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COMPARISON OF MIDAZOLAM-KETAMINE COMBINATION WITH ORAL MIDAZOLAM IN CHILDREN AGED FROM 1 TO 6 YEARS

Abid Hussain[1], Muhammad Sohail Umerani[2], Arshad Ahmed Khan Khanzada[3], Muhammad Shamoon Umerani[4], Aqil Qayoom[5*], Ahmed Uddin Soomro[6]

[1]Abid Hussain, Anesthesiologist Department of Anesthesiology, Royal Commission Health Services Program / Royal Commission Hospital Jubail Saudi Arabia. email: anaesthesia001@gmail.com
[2]Muhammad Sohail Umerani, Consultant Neurosurgeon Department of Neurosurgery, Royal Commission Hospital Jubail Saudi Arabia. email: drumerani@yahoo.com
[3]Arshad Ahmed Khan Khanzada, Specialist Anesthesiologist Department of Anesthesiology, Tawam Hospital Al Ain UAE. email: arshadkhanzada@yahoo.com
[4]Muhammad Shamoon Umerani, 4th Year Medical Student, Al Faisal University, Riyadh, Saudi Arabia. email: shamoonsmart03@gmail.com
[5*]Aqil Qayoom, Assistant Professor / Consultant Department of Anesthesiology, Liaquat National Hospital and Medical College Karachi Pakistan. email: aqilqayoom26@gmail.com
[6]Ahmed Uddin Soomro, Associate Professor Department of Anesthesiology, Chandka Medical College Hospital @ SMBBMU Larkana Pakistan. email: soomroahmeduddin@gmail.com

***Corresponding Author:** Aqil Qayoom
*Aqil Qayoom, Assistant Professor / Consultant Department of Anesthesiology, Liaquat National Hospital and Medical College Karachi Pakistan. email: aqilqayoom26@gmail.com

ABSTRACT

Background: In paediatric anaesthesia, an important and common issue that has been reported is preoperative anxiety. It happens especially in children who are between 1 to 6 years old. Children express this anxiety in terms of crying restlessness, not cooperating in the start of anaesthesia, and not leaving their parents. Due to this, the need for more anaesthesia arises which can create behavioural problems after the surgery. In order to reduce anxiety in children before any treatment, pharmacologic premedication is used. Midazolam is one common medicine which is used for this purpose. It is a short-acting benzodiazepine which has an anxiolytic effect (reduces anxiety quickly). Combination regimens, such as Ketamine (an MNDW receptor antagonist), are used by doctors to make the sedation more effective.

Objective: To compare how well midazolam-ketamine combination works as compared to oral midazolam in children who are aged from 1 to 6 years

Study design: A randomised, prospective, and double-blind clinical study

Duration and place of study: this study was conducted in Liaquat National Hospital and Medical College Karachi from January 2024 to January 2025

Methodology: This study is a randomized, prospective, and double-blind clinical research which was performed in the Department of Anaesthesiology. There were a total of 80 children involved in this research. All of the participants were aged from 1 year to 6 years. All the children included in this research were classified as ASA (American Society of Anaesthesiologists) physical status I or II. Every patient was given general anesthesia and had elective surgeries. All 80 children were divided into two groups called group A and group B. Group A received oral midazolam 0.5 mg/kg. Group B received the same plus ketamine 3 mg/kg. SPSS version 22 was used to analyse the data. A p-value of less than 0.05 was considered significant.

Results: There were a total of 80 children included in this research. All of the participants were aged from 1 year to 6 years. All the children were divided into 2 groups called group A and group B. Group A received oral midazolam and group B received the combination of midazolam and ketamine. Both the groups had equal numbers of patients (40 patients in each group). At the time of induction, the behavioral score in group A was 2.00 while it was 1.07 in group B. At parental separation, the behavioral score in group A was 1.52 while it was 1.07 in group B.

Conclusion: In conclusion, it was revealed that the combination of midazolam with ketamine is significantly more effective as compared to oral midazolam alone.

INTRODUCTION

In paediatric anaesthesia, an important and common issue that has been reported is preoperative anxiety [1]. It happens especially in children who are between 1 to 6 years old [2]. Children express this anxiety in terms of crying restlessness, not cooperating in the start of anaesthesia, and not leaving their parents [3]. Due to this, the need for more anaesthesia arises which can create behavioural problems after the surgery [4]. Due to this, parents are not fully satisfied with their experience. Before the surgery, when the children are separated from their parents and the anaesthesia mask is put on, children get very stressed as the hospital environment is strange to them and they don't have strong coping skills [5].

In order to reduce anxiety in children before any treatment, pharmacologic premedication is used [6]. This helps in separating the children from their parents smoothly and calmly inducts anaesthesia. Midazolam is one common medicine which is used for this purpose [7]. It is a short-acting benzodiazepine which has an anxiolytic effect (reduces anxiety quickly). It also causes anterograde amnesia which means that the child will not remember any events after taking this medicine. However, enough sedation for all children is not always given through midazolam. Some children have paradoxical reactions which include not accepting the mask well and still feeling anxious.

Combination regimens, such as Ketamine (an MNDW receptor antagonist), are used by doctors to make the sedation more effective [8]. This medicine has strong analgesic effects which means it has pain relieving and strong sedative effects. Moreover, it also maintains hemodynamic stability which means the airway reflexes are working, and the blood pressure and heart rate is stable [9]. Ketamine combined with midazolam works best to make deeper sedation without causing more side effects. According to research studies, when ketamine and midazolam are used together, they give better sedation instead of using midazolam alone. This ultimately helps in separating the child from their parents easily and improves cooperation during induction [10,11].

Mostly children are given the medicine through oral route as it is easy and children also accept this route. Flavouring agents such as paracetamol syrup are added to the medicine so that it tastes better and makes it easier for the kids to take. This lowers the chances of refusal to swallow and vomiting. The interest is growing in using combination premeditation. However, there is limited research on the comparison of using midazolam with ketamine with midazolam alone in children. Therefore,

this study was performed to compare how well midazolam-ketamine combination works as compared to oral midazolam in children who are aged from 1 to 6 years.

METHODOLOGY

This study is a randomized, prospective, and double-blind clinical research which was performed in the Department of Anaesthesiology. There were a total of 80 children involved in this research. All of the participants were aged from 1 year to 6 years. All the children included in this research were classified as ASA (American Society of Anaesthesiologists) physical status I or II. Every patient was given general anesthesia and had elective surgeries. The Ethical Review committee approved this study. Every participant's parents or legal guardians were informed about this study and their written consent was also obtained.

Exclusion criteria: Children who were having drug allergies such as upper respiratory tract infections were not a part of this study. Those who had ASA grade III were also not a part of this research. Moreover, kids who had developmental disorders were also excluded.

All 80 children were divided into two groups called group A and group B. Group A received oral midazolam 0.5 mg/kg. Group B received the same plus ketamine 3 mg/kg. The total volume was adjusted to 0.5 mL/kg. To improve its taste, it was mixed with paracetamol syrup. To ensure double-blinding, an anaesthesiologist, who was not a part of assessing or observing outcomes, prepared and gave the medicines to the kids. Sedation levels were recorded after every 5 mins for a total of 20 mins. Scores of sedation that were considered acceptable were 1 or 2. After 20 mins, children were taken to the operating room separated from their parents. Parental Separation Anxiety Scale was used to assess their behaviour. Mask acceptance during the induction of anaesthesia was also recorded. Oxygen saturation and heart rate were recorded at the start and after every 5 mins for a total of 20 mins. Events such as hypoxia, vomiting, bradycardia, and medication refusal were also recorded.

SPSS version 22 was used to analyse the data. Continuous variables were expressed in terms of mean and SD. Student's t-test was used to compare these variables. Fisher's exact or chi-square test was used to analyze categorical variables. A p-value of less than 0.05 was considered significant.

RESULTS

There were a total of 80 children included in this research. All of the participants were aged from 1 year to 6 years. All the children were divided into 2 groups called group A and group B. Group A received oral midazolam and group B received the combination of midazolam and ketamine. Table number 1 shows the baseline and demographic features of all the participants.

Table No. 1:

Parameters	**Group A (n=40)**	**Group B (n=40)**
Gender		
● **Male**	16	26
● **Female**	24	14
Age (yrs in mean)	3.13	2.73
Weight (kg in mean)	14.12	13.49

Table number 2 compares the sedation scores between both the groups. All the values are expressed in terms of mean.

Sedation Scores		
Time (Min)	**Group A (n=40)**	**Group B (n=40)**
Before pre-med	3.27	2.59
0	3.27	2.10
5	3.32	1.97
10	3.20	1.71
15	2.30	1.77
20	1.97	1.53

At the time of induction, the behavioral score in group A was 2.00 while it was 1.07 in group B. At parental separation, the behavioral score in group A was 1.52 while it was 1.07 in group B.

Table number 3 compares the heart rate between both the groups. Table No. 3:

Heart Rate (bpm)		
Time (Min)	**Group A (n=40)**	**Group B (n=40)**
Before pre-med	103.16	104.00
0	103.41	105.69
5	102.79	107.16
10	102.69	108.52
15	98.54	100.34
20	102.55	99.87

DISCUSSION

Preoperative anxiety is a very common challenge in children who are aged between 1 to 6 years and need anaesthesia [12]. Children express this anxiety in terms of crying restlessness, not cooperating in the start of anaesthesia, and not leaving their parents. Due to this, it becomes difficult for the induction of anaesthesia to take place properly and also affects recovery after the treatment [13,14]. In order to reduce anxiety in children before any treatment, pharmacologic premedication is used. This helps in separating the children from their parents smoothly and calmly inducts anaesthesia [15]. In this research, we examined how well midazolam-ketamine combination works as compared to oral midazolam in children who are aged from 1 to 6 years. According to the results of our study, the better way is the combination of midazolam and ketamine because it allows the children to stay calm, improve behaviour, have deeper sedation, and treat them smoothly.

It was reported that kids have lower sedation scores at 5, 15, and 20 mins after receiving the combination of midazolam and ketamine as compared to those who only received midazolam. This means the combination kept the kids more sedated for a longer time and worked faster. The results

of our study were similar to another study which was conducted by Funk et al. They found that the combination of midazolam with ketamine leads to deeper sedation [16]. Similarly, Ghai et al. also revealed that the combination of ketamine with midazolam provides better cooperation during anaesthesia induction and better anxiety relief [17].

Children from group B showed better behaviour during the separation from their parents and accepting anaesthesia mask. This shows that the combination of midazolam and ketamine is really helpful in reducing anxiety before the treatment. This combination is important especially for young kids because they are more emotionally attached with their parents and are highly sensitive and reliable on their parents [18]. Even if the dose given to the kid is low, oral ketamine still causes dissociative sedation which means the kid appears calm with normal breathing and airway reflexes [19].

Group B showed significant increase in heart rate at 5, 10, and 20 minutes. It is because of ketamine's known stimulant effects. However, these increases didn't require any treatment as they stayed within normal limits. Darlong et al. reported that mild and short-term heart rate increases with oral ketamine which is similar to our study [20].

CONCLUSION

In conclusion, it was revealed that the combination of midazolam with ketamine is significantly more effective as compared to oral midazolam alone.

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This study was conducted without receiving financial support from any external source.

Conflict in the interest

The authors had no conflict related to the interest in the execution of this study.

Permission

Prior to initiating the study, approval from the ethical committee was obtained to ensure adherence to ethical standards and guidelines.

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