, the readily was the most common acceptance of mask before induction, 31 (47.0%) and 36 (54.5%), respectively, (p=0.362).

Conclusion: Midazolam is a better choice for premedication as its rapid onset of sedation characterizes it and facilitates smooth intravenous access with minimal resistance, ensuring patient hemodynamic safety. Additionally, it is associated with a short recovery time and fewer side effects, representing its safety profile.

Keywords: Pediatrics, Premedication, Midazolam, Ketamine, Intranasal administration.

Cite this article as: Riaz A, Mumtaz M, Tariq H, Shahid M, Mohsin MU, Umair HM. Comparison of Intranasal Ketamine with Midazolam as Premedication in Children. Ann Pak Inst Med Sci. 2024; 20(4):722-726. doi. 10.48036/apims.v20i4.1336

Introduction

In pediatric anesthesia, managing anxiety and psychological trauma is important due to the impact it has on post-operative behavioral changes and recovery.[1] The fear associated with the operating room, injections, doctors, and separation from parents before anesthesia can lead to traumatic experiences for young patients.[2] This anxiety triggers the stress response, causing an increase in stress hormones like cortisol and epinephrine, which can affect hemodynamics and recovery rates.[3]

Various pharmacological and non-pharmacological techniques have been suggested as preoperative anxiolytics.[4] Commonly used premedications in children include midazolam, fentanyl, sufentanil, ketamine, dexmedetomidine, clonidine, meperidine, and promethazine. These medications can be administered via different routes such as oral, intramuscular, rectal, intravenous, or intranasal[5]. Intranasal administration is particularly advantageous in pediatric patients as it is practical, simple, painless, and avoids the need for intravenous access, especially in combative children.[6]

Ketamine, an N-methyl-d-aspartate receptor antagonist, is known for its sedative and analgesic properties.[7] It has a rapid nasal absorption time of 2 minutes and a bioavailability of 45%, with onset of action within five minutes and peak blood levels reached after 30 minutes. Midazolam, a water-soluble benzodiazepine with amnesia and anxiety-reducing effects, is also commonly used for premedication.[8]

Intranasal midazolam has a quick onset of action and brief duration, making it useful for conscious sedation.[9] Avoiding first-pass hepatic metabolism maximizes its systemic bioavailability, typically peaking in plasma concentrations after 10 minutes. Prescription drugs, including intranasal midazolam and ketamine, can effectively reduce anxiety and facilitate separation from parents in pediatric patients.[10]

The better drugs can be assessed by using a five-point sedation score and venipuncture score with complications and recovery time. The five-point sedation scale includes scores from 1-5, ranging from alert (score 1) to unresponsive (score 5). Sedation reduces natural activity in three parts of the brain (brainstem, thalamus and cortex. Benzodiazepines and their derivatives act on alpha or GABA receptors, enhance their inhibitory response and delay arousal.[11]

Venipuncture scoring was designed to evaluate the ease of intravenous access, which depends upon the visibility and palpability of the vein, along with the age, obesity, and hydration status of patients. Reduced vein size, too much fat, and reduced skin elasticity due to dehydration can cause difficulty in venous access. Vasoconstriction, oedema, or scarring can further impair access, requiring tailored techniques and tools for success.[12]

Several studies have explored the comparative efficacy of intranasal (IN) ketamine and midazolam, reporting mixed results[13,14.] These studies have predominantly focused on procedures other than intravenous (IV) access. We hypothesized that IN ketamine, administered at a dose of 3 mg/kg, is as clinically effective as IN midazolam in facilitating IV-line access in children. To test this hypothesis, we conducted a study to investigate and compare the clinical efficacy of sedation and analgesic effects of IN ketamine and midazolam in achieving successful peripheral IV access in pediatric patients.

Methodology

This randomized clinical trial was conducted in Department of Anesthesia, Sahiwal Teaching Hospital form March 2023 to February 2024. Total 132 patients aged 2-10 years with ASA physical statuses I or II scheduled for elective surgery under general anesthesia, randomly assigned to Group K (n=66) receiving 3mg/kg of ketamine and Group M (n=66) receiving 0.1mg/kg of midazolam 30 minutes before anesthesia induction, administered intranasally. Vital signs were monitored, and an anesthetist was present throughout. Patients were maintained on room air, with oxygen administered if needed. Sedation score, oxygen saturation, pulse rate, response to venipuncture, and mask acceptance were evaluated before induction. Anesthesia was induced with propofol, intubation with suxamethonium, and maintained with atracurium, isoflurane, and nitrous oxide. Paracetamol was administered intravenously, and at the end of surgery, reversal agents were given, and tracheas were extubated.

Intraoperative oxygen saturation and pulse rate was recorded throughout the procedure and postoperative oxygen saturation, nausea vomiting, pulse rate also recorded. Sedation score was recorded in all patients .The degree of sedation was assessed using a five-point Sedation Scale: 1 represented being angry and clinging to a parent or crying, 2 indicated alertness without clinging, 3 denoted calmness while sitting or lying comfortably with natural eye openness, 4 meant drowsiness with responsiveness to minor stimuli while eyes were closed, and 5 indicated being asleep with eyes closed.[15]

Acceptance of intravenous cannulation was assessed on a scale of 1 to 4, with scores of 3 or 4 indicating satisfactory acceptance and scores of 1 or 2 indicating unsatisfactory acceptance. Acceptance of the face mask was evaluated as refusal, acceptance with persuasion, or readily accepting.[15]

Superiority of medication was assessed in terms of early onset of sedation and better sedation score and grading, recovery from sedation after the procedure and minimum complications.

SPSS version 27 was used for data analysis. Mean ± standard deviation were calculated for numerical variables and independent samples t test was applied to compare the mean. Frequency and percentages were calculated for categorical variables and chi-square test was applied to compare percentages. P value less than or equal to 0.05 was taken as significant.

Results

The study included 132 patients, half of whom were treated with ketamine and half with midazolam. The demographics and baseline profile are shown in Table I.

Table I: Demographics and baseline profile.

Variable	Group		p-value
	Ketamine	Midazolam	
Age (years)	7.56±1.36	8.36±1.45	0.423
Weight (kg)	13.93±2.44	13.68±2.44	0.544
HR before premedication	112.48±7.59	108.08±8.77	0.002
HR after premedication	104.17±4.92	103.30±6.16	0.375
Intraoperative HR	121.08±2.72	106.80±3.02	<0.001
Postoperative HR	112.80±6.78	111.00±7.26	0.143

Mean ± standard deviation, independent samples t test was applied.

The mean preoperative SPO2 of the ketamine and midazolam group was 97.07±2.75 and 97.01±2.56, respectively. (p=0.896). The mean SPO2 after medications of ketamine and midazolam group was 96.38±2.80 and 96.98±2.98 respectively. (p=0.232). The mean postoperative SPO2 of the ketamine and midazolam group was 98.15±3.95 and 98.16±4.15, respectively, (p=0.949). (Table II).

Table II: Comparison of SPO2 in both the groups.

SPO2	Group		p-value
	Ketamine	Midazolam	
Pre-operative	97.07±2.75	97.01±2.56	0.896
After pre-medication	96.38±2.80	96.98±2.98	0.232
Post-operative	98.15±3.95	98.16±4.15	0.949

Mean ± standard deviation, independent samples t test was applied.

Most patients in both groups had an alert five-point sedation scale, 22 (33.3%) and 22 (33.3%). (p=0.644). (Figure I).

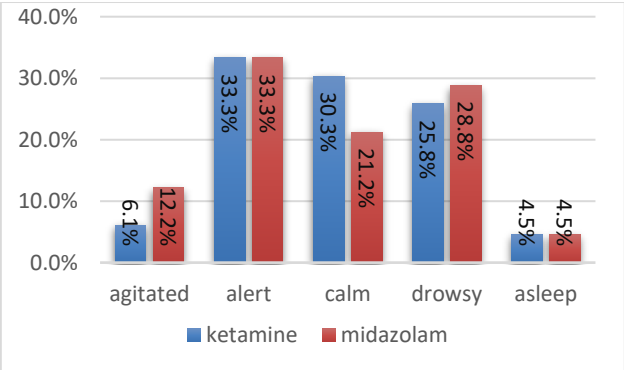

Figure I. Five-point sedation scale at 20 minutes in both the groups.

The mean onset of sedation for the ketamine and midazolam groups was 14.72±2.01 and 11.43±1.34, respectively, (p<0.001). The most common venipuncture score in the ketamine and midazolam group was grade II, 27 (40.9%) and 39 (59.1%), respectively. (p=0.012). In the ketamine and midazolam groups, the readily was the most common acceptance of mask before induction, 31 (47.0%) and 36 (54.5%), (p=0.362). Nausea/vomiting was the most common postoperative observation in ketamine 22 (33.3%), and secretions were the most common postoperative observation in midazolam 26 (39.4%) (p<0.001). The mean recovery time of the ketamine and midazolam group was 40.32±5.74 minutes and 25.63±7.85 minutes, (p<0.001). (Table III).

Table III: Comparison of onset sedation, venipuncture score, acceptance of mask before induction, and postoperative observations in both the groups.

Variable	Group		p-value
	Ketamine	Midazolam	
Onset of sedation	14.72±2.01	11.43±1.34	<0.001
Venipuncture score			
Grade I	11 (16.7)	5 (7.6)	0.012
Grade II	33 (50)	33 (50)	
Grade III	12 (18.2)	24 (36.4)	
Grade IV	10 (15.2)	4 (6.1)	
Acceptance of mask before induction			
Readily	31 (47.0)	36 (54.5)	0.362
With persuasion	21 (31.8)	22 (33.3)	
Refuse	14 (21.2)	8 (12.2)	
Postoperative complications			
Restlessness	20 (30.3)	16 (24.2)	<0.001
Emergence	17 (25.8)	24 (36.4)	
Nausea and vomiting	22 (33.3)	0 (0.0)	
Secretions	7 (10.6)	26 (39.4)	
Recovery Time	40.32±5.74	25.63±7.85	<0.001

N (%), Mean ± standard deviation, independent samples t test and chi-square test were applied.

Discussion

Numerous pre-anesthetic sedation techniques have been tried, sometimes at the expense of the child's psychological preparation for surgery. The best premedication or administration method is still unknown. Premedication in the pediatric age range is a challenging circumstance. The young children are not likely to be receptive to a logical explanation and are not fully capable of understanding the significance of their surgery. Narendra et al[15] reported a sedation score of 10.76 ± 2.0352 min in the midazolam group and 16.42 ± 2.0696 min in the Ketamine group. These findings are identical to the present study as the time of onset of sedation in the midazolam group was 11.43±1.34 min, and in the Ketamine group, it was 14.72±2.01 min.

In this study, acceptance of IV cannulation showed an insignificant P-value of 0.012, showing a statistically significant difference in response to acceptance of intravenous cannulation in both groups. In the Ketamine group, 15.2% of patients said that IV cannulations were impossible, but in the Midazolam group, only 6.1% were. Similarly, a previous study by Verma et al[16] showed the score for acceptance of intravenous cannulation for the ketamine group was 27% and for the midazolam group was 30%, which supports this study.

This study observed face mask acceptance in 47% of pediatric patients and postoperative nausea and vomiting in 33%. Research by Poonai et al. 17 reported 70% IV cannulation acceptance and vomiting in 2.2% of patients only. A study conducted by Oriby et al[18] reported that midazolam premedication has minimal side effects of nausea and vomiting, with an incidence of 13.2% in the midazolam group and 15.8% in the ketamine group.

In this study, the mean heart rate in the ketamine group was 104.17±4.92 after premedication, and in the midazolam group, it was 103.30±6.16. There was no significant difference, as p =0.37. Similar findings were reported by Jafarnejad et al[19], as the heart after premedication with Ketamine was 108.62±12.39 beats/min, and in the midazolam group, it was 107±10.37 beats/min.

In the present study, mean oxygen saturation was 96.38±2.80 in the ketamine group, and 96.98±2.98 after premedication with midazolam, but the difference was not statistically significant. These findings align with those reported by García-Velasco et al.[20] One patient in the midazolam group (2%) experienced a decrease in oxygen saturation to 90% following administration, which was successfully reversed with oxygen supplementation via a face mask.

In the present study, recovery time is 40.32±5.74 min in the Ketamine group and 25.63±7.85 min in the midazolam group. Midazolam group has a much shorter recovery time as compared to Ketamine. Khatavkar et al[21] conducted a study and reported post-operative recovery time in the Midazolam group at 23±8.17min and in the Ketamine + Midazolam group at 27.3±6.15min.

Conclusion

Midazolam is a better choice for premedication as its rapid onset of sedation characterizes it and facilitates smooth intravenous access with minimal resistance, ensuring patient hemodynamic safety. Additionally, it is associated with a short recovery time and fewer side effects, representing its safety profile.

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