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Original Article

Comparing The Effects of Ketamine-Midazolam Combination and Propofol on Sedation-Related Adverse Events and Quality of Magnetic Resonance Imaging in Pediatric Patients

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ABSTRACT

Objective: To compare the effects of Ketamine-Midazolam and Propofol on the sedation related adverse events and quality of Magnetic Resonance Imaging in pediatric patients undergoing Magnetic Resonance Imaging under sedation.
Study Design: Quasi-experimental study.
Place and Duration of Study: Department of Anesthesia, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Mar to Aug 2021.
Methodology: A total of 100 pediatric patients undergoing Magnetic Resonance Imaging under sedation were divided in to two groups, Group-A and Group-B of 50 patients each. Group-A received 1.5 mg/kg Ketamine and 0.1 mg/kg Midazolam and Group-B received 1.5mg/kg Propofol to achieve Ramsay sedation score ≥4. Bolus doses of O.50 to 1mg/kg Ketamine and 0.50- 1mg/kg Propofol were used to maintain Ramsay sedation score ≥4 during the Magnetic Resonance Imaging. Primary outcome was frequency of sedation related adverse events during Magnetic Resonance Imaging and in immediate post-sedation period. Secondary outcome was Quality of Magnetic Resonance Imaging.
Results: One (2%) patient in Ketamine-Midazolam-Group developed intraoperative hypotension versus 15(31.9) patients in Propofol -Group (p-value<0.001), which is significant. Other Intraoperative adverse effects were, bradycardia 1(2%) versus 7(14%), desaturation 0.00(0%) versus 11(23.9%), movement 4(8%) versus 3(6.4%) in Ketamine-Midazolam versus Propofol-Group with p-value of 0.020, <0.001 and 0.056 respectively. Two adverse effects seen in post-anesthesia care unit were nausea-vomiting and desaturation.
Conclusion: Ketamine-Midazolam is a better choice for sedation than Propofol due to cardiovascular stability without causing respiratory compromise and can be a useful alternative for sedation in unfamiliar environment like magnetic resonance imaging suite.

Keywords: Ketamine, Magnetic resonance imaging, Midazolam, Propofol, Sedation

How to Cite This Article: *Niazi WA, Majeed K, Saqib NU, Maqsood S, Zafar A, Ahsan A. Comparing The Effects of Ketamine-Midazolam Combination And Propofol on Sedation-Related Adverse Events And Quality of Magnetic Resonance Imaging In Pediatric Patients. Pak Armed Forces Med J 2024; 74(4): 936-941. DOI: https://doi.org/10.51253/pafmj.v74i4.9283*

INTRODUCTION

Non-Operating Room Anaesthesia (NORA) or Daily Anaesthesia is a very common but one of the most challenging aspects of administrating anesthesia.[1] Magnetic Resonance Imaging (MRI) scans, Computerized Tomography (CT) scans and endoscopic procedures are the most frequent outpatient procedures requiring anaesthesia. MRI provides a significant advantage over other imaging techniques as it does not involve exposure to ionizing radiation. Moreover, MRI provides extensive information about anatomic structures and has an important place in the diagnosis of numerous disease.[2] Paediatric MRIs, especially infants and neonates require sedation or General Anaesthesia to keep them motionless for entirety of the procedure to capture the best image quality. Most of the children requiring an MRI scan have neurological symptoms such as epilepsy and mental retardation.[3]

Anaesthetic Challenges of MRI scans range from limited airway access, inadequate monitoring, availability of specialised nonmagnetic anaesthesia machines, vaporisers and other monitoring equipment.[4,5] Ideal anaesthetic for sedation constitutes anaesthetic agent with properties like short duration of action, adequate depth of anaesthesia, hemodynamic stability, quick and smooth recovery with minimum side effect like nausea and vomiting, bronchospasm and laryngospasm.[6] Agents like Propofol , Ketamine, Midazolam are being used alone or in combination as per Anaesthetist's choice.[7] Newer

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Received: 16 Sep 2022; revision received: 05 Oct 2022; accepted: 10 Oct 2022

agents like dexmedetomidine are also popular but require adequate patient loading and are more suitable for longer outpatient procedures.[8] Propofol is a GABA agonist that can be given alone in 1-2 mg/kg dose and provides adequate depth of anesthesia with short duration of action and quick recovery but has the risk of inducing apnoea and hypotension.[9] Ketamine is NMDA receptor antagonist which causes dissociative anaesthesia and provide quick anaesthesia with hemodynamic stability and preserved airway reflexes but has risks of emesis and hallucinogenic properties. It is therefore combined with a short acting benzodiazepine like midazolam in 0.1 mg/kg dose to counter the delirium effects. Midazolam can also be given with low-dose Propofol for synergistic effect.

The aim of the study is to find out whether Ketamine-Midazolam combination or Propofol alone is a better anaesthetic choice for MRI under sedation by comparing the effect on Quality of MRI, and frequency of sedation related adverse events both during procedure and in PACU.

METHODOLOGY

The quasi-experimental study was conducted at Department of Anaesthesia at Armed Forces Institute of Radiology and Imaging (AFIRI), Pak Emirates Military Hospital, Rawalpindi, Pakistan, from March to August 2021. After approval from Hospital Ethical Committee (IERB ltr no.: A/28/EC/263I/2021), patients brought by parents in Pre-Anesthetic Assessment clinic for MRI under sedation were recruited. Using the Lawson GR study, population proportion requiring intravenous sedation was taken as 8%, the sample size was calculated utilizing WHO sample size calculator.

Inclusion criteria: Patients of either gender aged 2 to 12 years with ASA I and II status undergoing MRI under sedation were included.

Exclusion Criteria: Patients with any abnormality or disability on the basis of history, examination and lab findings were excluded.

Written informed consent was taken and to optimize the study, confounding factors are addressed in exclusion criteria. A total of 100 pediatric patients undergoing MRI under sedation were divided in to two groups using random tables, Group-A and Group-B of 50 patients each (Figure).

Magnetic resonance imaging (MRI) was performed using a 3T MRI scanner according to standard protocols. Before transferring to MRI room IV cannula 24 G (vasofix IV Catheter 24G by B/Braun) was inserted in suitable forearm vein. After intravenous access, all the Group-A patients received 1.5 mg/kg Ketamine and 0.1 mg/kg Midazolam and the Group-B patients received 1.5mg/kg Propofol. The patients were placed on MRI room table in supine position with a roller under shoulder. Standard monitoring was attached. Depth of sedation was evaluated by using 6-point Modified Ramsay sedation scale (RSS) as a guide during the procedure. A score of 4 or higher was targeted after induction dose to start the MRI. Group-A received additional aliquots of 0.5-1mg/kg Ketamine and Group-B received aliquots of 0.5- 1mg/kg Propofol for maintenance of sedation level≥ 4 during the MRI. Spontaneous respiration was confirmed before the MRI. Hemodynamic parameters including mean arterial pressure (MAP) and heart rate (HR) and peripheral oxygen saturation was performed with an MRI-compatible anesthesia monitor. Oxygen was administered continuously at 2L/min rate with face mask throughout the procedure. Due to risks of apnea (cessation of breathing >10 sec) and respiratory complications.backup emergency resuscitation equipment was kept ready including laryngeal mask, endotracheal tubes, masks, airway, pediatric laryngoscope set, sedatives, induction agents and aspirator devices.

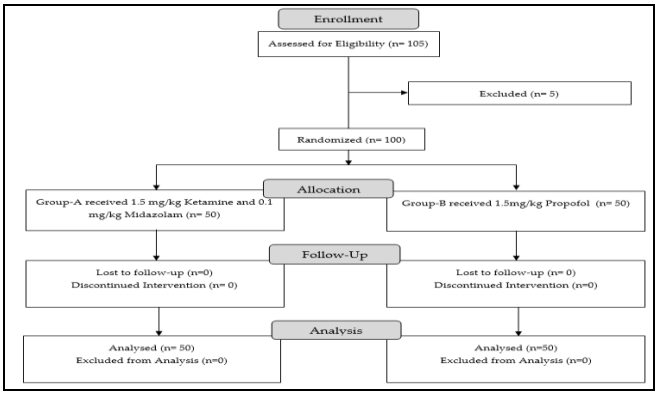

Figure: Patient Flow Diagram (n=100)

Demographic findings, total duration of sedation, duration of MRI and scanning quality were recorded for each patient. Intra-procedure adverse events i.e. hypotension, bradycardia, desaturation and movement were carefully monitored. Hypotension was defined as <20% decrease in mean arterial pressure (MAP) below the baseline and bradycardia was defined as <100 beats/min. Hypotension was treated with 5ug/kg IV boluses of phenylephrine and

20ml/kg fluid bolus.as per requirement. Bradycardia was treated with 4ug/kg IV bolus of Glycopyrrolate. Desaturation was defined as sp02 <90%. Movement of the patient during procedure was monitored visually or detected by MRI technician on the MRI scan screen. All the images were evaluated by a single radiologist. Subjective quality of the scans was evaluated using a three-grade scale: 1 = very good (perfect scanning), 2= moderate (scan completed), 3 = poor. After the procedure, the patients were transferred to the post-anesthesia care unit (PACU) and were continuously monitored for adverse events i.e. nausea and vomiting, agitation, hypotension, bradycardia or desaturation. Aldrete score was used for assessment of recovery and a score of 9 or above was used to discharged the patients for PACU. Nausea and Vomiting in PACU was treated by intravenous Ondansetron 0.15 mg/kg To adequately address the ethical issues, written informed consent was taken. Female nursing staff was present in MRI room and Post-Anesthesia Recovery for female patients during administration of sedation and shifting to recovery. All patients were ethically entitled to the treatment of post-procedure nausea and vomiting. All respondents were given due respect.

All data was entered and analyzed using Statistical Package for Social Science (SPSS) version 26. Mean and standard deviation were calculated for age, weight and other qualitative variable. Frequency and percentage were calculated for qualitative variables. Comparisons were made using chi-square test and t-test and *p*-value of ≤0.05 was considered as significant.

RESULTS

Ninety-seven out of hundred patients successfully completed study protocol. One patient in Group-B developed profound hypotension and bradycardia that's why procedure was abandoned in that patient and 2 other patients in same group had to be converted into general anesthesia due to desaturation. Rest of patients in both study groups completed the study protocol. Since those cases were not done in sedation that is why there were not included in results.One (2%) patient in Ketamine-Midazolam group developed intraoperative hypotension versus 15(31.9) patients in Propofol group (*p*-value <0.001), which is significant. Other Intra-operative adverse effects were, bradycardia 1(2%) versus 7(14%), desaturation 0.00(0%) versus 11(23.9%), movement 4(8%) versus 3(6.4%) in Ketamine-Midazolam versus Propofol Group with *p*-value of 0.020, 0.001 and 0.056 respectively. The intraoperative adverse effects were fewer with Ketamine-Midazolam group versus Propofol group despite the fact that quality of MRI was almost same in both groups. In post-anesthesia care unit, no patient developed hypotension or bradycardia. Two adverse effects were seen in post-anesthesia care unit: post-operative nausea and vomiting and desaturation. In Ketamine-midazolam group 2(4%) patients developed post-MRI nausea and vomiting = versus 2(4.3%) in Propofol group which is not significant (*p*-value 0.383) similarly 4(8%) patients developed post-operative agitation in Ketamine-Midazolam group versus 1(2.1%) in Propofol group (*p*-value 0.270) (Table-I). Demographic characteristics were analogous in both study groups which are mentioned in Table-II. There were 24(48%) females and 26(52%) males in Group-A and 20(42.6%) females and 27(57.4%) males in Group-B. The mean weight was 12.926± 3.188 kg, age 6±1.325 years, MRI time 17.37±3.977 minutes and total sedation time was 22.47±4.807 minutes.

DISCUSSION

Non-Operating Anesthesia (NORA) has always been challenging for anesthetists especially pediatric MRI. Unfamiliarity of environment coupled with the difficult handling of pediatric patients puts an anesthetist under extra pressure. Sometimes MRI compatible monitoring equipment is not yet readily available in hospitals which makes things ever more daunting.

Dalal *et al.* have reported a 13.6% incidence of respiratory events with Propofol sedation for MRI in infants.[10] Pershad *et al.* also found a 26.6% incidence of adverse events including respiratory depression and hypotension with use of Propofol infusion for pediatric MRI.[11] Boriosi *et al.*[12], Eastwood *et al.*[13] and Cravero *et al.*[14] showed that the use of Propofol alone tends to increase the incidence of sedation-related serious adverse events. In our study frequency of cardiovascular adverse events that is hypotension, bradycardia and respiratory adverse events (desaturation and apnea) was significantly higher (*p* <0.05) in Group-B receiving Propofol.Fifteen patients in Group-B developed hypotension, 10 of which developed it at induction dose of Propofol which remaining became hypotensive during the procedure. It can be attributed to the hypotensive effects of Propofol dehydration due to Nil Per Oral status. Only 1(2%) patient developed Hypotension in Group-A. The low frequency is due to the stable Hemodynamic

profile of Ketamine. 9(19.2%) Patients in Group-B developed bradycardia which can be attributed to the cardio-depressive effects of Propofol with underlying dehydration due to NPO status.

Movement during MRI is very common especially under sedation. It can be minimized by using maintenance by MRI compatible infusion pumps which are quite expensive and are not commonly available. In our study method of maintenance was additional boluses of Ketamine (0.5-1mg/kg) and Propofol (0.5-1mg/kg) and therefore frequency of movement was almost equal and comparable in both groups.

Table-I: Demographics and Sedation Scores of Both Study Groups (n=100)

Parameters		Group-A Mean±SD n=50	Group-B Mean±SD n=50	*p*-value
Age (YEARS)		2.91±1.388	2.50±1.234	0.940
Weight (KG)		13.474±3.47	12.343±2.76	0.857
Duration Of MRI (minutes)		17.48±3.732	17.26±4.260	0.635
Duration Of Sedation (minutes)		223.32±4,312	21.57±5.178	0.431
		Frequency n(%)	Frequency n(%)	
Ramsay Sedation Score During MRI	4	37(74)	15(31.9)	<0.001
	5	13(26)	32(68.1)	
Gender	Male	26(52)	27(57.4)	0.369
	Female	24(48)	20(42.6)	
ASA Status	ASA I	37(74)	35(74.5	0.572
	ASA II	13(26)	12(25.5)	

Table-II: Comparisons of Quality of MRI and Adverse Outcomes of Both Study Groups (n=100)

Parameters		Group-A Frequency (%) n=50	Group-B Frequency (%) n=50	*p*-value
Quality Of MRI	Very good	39(78)	36(76.6)	0.530
	Moderate	11(22)	11(23.4)	
Intraoperative hypotension	Yes	1(2)	15(3)1.9	0.001
	No	49(98)	32(68.1)	
Intraoperative bradycardia	Yes	1(2))	9(19.2))	0.010
	No	49(98)	38(80.9)	
Intraoperative Desaturation	Yes	0(0))	11(23.4)	0.001
	No	50(100)	36(76.6)	
Intraoperative Movement	Yes	4(8)	3(6.4)	0.093
	No	46(92)	44(93.6)	
PACU Desaturation	Yes	0(0)	1(2.1)	0.485
	No	50(100)	46(97.9)	
PACU Agitation	Yes	4(8)	1(2.1)	0.270
	No	46(92)	46(97.9)	
Frequency Of Maintaince Doses	2	42(84)	12(25.5)	0.383
	3	8(16)	24(51.1)	
	4	0(0)	11(23.4)	

Airway compromise is a known side effect of Propofol at doses>2mg /kg. Care and vigilance is required when giving induction dose for sedation as the goal is to achieve sedation without respiratory compromise. In Group-B 11(23.4%) patients developed episodes of Desaturation. Most episodes were due to episodes of apnea at induction dose for sedation. Episodes of desaturation were also witnessed during maintenance of sedation due to tongue fall and were well managed by jaw thrust and chin lift maneuvers and giving oxygen by face mask. Ketamine even when coupled with midazolam keep the airway reflexes intact and episodes of desaturation and apnea are rarely seen and same was evident in our study.

Emergence Delirium is a known side effect of Ketamine and can cause profound agitation in pediatric patients. Acworth *et al*.[15] and Dachs *et al*.[16] suggested that the addition of midazolam to Ketamine reduces the adverse effects of Ketamine such as unpleasant dreams and hallucinations. Therefore, we used Ketamine in combination with midazolam to reduce the side effects of Ketamine. In our study the Group-A receiving Ketamine and midazolam

combination 4(8%) patients developed agitation in PACU as compared to only 1 patient in Group-B. The addition of Midazolam to Ketamine at induction dose for sedation played a role in reducing the agitation and the results are comparable to that of patients receiving Propofol.

Gürcan *et al*. studied the effects of Propofol-Ketamine and Propofol-fetanyl combinations on nausea and vomiting in pediatric patients undergoing MRI. Results showed no significant difference in the incidence of nausea and vomiting in both groups.[17] Aycan *et al*. also divided pediatric patients undergoing MRI in sedation into four groups and studied the effects of various combinations of anesthetic drugs given to each groups. Results here also showed no significant difference in the incidence of nausea and vomiting in all groups.[18] In our study in both Groups A and B, 2 patients each had episode of nausea and vomiting in PACU which treated was with ondansetron 0.15 mg/kg.

Uludağ *et al*. divided the pediatric patients undergoing into two groups M-K (Midazolam-Ketamine) and M-P (Midazolam-Propofol) and studied the effects of the combination on the quality of Mri. No significant difference was found between the two and results were comparable.[19] In our study Quality of MRI was rated by using a 3 point scale. 1 = very good (perfect scanning), 2= moderate (scan completed), 3=poor. In both Groups the MRI quality varied equally between 1 and 2. No Mri scan has poor quality.

CONCLUSION

Ketamine-Midazolam is a better choice for sedation than Propofol due to cardiovascular stability and no-to little risk of respiratory compromise. It minimizes the risk of major adverse events which can be difficult to handle in a non-operating room and unfamiliar environment like MRI. Both Ketamine-Midazolam and Propofol are comparable in terms other adverse events like movement, agitation and nausea and vomiting. MRI Quality is also equally good in both groups.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MZ & SZ: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

SS & SAS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SJ: & AMK: Conception, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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