ORIGINAL ARTICLE

Comparative Assessment of anxiety relief and ease of Parental Separation in Children undergoing Herniotomy with Oral Ketamine, Midazolam, or Combined Ketamine-Midazolam Premedication before General Anaesthesia: A Randomized Controlled Study

Okeke B I[1], Usman MA[2], Kolawole IK[3], Oyedepo OO[3], Ozor CC[4]

[1]Department of Anaesthesia and Intensive Care, Federal University Teaching Hospital, Birnin-Kebbi, Kebbi State, Nigeria
[2]Department of Clinical Pharmacology & Therapeutics Federal University, Dutse, Jigawa State, Nigeria.
[3]Department of Anaesthesia University of Ilorin/University of Ilorin Teaching Hospital, Kwara State, Nigeria.
[4]Department of Anaesthesia, National Orthopaedic Hospital, Enugu, Enugu State, Nigeria.

ABSTRACT

Introduction: Premedication is important to allay anxiety, produce sedation, and facilitate the smooth induction of anaesthesia, especially in children undergoing procedures or surgeries under general anaesthesia. However, there remains debate over the optimal drug or drug combination. This study aimed to compare the effectiveness of oral ketamine or oral midazolam alone versus combination oral ketamine and oral midazolam as paediatric premedication in children undergoing herniotomy under general anaesthesia in our tertiary centre.

Methods: The study was a prospective, randomised study involving 129 consented paediatric patients aged 1 to 8 years scheduled for day surgery. Subjects were divided into three groups: group M received 0.5mg/kg of midazolam, group K received 5mg/kg of ketamine, while group K+M received a mixture of 0.3mg/kg midazolam and 3mg/kg ketamine. Sedation and ease of separation scores were measured with a 4-point sedation score and ease of separation score, respectively.

Results: The level of sedation varied significantly across the groups at all time intervals ($p < 0.001$). More subjects in the K+M group had statistically significantly better sedation and satisfactory ease of parental separation scores compared to the other groups.

Conclusion: Our study revealed that combinations of oral ketamine and oral midazolam provided a more satisfactory level of pre-operative sedation and ease of parental separation than oral midazolam or oral ketamine alone in paediatric patients undergoing herniotomy under general anaesthesia. Unavailability of the bispectral index, which hindered the proper monitoring of the depth of sedation, was a limitation in our study.

Keywords: Premedication, Midazolam, Ketamine, Oral Sedation, Paediatrics patients.

Correspondence: Dr Mohammed Adinoyi Usman, Department of Clinical Pharmacology & Therapeutics, Federal University Dutse, Jigawa State, Nigeria.
Phone number: +2348036012698
E-mail address: doctormohagcon@gmail.com

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INTRODUCTION

Patients scheduled for procedures and surgeries under general anaesthesia often exhibit profound fear and anxiety and may be uncooperative due to an unfamiliar environment, needle phobia and separation from their parents.[1,2] Preoperative anxiety is common in paediatric patients and has been reported to have a prevalence of about 50-75%[3,4] Furthermore, preoperative anxiety can result in undesirable physiological and psychological effects, such as emergence delirium, increased analgesic requirements, sleep disturbance, separation anxiety, eating problems, new-onset enuresis and aggression towards parents and caregivers, if not relieved before administering anaesthesia.[5,6]

Therefore, premedication with relevant medications is important to allay anxiety, produce sedation, and

facilitate the smooth induction of anaesthesia.[7] Several drugs have been used over the years for premedication which included ketamine, chloral hydrate, promethazine, benzodiazepines and others. However, none perfectly fulfils these ideal properties of easy acceptance, rapid onset, short duration of action and lack of significant side effects.[8–10]

This study aimed to compare the effectiveness of oral ketamine or oral midazolam alone versus the combination of both drugs as premedication in paediatric patients undergoing herniotomy under general anaesthesia in our tertiary centre.

PATIENTS AND METHODS

This prospective, randomized double-blind study was approved by the institutional review board of the University of Ilorin Teaching Hospital (UITH) and was carried out from September 2019 to August 2020. All patients from the paediatric surgical outpatient clinic aged 1 to 8 years, with an American Society of Anaesthesiologists' status (ASA classification) of I-II scheduled for day-case herniotomy under general anaesthesia were eligible for inclusion in the study. The exclusion criteria included a recent respiratory tract infection, mental disorder, obstructive sleep apnoea, severe dysfunction of the central nervous system, increased intracranial pressure, a history of ketamine or midazolam allergy or parents'/caregivers' refusal to participate in the study. Consenting parents/caregivers of all the enrolled children in the study provided written informed consent.

Subjects were randomly assigned to the three different groups using a simple randomization procedure with computer-generated allocation i.e. computer-generated random numbers were used to randomize subjects into group M (0.5mg/kg of oral midazolam), group K (5mg/kg of oral ketamine) and group K+M (0.3mg/kg oral midazolam and 3mg/kg oral ketamine). The randomization was carried out by a trained research assistant and the allocation sequence were concealed from the principal investigator by using sequentially numbered, opaque, sealed, and stapled envelopes.

Preoperative assessment was conducted at the surgical outpatient clinic by the principal investigator. A detailed history was taken from the subjects and/or their parents/caregivers and a thorough physical examination was done. The potential side effects of the study drugs and procedure were explained to the patient's parents/caregivers. Basic laboratory investigations such as urinalysis and packed cell volume (PCV) were reviewed and consent for participation in the study was obtained from the caregiver. Pre-operatively, subjects were fasted for at least 6 hours for solid foods and artificial milk, 4 hours for breast milk and 2 hours for clear fluids. The subjects were reassessed on the morning of surgery and consent for the study was revalidated from the parents/caregivers. Thereafter, subjects were transferred to the waiting area of the operating theatre, where biodata and weight were taken.

The study drug for each group was prepared in the pharmacy department using injectable ketamine (KETAMINE HCL. ROTEX medical, Germany), injectable midazolam (HYPNOVEL, ROCHE, UK), mixed with vitamin C syrup (EM-VIT-C, Emzor Pharmaceutical). The study drug was mixed with an equal volume of Vitamin C syrup (Ratio 1:1) to make them palatable to the subjects and were put in identical containers contents known only by the second research assistant.

On arrival to the operating theatre at the preoperative holding area, vital signs values for peripheral oxygen saturation, respiratory rate, non-invasive blood pressure and pulse rate were measured and recorded. The study drugs were administered by a second research assistant in the waiting area of the theatre afterwards.

The primary outcome variable was sedation as measured by 4-point sedation score (Table I)[11–13] while secondary outcome variable was ease of separation as measured with ease of separation score (Table II)[11–13]. Sedation was assessed every 10 minutes for 30 minutes before induction while ease of separation from the parent or caregiver was measured 30 minutes after the administration of the study drug. These timelines were chosen because the peak action of these drugs was approximately 30 minutes after oral administration.[7]

The sample size of 43 subjects per group was needed to achieve a power of 80% to detect a significant difference ($P < 0.05$) using sample size calculation for difference in proportions (equal-sized groups)[14] and data from the study by Oyedepo et al. in 2016.[15] Data were analysed with IBM SPSS Statistics version 20 for windows (SPSS Inc., Chicago, IL, USA). The normal distribution of numerical data was tested using the Kolmogrov-Smirnov test and presented as mean ± standard deviation or median with range depending on the skewness of the variables; and demographic data of age and weight were further categorised. For bivariate analysis, Chi-square test or Fisher's exact test where appropriate was used to compare categorical variables. Wilcoxon's rank sum test was used to compare ranked data (sedation scores). $P < 0.05$ was considered statistically significant.

Table I: Sedation score

Sedation score	Details
1	Alert
2	Awake
3	Drowsy-eyes closed, wakes up when called softly or lightly touched or eyes open spontaneously
4	Asleep-Rarely awake, needs shaking or shouting to wake up

Table II: Separation score

Separation score	Details
1	Combative-Thrashing, crying with the movement of arm and leg or resisting
2	Anxious- Apprehensive, not smiling, tentative behaviour, withdrawn
3	Calm
4	Sleeping

RESULTS

A total of 129 subjects were recruited into the study (43 per group). There was no significant difference in the gender of subjects, however there was significant difference in their age and weight as shown in Table III.

Table III: Demographic characteristics of participants across the three groups

Demographic details	K	M	K + M	P-value
Age (years)				
1-3	25 (58.1%)	35 (81.4%)	34 (79.1%)	
4-6	16 (37.2%)	5 (11.6%)	5 (11.6%)	0.020
7-8	2 (4.7%)	3 (7.0%)	4 (9.3%)	
Weight (Kg)				
1-10	9 (20.9%)	18 (41.9%)	11 (25.6%)	
11-20	32 (74.4%)	14 (32.6%)	24 (55.8%)	0.002
21-30	2 (4.7%)	11 (25.6%)	8 (18.6%)	

More subjects in the K+M group were sedated compared to the K or M group at 20 min (67.4% versus 23.3% versus 0.0%). Premedication with K+M group significantly decreased the sedation score at 20 and 30 min compared to premedication in K or M group ($P < 0.05$). (Table IV)

Table IV: Comparison of Sedation at 10, 20 and 30 minutes (n= 43 per group)

Sedation	K	M	K+M	P-value
10 minutes				
Alert	2 (4.7%)	36 (83.7%)	0 (0.0%)	
Awake	41 (95.3%)	7 (16.3%)	37 (86.0%)	<0.001
Drowsy	0 (0.0%)	0 (0.0%)	6 (14.0%)	
Asleep	0 (0.0%)	0 (0.0%)	0 (0.0%)	
20 minutes				
Alert	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Awake	33 (76.7%)	43 (100.0%)	2 (4.7%)	
Drowsy	10 (23.3%)	0 (0.0%)	29 (67.4%)	<0.001
Asleep	0 (0.0%)	0 (0.0%)	12 (27.9%)	
30 minutes				
Alert	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Awake	4 (9.3%)	21 (48.8%)	0 (0.0%)	
Drowsy	34 (79.1%)	22 (51.2%)	8 (18.6%)	<0.001
Asleep	5 (11.6%)	0 (0.0%)	35 (81.4%)	

As seen in Table V, separation score across the three groups were significant as anxiety was least in K+M group (7.0%versus18.0% versus 41.9%) ($p<0.001$). However, none of the subjects were combative across the three groups at the time of separating the subjects from their parents/caregivers.

Table V: Comparison of Separation score across the study groups (n= 43 per group)

Separation Score	K	M	K+M	P-value
Median (Range)	3(1-3)	3(1-2)	3(1-3)	0.002
Combative	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Anxious	18 (41.9%)	8 (18.6%)	3 (7.0%)	<0.001
Calm	23 (53.5%)	35 (81.4%)	30 (69.8%)	
Sleeping	2 (4.7%)	0 (0.0%)	10 (23.3%)	

DISCUSSION

In this study, the effectiveness of premedication with oral ketamine 5 mg/kg, oral midazolam 0.5 mg/kg and a combination of oral ketamine-midazolam 0.3 mg/kg plus 3mg/kg were compared in subjects scheduled for herniotomy under general anaesthesia.

The study noted a significant difference in age and weight distribution**,** introducing potential confounders such as non-linear growth patterns**,** weight-based dosing challenges**,** age-dependent metabolism and weight-dependent volume of distribution. Although researchers did not adjust for these factors, they acknowledged that age and weight could have influenced the drugs' effectiveness. Despite this, no patient experienced life-threatening side effects thirty minutes post-intervention, and no combative behaviour was reported. Consequently, the team concluded that any confounding impact of age or weight on study outcomes was likely minimal.

Our study revealed inadequate sedation within the first 10 minutes in the ketamine alone and midazolam alone groups. This could be because the onsets of action of these drugs had not yet been reached. However, six subjects (14%) were noticed to be sedated in the combination group at 10 minutes. These findings align with that from Darlong et al[16] where no patients in the ketamine or midazolam groups were sedated 10 minutes post-administration. However, in their study, three subjects in the ketamine + midazolam group did achieve sedation after 10 minutes. The sedation noticed among the combination group in both studies at 10 minutes may have occurred because of the synergistic effects of both drugs.

The present study showed that at 20 minutes, sedation scores was highest in the K + M group in concordance with the result of Darlong et al[16] and could also be accounted for by the synergistic effect of combining the two drugs to optimize their sedative-hypnotics properties. This is further attested to by the percentage of subjects sedated at 20 minutes in each group in our study, which showed that 23.3% of the subjects in the ketamine group, none in the midazolam group, and 95.3% (drowsy plus asleep) of the subjects in the combination group were adequately sedated. However, the percentages of sedated subjects in the various groups in the current study differ from the results of Amanor-Boadu et al[17] who found that 80% of subjects in their ketamine group and 60% in their midazolam group were adequately sedated at 20 minutes. Their study did not include a combination group.

The discrepancy in the findings could be attributed to the small sample size of 20 participants per group and the age distribution of the subjects in their study, who were relatively older (2-10 years) compared to the 1-8 years range in the present study. Younger subjects tend to be more anxious and less cooperative than older subjects with more advanced cognitive development. Damle et al[18] even reported a higher sedation rate of 90% for both groups in their study compared to the index study and that of Amanor-Boadu and colleagues.[17]

In this study, a sedation score of ≥3 was considered adequate, meaning that adequate sedation was achieved in both the ketamine and the combination groups at 30 minutes into the study. This finding also agrees with that of the previously cited literatures.[18,19] However, Kumar et al[20] who also used similar drug dosage with the index study reported adequate sedation in their three groups, 30mins after the study drug was administered. This may have occurred because of the age distribution of subjects used in their study that were relatively older (3-10years) with less anxiety compared to younger subjects (1-8years) used in our study. Notably, in our study, there was significant difference in age and weight distribution of subjects and should be considered in interpreting the outcomes.

The study demonstrated that combining ketamine with midazolam produced **a** synergistic sedative effect**,** particularly evident in patients who were already drowsy or sleepy**.** This ensured sedation persisted throughout the entire study period. The authors propose that this interaction stems primarily from pharmacodynamic mechanisms - that is, the complementary actions at their respective receptors—rather than from any significant pharmacokinetic alterations in drug metabolism or distribution.

The K + M group exhibited better separation scores compared to the other groups 30 minutes after drug administration, indicating the effectiveness of the low-dose combination in managing separation anxiety in children scheduled for surgery. This finding contrasts with Darlong et al[16] who observed no difference in separation scores but did report quicker separation times in their combination group, likely due to the higher ketamine dose (6 mg/kg) used in their study ($p<0.001$). Horiuchi et al[21] administered either 50 mg of ketamine via a lollipop or 0.5 mg/kg of midazolam orally to children, using a 3-point separation score, they found that the midazolam group had significantly better separation scores than the ketamine group ($p=0.017$).

The discrepancy between our study and Horiuchi's findings[21] is likely due to Horiuchi's fixed ketamine dose, which may have resulted in under-dosing for some patients, and the 3-point scoring system, which could lead to higher scores due to fewer variables.[21] Both studies agreed that the ketamine group exhibited more anxiety, consistent with ketamine's known side effects, such as abnormal body movements and restlessness. Unlike our study, Horiuchi's study did not examine a combination group of midazolam and ketamine.

In the index study, 93.1% of patients in the combination group were calm or asleep 30 minutes post-administration, compared to 58.2% in the ketamine group and 81.4% in the midazolam group. This aligns with Damle et al[18] who found that 30% of patients in the ketamine group and 80% in the midazolam group were calm at separation. Similarly, Funk et al[22] reported calm behaviour in 51% of patients in the ketamine group, 70% in the midazolam group, and 90% in the combination group. However, Amanor-Boadu and colleagues[17]

observed that all patients were calm during separation in both the ketamine and midazolam groups, likely due to the longer drug absorption time during the induction of anaesthesia in their study. Overall, midazolam's anxiolytic properties led to greater patient cooperation in the midazolam-only group in our study. Introducing ketamine alongside midazolam likely diminished midazolam's anxiety-reducing effect, thereby reducing the cooperative advantage observed with midazolam alone. Thus, co-administering ketamine and midazolam probably yields a synergistic effect exclusively in terms of sedation.

CONCLUSION

This study demonstrated that combinations of oral ketamine and oral midazolam provided more satisfactory level of pre-operative sedation and ease of parental separation than oral midazolam or oral ketamine in paediatric patients undergoing herniotomy under general anaesthesia. Hence, the study recommends oral ketamine and oral midazolam combination as a preferred option for paediatric premedication.
Unavailability of bispectral index hindered the proper monitoring of the depth of sedation was a limitation in our study.

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Conflicts of interest: The principal investigator has no conflict of interest to declare.

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