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EFFECTIVENESS AND SAFETY OF INTRAVENOUS KETAMINE AND INTRAVENOUS MIDAZOLAM USE AS SEDATION AGENTS FOR PROCEDURES INVOLVING PEDIATRIC AGE GROUP

Dr Sana Ilyas[1*], Dr Inayat Ali Khan[2], Dr Abdul Sami[3], Dr Muhammad Asad khan[4], Dr Muhammad Uzair[5], Dr Khalid Khan[6], Dr Alvina Khan[7]

[1*]Postgraduate Resident MD Emergency Medicine, Dr. Ziauddin Hospital North, Karachi Pakistan. Email: sanailyas1693@gmail.com
[2]Neurosurgeon, Assistant Professor, HOD Emergency Medicine, Dr. Ziauddin Medical University Hospital Karachi Pakistan. Email: Inayatbrain@yahoo.com
[3]Senior Registrar, Emergency Medicine, Dr. Ziauddin Medical University Hospital Karachi Pakistan. Email: doctorsb78@yahoo.com
[4]Registrar, Emergency Medicine, Dr. Ziauddin Medical University Hospital Karachi Pakistan. Email: Dr.asad071@gmail.com
[5]Postgraduate MD Emergency Medicine, Ziauddin Hospital north Nazimabad Karachi Pakistan. Email: Uzair265@icloud.com
[6]Postgraduate MD Emergency Medicine, Dr. Ziauddin Hospital North Nazimabad, Karachi Pakistan. Email Khalidkhaan85@gmail.com
[7]Registrar, Emergency Medicine, Dr. Ziauddin Medical University Hospital Karachi Pakistan. Email: Khanalvina81@gmail.com

***Corresponding author:** Dr Sana Ilyas
*Email: sanailyas1693@gmail.com

ABSTRACT:

Background: In the emergency department, children are presented with pain and are at risk of developing significant anxiety due to fear of further pain. Effective sedation is essential for reducing child anxiety and pain, increasing parental satisfaction, and for successful surgical procedures.

Objective: To compare the safety and effectiveness of intravenous ketamine and midazolam as sedatives in children presented in the emergency department.

Methods: A quasi-experimental study was conducted at Ziauddin University Hospital Karachi. A total of 210 children aged 1–15 years who required surgical procedures were selected consecutively from the emergency department during the period of six months (January to June 2024). They were divided into groups of 105. 1 mg/kg of ketamine and 0.05 mg/kg of midazolam were administered intravenously in group A and B patients, respectively. Safety and effectiveness of both drugs were observed till discharge. Statistical package for social sciences (SPSS) version 24 was used for statistical interpretation of collected data.

Results: Of the total, 60.0% and 45.7% of children were male, while 40.0% and 54.3% were females in the midazolam and ketamine groups, respectively. The adverse effects were significantly higher (p-value <0.001) in midazolam group (40.0%) than ketamine group (5.7%). Similarly, median FLACC score was significantly higher (p-value <0.001) in the midazolam group (6.0) than ketamine group

(3.0). 94.3% and 92.4% of children were discharged from the emergency department, whereas 5.7% and 3.8% were admitted in the midazolam and ketamine groups, respectively.
Conclusion: Intravenous ketamine safely and effectively manage the children in the emergency department as a sedative agent.

Keywords: Ketamine, midazolam, pediatric, safety, sedative.

INTRODUCTION:

In the emergency department, children are presented with pain and are at risk of developing significant anxiety due to fear of further pain. In the past, children were the most neglected age group when it came to effective pain management. However, there has recently been considerable consideration and change in expanding pediatric pain and anxiety treatment plans and prioritizing procedural sedation and analgesia in pediatric emergency departments [1, 2].

The use of analgesic and procedural sedation has increased in pediatric health care, even for minor surgeries performed on adult patients without sedation. However, children are more likely to have adverse side effects from drugs used for both analgesia and sedation. However, selection of appropriate medicines for provision of analgesia and procedural sedation and strategies used for monitoring patients during surgical procedures are essential and should be optimized for reducing child anxiety and pain, increasing parental satisfaction, and for successful surgical procedures [3-5].

A variety of sedatives, including barbiturates, benzodiazepines, and opioids, are available in the pediatric emergency department. Ketamine, midazolam, nitrous oxide, alfentanil, and propofol are also commonly used sedatives in the pediatric emergency [6-8]. Ketamine is a safe FDA-approved sedative. It is the drug of choice in short-term clinical procedures. It inhibits the presynaptic release of glutamate, antagonises the muscarinic and nicotinic acetylcholine receptors, and acts noncompetitively at the NMDA (N-methyl-D-aspartate) receptor. Its peak intravenous concentration, which occurs within a minute, produces excellent sedation and analgesia in children. Intravenous administration of ketamine produces sedation and analgesia within one minute in children [9, 10].

Midazolam is another safe FDA-approved, short-acting benzodiazepine sedative. It competitively blocks the short-acting benzodiazepine receptor to produce sedative effects. It is widely used to induce general anesthesia in the pediatric population for diagnostic and therapeutic purposes. The two main uses of midazolam in children are conscious sedation and premedication to decrease anxiety prior to the initiation of surgical procedure [11, 12].

In Pakistan, increasing morbidity and mortality in children is a major problem for emergency physicians, as most children present with various injuries such as traumatic brain injury, sprains and fractures of upper and lower limbs, minor bruises, and lacerations. Safe and effective administration of sedation and analgesia for such injuries is critical for emergency physicians. Therefore, this study compares the safety and effectiveness of intravenous ketamine and midazolam as sedatives in children presented in the emergency department. The results of the study will help in improving the choice of analgesia and procedural sedation in children, which will ultimately lead to reduced child anxiety and pain, increased parental satisfaction, and successful surgical procedures.

METHODOLOGY:

A quasi-experimental study was conducted on the pediatric population in the emergency department of Ziauddin Medical University, North Campus, Karachi. Data were obtained from January 2024 to July 2024 for children requiring procedural anesthesia for minor surgical procedures or moderate surgical procedures. The pediatric research includes (1) children of either gender (male and female), (2) children aged 1–15 years, (3) children presented with minor or moderate lacerations secondary to trauma, (4) children with traumatic nail bed injuries such as nail removal, (5) children with traumatic joint dislocations in the absence of an underlying fracture, and (6) children with American Society of Anesthesiologists (ASA) class 1 or 2. The pediatric research excludes (1) children with deep traumatic injuries due to fractures, (2) children with traumatic injuries with neuro-vascular involvement, (3)

children with scalp deep lacerations involving connecting hematomas, (4) children with low Glasgow Coma Scale (GCS) scores, (5) children with deeply embedded foreign bodies who require surgical intervention, (6) children with difficult airways, (7) children with congenital anomalies, and (8) children with comorbidities.

According to the American College of Emergency Physicians (ACEP), procedural sedation is an approach used for administering sedatives with or without analgesics in order to attain a state in which the patient consents and tolerates the unpleasant surgical or therapeutic procedures while maintaining cardiorespiratory function. The effectiveness of intravenous ketamine and midazolam was measured using the Face, Legs, Activity, Crying, Comfort (FLACC) assessment scale for sedation. The safety of intravenous ketamine and midazolam was measured by reporting adverse effects. The final outcome of the study was treated and discharged or admitted for further treatment.

GPower software was used for sample size calculation with a sedation score of 3.29±0.78 for midazolam and 3.0±0.71 for ketamine reported by Khoshrang et al. [13]. The confidence level and power were set at 95% and 80%, respectively, to calculate a sample size of 210 (105 children in the midazolam group and 105 children in the ketamine group).

Permission for pediatric research was taken from the Hospital Research Committee and the Ethical Committee of Ziauddin University Karachi (Letter No. 0000, Date: 00-00-0000). The objectives and benefits of the research were explained to the children's parents before written informed consent was obtained. The inclusion and exclusion criteria of the research were strictly followed for the selection of children from the emergency department. Demographics, anthropometrics, and history of each child were obtained. The vitals of each child were measured, followed by physical examination. The cardiopulmonary health status of each child was continuously monitored. Selected children were distributed into two groups, i.e., the midazolam group and the ketamine group. In the midazolam group, children received the dose of 0.05 mg/kg, while in the ketamine group, children received the dose of 1 mg/kg. The dose of both drugs depends on the clinical status of the child and was decided by an emergency physician. The effectiveness of intravenous ketamine and midazolam was measured using the FLACC assessment scale for sedation. The safety of intravenous ketamine and midazolam was measured by observing adverse effects. Each child was followed till discharge from the emergency department for the final outcome of the study, i.e., treated and discharged or admitted for further treatment. SPSS version 24 was used for statistical interpretation of collected data. Chi-square test/Fisher`s exact test and independent sample t-test/Mann-Whitney U test was applied for comparing quantitative and qualitative variables between the midazolam and ketamine groups. A P-value of equal or less than 0.05 was used for statistical significance.

RESULTS:

Of the 210 children, 60.0% and 45.7% were male, while 40.0% and 54.3% were females in the midazolam and ketamine groups, respectively. The median (IQR) of age was 7.0 (7.0) years and 8.0 (5.5) years in the midazolam and ketamine groups, respectively. Most of the children were presented in the emergency department with falls (61.0% and 71.4%), followed by road traffic accidents (35.2% and 18.1%) in the midazolam and ketamine groups, respectively. Most of the children were managed in the emergency department by laceration repair (96.2% and 88.6%), followed by fracture repair (3.8% and 11.4%) in the midazolam and ketamine groups, respectively [Table 1]. The vitals of the children were normal and similar in the midazolam and ketamine groups [Table 2].

Administration of repeated doses of midazolam was significantly (p-value = 0.001) higher than ketamine (24.8% and 7.6%). Similarly, adverse effects were significantly (p-value <0.001) higher in midazolam than ketamine (40.0% and 5.7%). The most commonly reported adverse effect was headache/dizziness in the midazolam group (n = 18) and in the ketamine group (n = 4), followed by irritability in the midazolam group (n = 13) and in the ketamine group (n = 2), and nausea/vomiting reported in only the midazolam group (n = 11). Reassessed after thirty minutes of administration of midazolam and ketamine and post-sedation shows that all the patients were stable. 94.3% and 92.4%

of children were discharged from the emergency department, whereas 5.7% and 3.8% were admitted in the midazolam and ketamine groups, respectively [Table 3].
The median (IQR) FLACC score was significantly higher (p-value <0.001) in the midazolam group than the ketamine group [6.0 (2.5) and 3.0 (2.0)], indicating higher sedation with ketamine than midazolam [Table 4].

Table 1: Demographics and History of Children in Midazolam & Ketamine Group

Variables		Group Midazolam (n=105)	Group Ketamine (n=105)	P-Value
Gender	**Male**	63 (60.0%)	48 (45.7%)	0.038
	Female	42 (40.0%)	57 (54.3%)	
Age (Years)	**Median (IQR)**	7.0 (7.0)	8.0 (5.5)	0.536
	1-5	39 (37.1%)	35 (33.3%)	0.765
	6-10	39 (37.1%)	44 (41.9%)	
	11-15	27 (25.7%)	26 (24.8%)	
Height (m)	**Median (IQR)**	1.2 (0.4)	1.3 (0.3)	0.676
Weight (Kg)	**Median (IQR)**	25.0 (24.5)	27.0 (21.0)	0.439
History	**Fall**	64 (61.0%)	75 (71.4%)	0.007
	RTA	37 (35.2%)	19 (18.1%)	
	Polytrauma	4 (3.8%)	11 (10.5%)	
Reason	**Laceration Repair**	101 (96.2%)	93 (88.6%)	0.037
	Fracture Repair	4 (3.8%)	12 (11.4%)	

IQR: Interquartile Range; RTA: Road Traffic Accident

Table 2: Median (IQR) Vitals of Children in Midazolam & Ketamine Group

Vitals	Group Midazolam (n=105)	Group Ketamine (n=105)	P-Value
Heart Rate (beats per minute)	92.0 (23.0)	92.0 (22.5)	0.936
Systolic blood pressure (mmHg)	113.0 (11.5)	112.0 (13.5)	0.753
Diastolic blood pressure (mmHg)	75.0 (11.0)	72.0 (12.0)	0.911
Respiratory Rate (breaths per minute)	16.0 (2.0)	16.0 (3.0)	0.372
Oxygen Saturation (%)	97.0 (2.0)	97.0 (1.0)	0.297

IQR: Interquartile Range

Table 3: Outcome of Children in Midazolam & Ketamine Group

Variables		Group Midazolam (n=105)	Group Ketamine (n=105)	P-Value
Repeated Doses	**Yes**	26 (24.8%)	8 (7.6%)	0.001
	No	79 (75.2%)	97 (92.4%)	
Adverse Effects	**Yes**	42 (40.0%)	6 (5.7%)	<0.001
	Nausea / Vomiting	11 (26.2%)	0 (0.0%)	
	Headache / Dizziness	18 (42.9%)	4 (66.7%)	
	Irritability	13 (31.0%)	2 (33.3%)	
	No	63 (60.0%)	99 (94.3%)	
Reassessment	**Stable**	105 (100.0%)	105 (100.0%)	---
	Unstable	0 (0.0%)	0 (0.0%)	
Post-sedation	**Stable**	105 (100.0%)	105 (100.0%)	---
	Unstable	0 (0.0%)	0 (0.0%)	
Final Outcome	**Discharged**	99 (94.3%)	97 (92.4%)	0.110
	LAMA	0 (0.0%)	4 (3.8%)	
	Admission	6 (5.7%)	4 (3.8%)	
Length of Stay (Days)	**Median (IQR)**	1.0 (0.5)	1.0 (0.0)	<0.001

LAMA: Leave Against Medical Advice

Table 4: Median (IQR) FLACC of Children in Midazolam & Ketamine Group			
FLACC	**Group Midazolam (n=105)**	**Group Ketamine (n=105)**	**P-Value**
Face	1.0 (1.0)	1.0 (0.0)	<0.001
Legs	1.0 (1.0)	1.0 (0.0)	<0.001
Activity	1.0 (0.0)	0.0 (1.0)	<0.001
Cry	1.0 (0.0)	0.0 (1.0)	<0.001
Consolability	1.0 (0.0)	0.0 (1.0)	<0.001
FLACC	6.0 (2.5)	3.0 (2.0)	<0.001
IQR: Interquartile Range			

DISCUSSION:

In pediatric emergencies, sedation is frequently used on children for both therapeutic and diagnostic operations. Children's dread and anxiety make them less obedient than adult patients, even when testing and treatments are painless. Furthermore, children frequently exhibit inexplicable symptoms and indications that lead emergency physicians to order diagnostic testing. Therefore, provision of sedation with analgesic effects is necessary in pediatric emergencies. Furthermore, a safer and more effective drug for sedation is required because emergency physicians currently deliver sedatives more frequently than anesthesiologists [13-15].

Therefore, this quasi-experimental study was conducted in children visiting emergency department of Ziauddin University Hospital Karachi in order to compare the safety and effectiveness of intravenous ketamine and midazolam as sedatives in children presented in the emergency department. The research findings will help in improving the selection of analgesia and procedural sedation in children in emergency department, which will ultimately lead to reduced child anxiety and pain, increased parental as well as children satisfaction, and successful surgical procedures.

In this study, 210 children were evaluated, out of which 60.0% and 45.7% were male, while 40.0% and 54.3% were females in the midazolam and ketamine groups, respectively. The median (IQR) of age was 7.0 (7.0) years and 8.0 (5.5) years in the midazolam and ketamine groups, respectively.

There are wide variations in the usage of sedative drugs for procedural sedation in children both domestically and internationally. The intravenous method is preferred by most anesthesiologists because it facilitates the fastest possible onset of the desired sedation. On the other hand, children who are already in pain as a result of their accident or injury should not be subjected to extra discomfort and anguish caused by the placement of an intravenous access device. The most common causes of iatrogenic needle phobia in children include previous vaccination exposure, medical procedures, or long-term illnesses that require frequent treatments. For these children, proper sedation and analgesia are necessary to avoid emotional factors that might intensify their pain perception [16-19].

In this study, 0.05 mg/kg of midazolam and 1 mg/kg of ketamine was administered intravenously in the midazolam and ketamine groups, respectively. Administration of repeated doses of midazolam was significantly (p-value = 0.001) higher than ketamine (24.8% and 7.6%) for achieving sedation.

FLACC scale is a commonly used scale for assessing sedation level in pediatric populations. This scale is developed to analyze children's discomfort by studying their facial expressions and behavioural patterns, which aid in enhancing pain treatment and sedation [20, 21]. In this study, median (IQR) FLACC score of children managed with midazolam was 6.0 (2.5) whereas median (IQR) FLACC score of children managed with ketamine was 3.0 (2.0). FLACC score was significantly high (p-value <0.001) in ketamine indicating higher sedation with ketamine than midazolam.

Midazolam and ketamine are both safe and effective drugs for procedural sedation in the pediatric population [22-24]. The adverse effects were significantly higher (p-value <0.001) in midazolam group (40.0%) than ketamine group (5.7%). The most commonly reported adverse effect was headache/dizziness in the midazolam group (n = 18) and in the ketamine group (n = 4), followed by

irritability in the midazolam group (n = 13) and in the ketamine group (n = 2), and nausea/vomiting reported in only the midazolam group (n = 11).

The study's findings indicate that intravenous ketamine and midazolam are both useful for sedation and pain management by lowering the FLACC score, although intravenous ketamine is safer and more effective than midazolam. Ketamine sedates children and successfully lowers the FLACC scores. Compared to midazolam, intravenous ketamine has a substantially reduced requirement for repeated doses for sedation and also has lower side effects.

Our study has several limitations, such as a small sample size, a single-centre study, and the risk of bias. The fact that emergency physicians who gave children intravenous ketamine and midazolam were not blinded raised the possibility of bias. Children were not monitored following their discharge from the hospital, which made it impossible for physicians to find any delayed side effects of ketamine and midazolam.

CONCLUSION:

Intravenous ketamine safely and effectively manage the children in the emergency department as a sedative agent. Ketamine sedates children and successfully lowers the FLACC scores. Compared to midazolam, intravenous ketamine has a substantially reduced requirement for repeated doses for sedation and also has lower side effects.

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