East African Medical Journal Vol. 96 No. 1 January 2019
COMPARATIVE EFFECT OF SEDATION WITH ORAL MIDAZOLAM PLUS KETAMINE VERSUS MIDAZOLAM ONLY ON PRE-OPERATIVE BEHAVIOURAL CHANGES AMONG PADIATRICS DAY CASE DENTISTRY: A PROSPECTIVE RANDOMIZED CONTROL STUDY
Abdulmalik Rakiya, Senior Resident, Department of Anaesthesia and ICU, Usmanu Danfodiyo University Teaching Hospital Garba Nadama Road, PMB 2370 Sokoto, Code 840244 Sokoto, Nigeria, Rabiu Mohammed Bashir, Senior Consultant Department of Anaesthesia, Abubakar Tafawa Balewa University Teaching Hospital Bauchi, Off. Yandoka road PMB 0117, Code 930001 Bauchi, Nigeria, Alhassan Datti Mohammed, Chief Consultant/Senior lecturer Aminu Kano Teaching Hospital, PMB 3452 Zaria Road Kano, Code 70023 Kano State Nigeria.

Correspondent author: Rabiu Mohammed Bashir, Senior Consultant Department of Anaesthesia, Abubakar Tafawa Balewa University Teaching Hospital Bauchi, Off. Yandoka road PMB 0117, code 930001 Bauchi, Nigeria, Email: rabiu3754@gmail.com.

COMPARATIVE EFFECT OF SEDATION WITH ORAL MIDAZOLAM PLUS KETAMINE VERSUS MIDAZOLAM ONLY ON PRE-OPERATIVE BEHAVIOURAL CHANGES AMONG PADIATRICS DAY CASE DENTISTRY: A PROSPECTIVE RANDOMIZED CONTROL STUDY

A. Rakiya, R. M. Bashir and A. D. Mohammed

ABSTRACT

***Introduction*: Pediatrics required conscious sedation to allay anxiety and provide optimal conditions to perform procedures. This will enhance minimal separation of the children from their parents, ease of venous access, minimizing unwarranted peri-operative behavioral and psychological stress, and minimizing movement during the procedure**

***Methodology*: This was a prospective randomized double-blind study of ASA I and II patients aged between 3-10years schedule for outpatient dental procedures. Following institutional ethics committee approval, sixty eligible patients whose parents/guardians consented were randomly divided into two groups. Group (M) received oral midazolam 0.5mg/kg alone, and group (MK) received oral midazolam 0.25mg/kg combined with oral ketamine 3mg/kg. Both study drugs were mixed in 0.2ml/kg of Lucozade Boost and administered preoperatively. Data collected included were demographic variables, ease of parental separation, and level of cooperation at intravenous cannulation, onset and duration of sedation and associated of complications.**

***Results*: Our study revealed onset of sedation was significantly faster in group M than group MK; 23.20(±2.04) vs 27.83(±2.71) minutes. P value =0.002. The duration of sedation between the two groups though different was not statistically significant (*P*- value = 0.608). Sedation scores were higher after 30mins in group M but no excessive sedation was observed. Separation of patients from parents**

and cooperation at venipuncture was significantly better among patients in group MK compared to group M (*P*-value =0.036). Intra-operatively more patients had tachycardia and tachypnea in the MK than M group.
***Conclusion*: Combination of oral midazolam-ketamine is better anxiolytic for parental separation and ease to venipuncture than oral midazolam alone.**

INTRODUCTION

Pediatric patients undergoing any surgical procedure are usually frightened and distrusting of the environment, the staff due to the sight of unfamiliar environments which them usually uncooperative..[1] Drugs with rapid onset and short duration of action are often ideal for sedation or out- patient anaesthesia, aimed at early recovery and discharge. Outpatient anaesthesia also known as ambulatory or day case anaesthesia deals with preoperative, intra operative and post-operative anaesthetic care of patients undergoing elective, same day surgical procedures.[2] proper selection, preparation and information for outpatient anaesthesia is paramount, therefore these patients need to fulfill certain criteria before they are selected for day case surgeries. These include patient's physical status: ASA class 1 and 2 are often healthy, stable and fit for outpatient anaesthesia. The patient's place of residence should not be more than an hour drive from the facility and the presence of a responsible adult for the first post-operative night care should be ascertained. The surgical procedure should not last Routine preoperative testing is not mandatory in the typical case of ASA class I and II patients. Preoperative investigation and test should be performed on an individual basis from the information obtained during preoperative assessment.[3]

Special considerations should be given to pediatric patients scheduled for day case surgery. The child should be in good health or any systemic disease must be under control. Parents of pediatric patients for day case surgery should be capable of understanding and following pre-operative and post-operative instructions related to their children. These dental procedures are usually performed as day cases using conscious sedation.

The aim of sedation in pediatric dentistry includes reducing fear and anxiety minimizing unwarranted peri-operative behavioral and psychological stress, augmenting pain control and minimizing movement during the procedure. Conscious sedation with midazolam alone or midazolam combined with ketamine can be used to allay anxiety, and these drugs have a wide margin of safety when used appropriately. They are cheap and readily available even in limited resource setting. Anxiety and pain are discomforting to the pediatric patient, the parents, and the clinician. The mere sight of a hypodemic needle by a child elicits panic, fear of pain and distrust of the clinician and lack of cooperation on the part of the child for even painless procedures. Therefore, oral route of conscious sedation especially in pediatric patients is beneficial, because it has been shown to be safe and effective with less complications[4, 5] compared to the parenteral route. It is more acceptable to the patient and requires less sophisticated equipment for the conduct of sedation, all of which can be easily accomplished in a developing country environment .Although some studies have been done but there is still limited data on the

effect of addition of oral ketamine to oral midazolam for outpatient paediatric dentistry.

The purpose of this study was to compare pre-operative behavioral changes following oral combination of midazolam with Ketamine and midazolam alone for conscious sedation during dental procedures.

METHODOLOGY

This was a prospective randomized, double blind study of sixty ASA I and II patients aged between 3 and 10 years who had dental procedures as outpatient in the department of dental and maxillofacial surgery of Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria. The hospital ethics committee's approval was obtained before commencement of the study, ASA III and above, Children whose parents/guardian decline consent to participate, Current history of respiratory tract infection, Surgeries lasting more than one hour, Patient with any CNS disorder and Patients with hypersensitivity to midazolam or ketamine were excluded. Variables assessed as behavioral changes were ease of parental separation and intravenous (IV) cannulation, presence or absence of complications. The intended procedure to be carried out on the children was explained to parents/guardians. Possible complications such as drowsiness, blurred vision, abnormal behavior and nausea and vomiting were also explained to them verbally. Written informed consent was obtained. Patient's vital signs: pulse rate, systolic and diastolic blood pressures and peripheral oxygen saturation and respiratory rate were recorded at baseline and at every 5 minutes interval after administration of the study drug. EMLA was applied on the selected area for venipuncture. Sedation was carried out with midazolam 0.5mg/kg for group M and midazolam 0.25mg/kg with ketamine 3mg/kg for group MK. Parenteral formulation of both midazolam and ketamine was used, diluted in 0.2ml/kg of a sugar based clear drink (Lucozade boost to improve palatability). The drug was administered orally, and level of conscious sedation was assessed using Modified Ramsay Sedation Score.[6] Ease of parental separation was assessed using Parental Separation Anxiety Scale thirty minutes after administration of the drug. Intravenous access was secured, and ease of cannulation was assessed using the 5-point Likert Scale.[7] Atropine 0.02mg/kg was given IV and maintained with IVF 0.18% saline/4% glucose solution. Local anaesthetic lidocaine 2% with vasoconstrictor adrenaline 1:80000(QUAYLE DENTAL) at a dose of 7mg/kg not exceeding 500mg was injected as required by the dental procedure. Two patients had top up with 0.1mg/kg of midazolam was given by IV route. Intra operative monitoring was continued up to the end of the procedure, any deviation from the normal limit of vital signs occurring as complication was noted and appropriate action taken.

At the end of the procedure patients were taken to recovery room and vital signs (RR, PR, SBP, DBP and SPO_2) were monitored by the recovery nurse every five minutes, until the patient satisfied the Modified Aldrete's scoring system.[6,7] A score of 9 was fit for discharge. Post-operative instructions were given to parent/guardian, included reporting any unusual behaviour or reactions to the hospital emergency unit immediately, and they were also advised to avoid independent ambulation and oral intake at least 2hrs after the procedure. Parents were contacted 12hrs after discharge on telephone to enquire on post-operative complication.

Data collected were analyzed using SPSS (Statistical Package for Social Sciences) Version 25. Descriptive analyses for continuous variables were presented as mean and standard deviation, while categorical variables were presented as frequency and percentages. Student T-test was used to compare difference between mean of continuous variables. Difference between proportions was assessed using chi-square test. The result of analysis was presented using tables and charts, while level of statistical significance was set at P≤0.05.

RESULTS

Table 1:

Demographic variables and outcome

Parameters	Group M (n=30) Mean(±SD)	Group MK (n=30) Mean(±SD)	P value
Age (years)	5.67 (1.93)	4.93 (2.03)	0.829
Sex (M/F) (%)	18/12 (60/40)	23/7 (77/23)	0.133
Weight	14.63 (1.75)	13.87 (2.91)	0.009
ASA status (I/II) (%)	27/3 (90/10)	29/1 (97/3)	0.306

P value ≤0.05 significant

Table 1 shows the demographic profile of patient's age, sex and ASA physical status. The age range of the patient studied was between 3-10years. Patients in both groups were comparable in age distribution, with a mean age of 5.67(±1.93) for group M and 4.93(±2.03) for group MK. P value of (0.829).

Sex distribution of patients compared for both groups revealed 18(60.0%) males and 12(40.0%) females for group M, while group MK had 23(76.7%) males and 7(23.3%) females. P value = 0.133.

Weights of the patients when compared for both groups showed a mean of 14.63(±1.75) kg for group M and 13.87(±2.91) kg for group MK.

The ASA physical status classification distribution revealed 27(90%) as ASA I and 3(10%) as ASA II for group M, while for group MK 29(97%) were ASA I and only 1(3%) was ASA II, P value of (0.306). All the four (4) ASA II patients were sickle cell disease patients who presented for dental therapy. Onset of sedation was compared between the two groups, group M had 23.20(±2.04) minutes while group MK had 27.83(±2.71) minutes. The difference was statistically significant (P =0.002).

Table 2

Behaviour score of patients at separation from parents

Behavior score	M-group (%)	MK-group (%)
1	-	-
2	19(63.3)	26(86.7)
3	1(3.3)	2(6.7)
4	10(33.3)	2(6.7)
Total	**30(100)**	**30(100)**

Patients' behavioural scores in terms of ease of parental separation and IV cannulation are depicted in Table 3 and 4 respectively. PSAS score 1 and 2 were considered satisfactory, 3 and 4 were unsatisfactory, while 5-point Likert score 3,2 and 1 were considered satisfactory,5 and 4 were unsatisfactory for ease of parental separation and ease of IV cannulation respectively.

Table 3

Behaviour of patients at puncture of iv line

Behavior score	**M-group (%)**	**MK-group (%)**
1	2(6.7)	4(13.3)
2	4(13.3)	10(33.3)
3	18(60.0)	15(50.0)
4	6(20.0)	1(3.3)
Total	**30(100)**	**30(100)**

Ease of IV cannulation was satisfactory in 24(80%) and unsatisfactory in 6(20%) for group M, while for group MK, satisfactory score was 29(96.7%) and only 1(3.3%) was unsatisfactory. This also shows a statistically significant difference with a P value of 0.050.

Table 4

Comparison of sedation and behaviour score between groups

Type of score	**M group (%)**	**MK-group (%)**	**P value**
MRSS			
Satisfactory	27 (90)	25 (83.3)	0.353
Unsatisfactory	3 (10)	5 (16.7)	
PSAS			
Satisfactory	19 (63.3)	26 (86.7)	0.036
Unsatisfactory	11 (36.7)	4 (13.3)	
Behavior score at Venipuncture			
Satisfactory	24 (80)	29 (96.7)	0.050
Unsatisfactory	6 (20)	1 (3.3)	

P value ≤0.05 significant

Table 4 compared the scores between the two groups, for sedation 27(90%) in group M were satisfactory, only 3(10%) were unsatisfactory and for group MK 25(83.3) were satisfactory while only 5(16.7%) were unsatisfactory, with P value (0.353). Ease of parental separation was 19(63.3%) and 26(86.7%) for group M and MK respectively, while 11(36.7%) and 4(13.3%) were unsatisfactory for group M and MK respectively. This was a statistically significant finding (P value = 0.036).

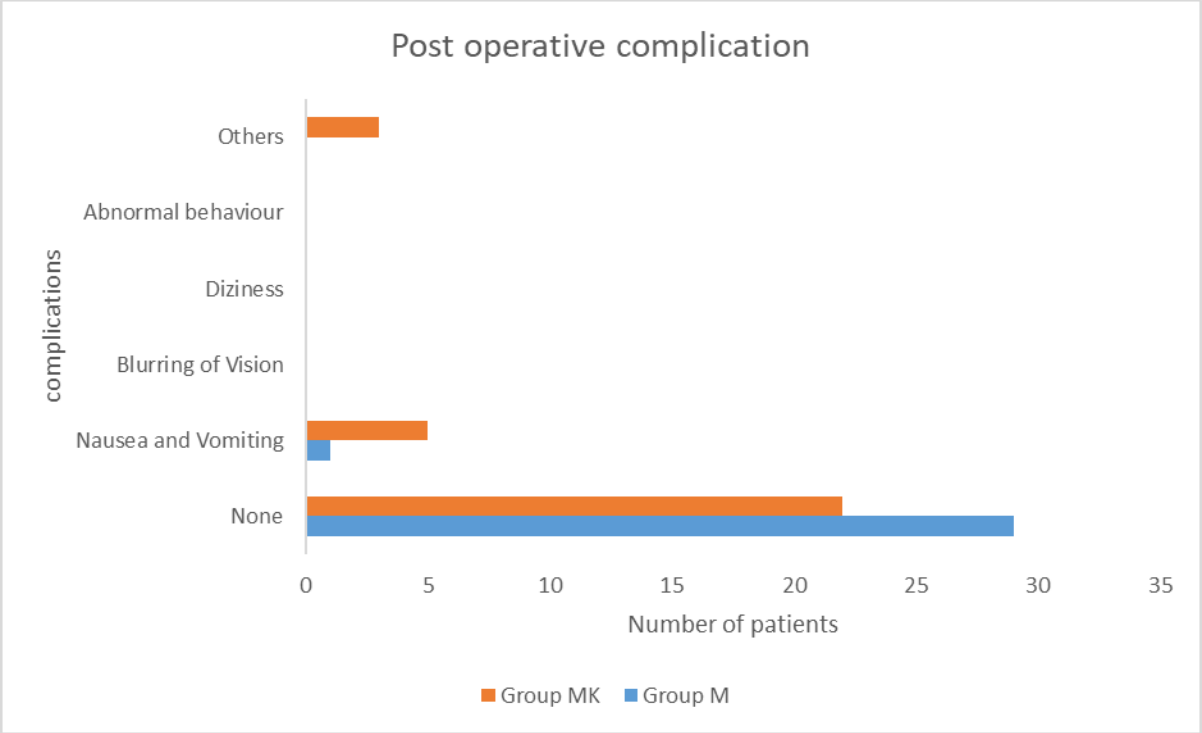

Figure I shows intra-operative complications observed between the two groups. Tachycardia occurred in 10(33.3%) in group MK, while only 5(16.7%) was seen in group M. Desaturation was seen in 5(16.7%) of patients in group MK and only 2(6.6%) in group M.

Postoperative complications consisted of nausea, vomiting and fever. Figure IV shows post-operative complications. In group MK, 5(16.7%) had nausea and vomiting, while only 1(3.3%) was seen in group M. Fever occurred in 3(10%) of patients in group MK, while none was seen in group M.

DISCUSSION

This study demonstrated that better satisfactory behavior regards to separation of patients from parents among group MK 26(86.7%) than group M 19(63.3%) of patients. Significant difference was seen when the two groups were compared. This shows that, even though less patients (83.3%) in MK group were sedated, majority of them (86.7%) were easily separated from their parents and only 4(13.4%) were not, compared to 11(36.6%) of patients in group M. The ease of separation of patients from parents was better in group MK 26(86.7%) compared to group M 19(63.3%) of patients. The difference was statistically significant when Fishers exact test was applied P=0.002. This is in agreement with findings in a similar study by Sonal et al[8] where the mean parental separation score was 2.43(±0.5) for midazolam group and 2.77(±0.4) for midazolam-ketamine group with a P value of <0.05.

In contrast to what was obtained in this study, Jyoti et al[9] studied sixty patients aged between 3-10 years undergoing surgical procedures under standardized general anaesthesia. They were assigned to two groups of 30 patients each for premedication with midazolam and midazolam-ketamine. Their study demonstrated that 93.32% of patients who received midazolam alone were

easily separated from their parents compared to 96.66% of patients who received midazolam-ketamine combination. The difference was statistically not significant (P=1.000). The researchers used a separate scale to assess anxiolysis and parental separation, with overlaps between the two scales. This might be the reason why no significant difference was seen between the groups.

In another study conducted by Rabie et al[4] that compared oral midazolam alone to oral midazolam-ketamine as premedication in children undergoing tonsillectomy, better parental separation was seen in the midazolam group 24(80.0%) compared to the midazolam-ketamine group 22(73.3%). The difference was not significant P=0.52. In their study Rabie et al[4] used a scale which does not depict what a score represents in terms of the response of patients and this may affect scoring of the patients. Debnath et al[10] compared the two drugs separately in children aged between 1-10yrs, group A received oral ketamine (6mg/kg) while group B received oral midazolam (0.5mg/kg), parenteral formulation of the drugs were used mixed with sugar. A statistically significant difference was seen between with group A who received ketamine and 90% of the patients were calm at separation from their parents, compared to 70% in group B, P<0.05. The findings in the present study are similar to that of Debnath et al[10] even though they did not combine the two drugs in their study. The presence of ketamine which causes dissociative anaesthesia in the drug combination might have accounted for achieving better parental separation conditions.

Cooperation at intravenous cannulation was also better in group MK 29(96.7%) compared to group M 24(80.0%). Similar results were obtained by Jyoti et al[9] who reported that the M group had 22(73.32%) compared to the MK group 29(96.66%). This observation might have been since EMLA cream was applied before venous cannulation in both studies.

Contrary to what was seen in this study, Damle et al[11] who studied twenty children between the ages of 2-6 years, and compared oral midazolam alone to oral ketamine alone, found that acceptance of intravenous line insertion was better in the oral midazolam group, with 40% showing minor resistance and 30% no resistance. The oral ketamine group had only 20% of patients with no resistance. The difference was also statistically significant between the two groups. These researchers[12] use a scale with a score of 4 that spanned from fight (score 1) to no reaction (score4). A modification of the scale was used in this study on a 5-Point Likert scale to include total resistance where the child will not allow even attempt at the IV cannulation. Ketamine is known to have analgesic properties. This is likely to be the reason why significant difference is seen between the two groups because EMLA was used for all the patients in both study groups.

Parents of patients were contacted the following morning after the procedure by telephone call to enquire on post-operative complications. Five patients (16.7%) had nausea and vomiting in group MK and only 1(3.3%) patient in group M. Jyoti et al[9] had only 1(3.3%) patient with vomiting in midazolam-ketamine group with none in midazolam group. Oral ketamine is likely to be responsible for the vomiting seen in midazolam-ketamine combination; this can be explained by what was obtained by Damle et al[11] where he compared oral midazolam alone to oral ketamine alone. Twenty uncooperative patients were grouped into two, group A received oral ketamine alone while group B

received oral midazolam alone. Fifty percent (50%) of patients in group A had vomiting while none was seen in group B. Debnath et al[10] in a similar study compared oral midazolam alone to oral ketamine alone. Vomiting was seen in (10%) of patients who had oral ketamine alone and none in oral midazolam group. There was no hallucination seen in both groups in this study. This is contrary to what was obtained by[13, 9] who had 1 and 3 patients with hallucination respectively. Debnath et al[10] reported increased salivation in midazolam group, which was not seen in this study. This is likely due to intravenous atropine administered to patients in both groups.

Fever was seen in 3(10%) of patients in midazolam-ketamine group, all the 3 patients had fever overnight which subsided by morning without any intervention. This is similar to what was obtained by[18], this is expected because the study area is endemic for malaria and might be the reason why fever is seen in studies conducted in the tropical area. All the other researchers[4,9, 14] who used similar drug combination, did not report fever as part of post-operative complications. Some of the limitation of this study include the diversity in dental procedures is a limitation in this study. Patients were not subjected to the same surgical procedure; some surgeries tend to be more traumatic than others, Pain was not assessed in this study, this correlate with the vital signs obtained in this study. Patients were not followed up beyond 24 hours post operatively to ascertain other complications.

CONCLUSION

This study demonstrated that combination of oral midazolam plus ketamine provide better anxiolytic compared to oral midazolam, satisfactory pre-operative parental separation, ease of intravenous cannulation with self-limiting side effects. The results of this study affirm the fact that, routine used of oral premedication with midazolam and ketamine for outpatient paediatric dentistry will continue to be popular due to encouraging desired outcomes, especially in limited resource settings.

REFERENCE

1. Abdulkareem IH. Day Case Surgery in Nigeria. Nig J ClinPrac.2011; 14(4):383-389.
2. Butterworth JF, David CM, John DW. Morgan and Mikhails: Clinical Anesthesiology, 5th Ed. Newyork: McGraw-Hill LANGE; 2013:179-182.
3. Jakobsson J. Anaesthesia for Day Case Surgery. Revised Edition; 2012.
4. Rabie ME. Combination of Oral ketamine and midazolam versus midazolam alone as a premedication in children undergoing tonsillectomy. AJAIC.2005;8(3):58-64.
5. Khatri M L. Comparative Evaluation of Oral Midazolam, Oral Ketamine And Oral Midazolam-Ketamine Combination as Conscious Sedative Agent in Uncooperative paediatric dental patients. IOSR-JDMS.2016; 15(11):31-36.
6. Adewale L. Anaesthesia for paediatric dentistry. Contin Educ Anaesth Crit Care Pain.2012; 12(6):288-294.
7. 15. American Society of Anesthesiologist. Continuum of depth of sedation: Definition of General Anaesthesia and levels of sedation/analgesia [homepage on the internet]. C 2014[updated 2014 Oct 15]. Available from http://www.asahq.org/pdfs/standards and guidelines.pdf.
8. Sonal S, Trupti P, Sameer Z, Manoj Z, Pranita K. Comparison of Oral Midazolam with Ketamine versus Oral Midazolam as Premedication in Children. International

Journal of Pharmaceutical Chemistry and Analysis.2016; 3 (2): 66-72

9. Jyoti M, Manish B, Suhas K. A double blinded comparative study of oral premedication in children with midazolam alone or in combination with ketamine. Int J Contemp Paediatr.2016; 3(3):739-746.
10. Debnath S, Pande Y. A Comparative Study of Oral Premedication in Children with Ketamine and Midazolam. Indian J Anaesth 2003;47:45-47.
11. Damle SG, Gandhi M, Laheri V. Comparison of oral ketamine and oral midazolam as sedative agent in paediatric dentistry. J Indian Soc Pedod Prev Dent 2008;26(3):97-101.
12. Benerjee B, Bose A, Pahari S, Dan AK. A comparative study of paediatric oral premedication: midazolam, ketamine and low dose combination of midazolam and ketamine. J Indian Med Assoc. 2011;109 (6):386-388.
13. Folayan MO, Faponle FO, Oziegbe EO, Adetoye AO. A prospective study on the effectiveness of Ketamine and diazepam used for conscious sedation in paediatric dental patients' management. Eur J Paediatr Dent.2014; 15(2):132-136.
14. Majidenejad S, Teherian K, Khazaei K, Samaie V. Oral Midazolam-ketamine versus midazolam alone for procedural sedation of children undergoing computed tomography: A randomized clinical trial. Emergency.2015;3(2):64-69.