



## Sedation with Midazolam - Ketamine Versus Propofol In Children Undergoing Magnetic Resonance Imaging: A Randomized Comparative Study

Palak Garg<sup>1\*</sup>, Padam Yadav<sup>2</sup>, Susheel Kumar Saini<sup>3</sup>, Priyadarashani<sup>1</sup>, Ajay Kumar Saini<sup>4</sup>, Seema Kumari<sup>5</sup>

### Abstract

**Objective:** To evaluate the sedative effect, hemodynamics, respiratory effects, and incidence of complications of Propofol compared with Ketamine-Midazolam in children undergoing MRI examination.

**Study design:** In this prospective single-blinded randomized comparative study, conducted at the Department of Pediatrics, Artemis Hospital, Gurugram 100 children admitted for MRI on a daycare basis were included. Children were assigned in two groups randomly; 50 children in each group. One group was given Midazolam – Ketamine (Group A) while other was given Propofol (Group B) for sedation during MRI. The effectiveness of sedation during the procedure was evaluated according to the modified Ramsay sedation score (RSS). Mean arterial pressure (MAP), Heart rate (HR), peripheral oxygen saturation (SpO<sub>2</sub>), and respiratory rate (RR) were monitored continuously. All observed complications were also recorded.

**Results:** 26% of patients in group A and 20.8% of patients in group B had no movement during the examination while 74% of patients in group A and 79.2% of patients in group B had minor movement. The mean induction dose of propofol administered to the patients of group B was significantly higher than the dose of ketamine administered to group A. The recovery time of groups A was significantly higher than group B. No patients developed major complications such as cardiac arrest, apnea or laryngospasm during the procedure.

**Conclusions:** Midazolam-Ketamine was found to be better than single-dose Propofol in children undergoing magnetic resonance imaging. Although Propofol had rapid awakening after MRI but it needed more induction dose. Maintenance of sedation is a problem with single-dose Propofol as patients might need additional doses.

### Objective

Sedation and analgesia is generally required for the patients undergoing magnetic resonance imaging (MRI), computed tomography (CT) scans, angiography, and radiotherapy in the emergency setting [1–4]. The main goals of the pediatric sedation/general anesthesia are pain control, relief of anxiety, and control of excessive movement [5]. The American Academy of Pediatrics (AAP) defines the goals of pediatric sedation as follows [6]:

1. To guard the patient's safety and welfare.
2. To minimize physical discomfort and anxiety.
3. Minimize psychological trauma and maximize the potential for amnesia.
4. To control behavior and/or movement to allow for the safe completion of the procedure.

### Affiliation:

<sup>1</sup>MBBS, DNB Pediatrics, Artemis Hospital, Gurugram, Haryana

<sup>2</sup>MBBS, MD Pediatrics, Consultant, Artemis Hospital, Gurugram, Haryana

<sup>3</sup>MBBS, MD Pediatrics, FNB Pediatric Critical care, Assistant Professor, NIMS Medical College, Jaipur

<sup>4</sup>MBBS, DNB Pediatrics, SGMH, New Delhi

<sup>5</sup>MBBS, MD Anesthesiology and Critical Care, Pt. B.D. Sharma PGIMS, Rohtak, Assistant Professor, NIMS medical college, Jaipur

### \*Corresponding author:

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**Email:** palak.garg0777@gmail.com

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5. To return the patient to a state in which safe discharge from medical supervision is possible.

Nowadays the need for magnetic resonance imaging (MRI) in children is increasing for accurate diagnosis and appropriate medical treatment [6]. Sedation is required in the pediatric population as they cannot remain immobile for a sufficient length of time for a sequence to be completed. Thus necessitating the need for sedation [7]. There has been continuous debate about the use of appropriate drugs and dosage regimens for sedation during MRI in children. An ideal sedative should have a shorter induction time, should not cause hemodynamic instability and more rapid discharge from the emergency room. Several anesthetic drugs such as intravenous midazolam, dexmedetomidine, fentanyl, propofol, Ketamine and oral chloral hydrate have been used for sedation for pediatric MRI [8,9].

At our Hospital, we use intravenous Midazolam and ketamine to facilitate MRI procedures in children for years. Propofol has been used by various intensivists and anaesthesiologists commonly. As there is lack of studies to compare them. So, our study was planned to compare Ketamine plus Midazolam versus Propofol for sedation in children undergoing MRI.

## Methods

This study was conducted in the Department of Pediatric Medicine, Artemis Hospital, Gurugram, Haryana (Tertiary Health care center) from September 2018 to June 2020. A total of 100 patients between the ages 1 month and 16 years who belong to the American Society of Anaesthesiologist status 1 and 2 [10] admitted for MRI and required sedation at Artemis hospital during the study period were included.

Children whose guardians refuse to give positive consent and those who were not induced by sedative were excluded. Children having allergy to any of the drugs studied, hemodynamically instability, H/O allergy to eggs as propofol emulsion contains egg, ASA status III and above were also excluded. This study was prospective single-blinded randomized comparative study. The clinical and the demographic information were recorded on a pre-structured proforma, together with the detail history, physical and detailed systemic examination.

This study was conducted after the approval of Scientific and Ethics committee in Artemis Hospital, Gurugram, Haryana. The study was planned on 100 Children of age between 1 month to 16 years who were scheduled to undergo Magnetic resonant imaging for the diagnostic purpose at our institute. The patients were shifted to the MRI induction room accompanied by parents after a period of fasting as per fasting guidelines proposed by the American Society of anaesthesiologist [48]. The intravenous line was

secured and monitoring lines were attached which included Electrocardiogram, non-invasive blood pressure, and pulse oximetry for SpO<sub>2</sub> monitoring. Baseline heart rate, respiratory rate, NIBP and SpO<sub>2</sub> values were recorded. Drugs were given according to group assignments determined by a computer-generated number sequence and were contained in sequentially numbered opaque envelopes to ensure blinding. All the procedures were performed by the pediatric intensivist. Drugs were given according to the group assigned.

Group A-These patients received intravenous midazolam at a bolus dose 0.1 mg/kg (maximum 4 mg) along with Ketamine at bolus dose 1 mg/kg intravenously. Patient responses to verbal and tactile stimuli were evaluated 2 min after the administration of the drug. Ketamine 0.5 mg/kg (maximum of 2 mg/kg) was added at 2-min intervals if adequate sedation was not achieved.

Group B- These patients received intravenous Propofol at a bolus dose of 1 mg/kg. Patient responses to verbal and tactile stimuli were evaluated 2 min after the administration of Propofol. Propofol 0.5 mg/kg was added at 2-min intervals if adequate sedation was not achieved.

The effectiveness of sedation during the procedure was evaluated according to the modified Ramsay sedation score (RSS). A score from 1–6 was assigned according to the response of the patient to the stimuli. A score of 5 or above indicates adequate sedation [11]. RSS of 5 or above was aimed at for a comfortable procedure in our study. The imaging was initiated when the child was well sedated. Oxygen (2 l/min) by a nasal cannula /facemask was administered to all patients during the procedure. Mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO<sub>2</sub>), and respiratory rate (RR) were monitored continuously and recorded at 5-min intervals during the study period. Additional doses of Ketamine and Propofol according to the group respectively at the dose of 0.5 mg/kg was also administered in between in case of inadequate sedation if needed. The observer who collected data was not blinded to whether the patient has received Midazolam plus Ketamine or Propofol during magnetic resonance imaging. All complications were recorded. Cardiac arrest, apnea, and laryngospasm were assessed as major complications, whereas hypoxia (peripheral oxygen saturation <90% during 60 s), tachycardia (defined as 30% more than the average HR by age), bradycardia (30% less than the average HR by age), increase in oral secretions (copious oral secretions requiring suctioning), flushing, coughing, and vomiting were assessed as minor complications. In case of complications, the intervention was done by a pediatric intensivist as per protocol. The completion of the procedure without any major complications indicated the success rate of sedation.

The patients follow-up was performed in the pediatric ward after the procedure. Complications during the recovery

time such as double vision, dizziness, nausea and vomiting agitation, and emergence reactions were recorded. Recovery time was recorded. Recovery time was the time between the start of the scan and when the patient reaches a Ramsay score of 2. The quality of the MRI examination was evaluated using a three-point scale (1 = no motion; 2 = minor movement; 3 = major movement necessitating another scan).

Data was collected in Microsoft Word 2010 and Microsoft Excel 2010. The continuous data was shown as Mean +/- Standard Deviation and categorical data were represented as absolute numbers and percentages. For continuous data, the Kolmogorov-Smirnov tests were performed to assess normality and where appropriate the data was analyzed with required statistical tests and descriptive statistics. Parametric data were analyzed with student's T-Test/ Z-Test. Non-parametric data were analyzed by Kruskal Wallis test and further paired comparisons were done using the Mann Whitney U test. Nominal categorical data between the groups were compared using the Chi-square test or Fisher's exact test as appropriate and used correlation coefficient to observe the linear relationship. For all statistical tests, a p-value of less than 0.05 was taken to indicate a significant difference.

## Results

In this prospective study, 100 patients belonging to ASA physical status I or II who were admitted for MRI on a daycare basis were included. After enrollment, group assignments were determined by a computer-generated number sequence and were contained in sequentially numbered opaque envelopes to ensure blinding. A total of 100 patients were randomly allocated in 2 groups. Group A patients received Midazolam plus Ketamine combination for sedation were as Group B patients received Propofol. 2 patients were excluded from group B because of the failure of induction by Propofol and Midazolam had to be given to these patients. So total analysis was done on 98 patients -50 from group A and 48 in group B .

In our study, the mean age was  $46.07 \pm 29.92$  months in Group A and  $44.98 \pm 31.20$  months in Group B. Mean age was comparable without significant intergroup difference. There were 38% Female and 62% Male in group A while Group B consists of 33.3% Female and 66.7% male. The difference in gender distribution was not statistically significant. The average weight was  $13.60 \pm 4.71$  kg in Group A and  $13.95 \pm 6.63$  kg in Group B. Mean weight was comparable in both the groups. Average height in the current study was  $93.10 \pm 18.45$  cm in patients belonging to Group A and  $93.88 \pm 18.39$  cm in patients belonging to Group B. Mean height was comparable in both the groups.

In this study, out of 98 patients, 28 were interpreted as ASA 1 and 70 patients belong to ASA 2. In patients belonging to Group A, out of 50 patients 13 (26%) were ASA 1, and

37 (74%) were ASA 2. In patients belonging to Group B out of 48 patients, 15 (31.3%) were ASA 1 and 33 (68.8%) were ASA 2. ASA status distribution was comparable in both groups without significant intergroup difference. MRI brain was done in 96 % of patients in group A and 93.8% of patients in group B while 4% in group A and 6.3% in group B had an MRI spine. Part of the MRI examination was comparable in both groups with no significant intergroup difference. The average duration of MRI in group A was  $30.29 \pm 15.16$  min while in group B was  $28.96 \pm 9.79$  min. The two groups were comparable in terms of the duration of the MRI procedure.

The quality of the MRI examination was evaluated using a three-point scale (1 = no movement; 2= minor movement; 3= major movement necessitating another scan). In this present study 23 (23.4%) patients had no movement during the procedure. Out of which 13 patients (26%) belong to group A and 10 (20.8%) patients belong to group B .75(76.5%) patients had minor movement. Out of which 37 (74%) patients belong to group A and 38 patients (79.2%) belong to group B. No patient had major movement necessitating another scan. Quality of MRI examination was comparable in both groups without significant intergroup difference.

In our study, all patients in group A were administered Midazolam at a fixed dose of 0.1mg/kg. The average dose of Ketamine administered to the patients in group A was  $1.39 \pm 0.45$  mg/kg and the average dose of Propofol administered to the patients in group B was  $1.86 \pm 0.41$  mg/kg. The dose of the sedating agent was significantly high in Propofol group (p-value - 0.01). In our study, 24% of patients in group A required additional doses of Ketamine while in group B 75% of patients require additional doses of Propofol during the procedure. The need for additional sedation was significantly higher in group B than group A (P value < 0.001). Group A recovered with a recovery time of  $44.76 \pm 11.53$  min and the recovery time of group B was  $35.79 \pm 2.64$  min. The recovery time of Group A was significantly higher than that of group B ( $44.76 \pm 11.53$  min vs.  $35.79 \pm 2.64$ min, P = 0.01).

No patients developed major complications such as cardiac arrest, apnea, or laryngospasm during the procedure. A total of 25 (25.5%) patients out of 98 developed minor complications; 13(26%) patients in group A and 12 (25%) patients in group B developed complications. Cough (1 patient), tachycardia (3 patients) was observed only in group A. Increased oral secretions (6 patients in group A while

**Table 1:** Ramsay sedation assessment scale.

Patient anxious or agitated or both	1
Patient cooperative, oriented and tranquil	2
Patient responds to commands only	3
A brisk response to a light glabellar tap	4
A sluggish response to a light glabellar tap	5
No response	6

**Table 2:** Comparison on basis of Indication for MRI between the groups.

Statistics	Diagnosis				P-Value
	M+K		P		
	Frequency	Percent	Frequency	Percent	
Bladder Bowel Disturbances	1	2	0	0	
Seizure	19	38	15	31.3	
Developmental delay	13	26	17	35.4	
Hemiparesis	2	4	1	2.1	
Cerebral palsy	10	20	7	14.6	0.71
Hypoxicischemic encephalopathy	2	4	3	6.3	
Neuroregression	1	2	2	4.2	
Paraparesis	1	2	2	4.2	
Others	1	2	1	2.1	
<b>Total</b>	<b>50</b>	<b>100</b>	<b>48</b>	<b>100</b>	

**Table 3:** Comparison on basis of minor complications between the groups.

Statistics	Minor Complications				P-value
	M+K		Propofol		
	Frequency	Percent	Frequency	Percent	
HYPOXIA	0	0	2	4.2	0.71
TACHY	3	6	0	0	
BRADY	0	0	2	4.2	
FLUSHING	3	6	4	8.3	
SECRETION	6	12	4	8.3	
COUGH	1	2	0	0	
VOMITING	0	0	0	0	

**Table 4:** Comparison on basis of peripheral oxygen saturation between the groups.

Statistics		Group		p-value
		M+K	P	
		(n = 50)	(n = 48)	
SPO <sub>2</sub>	0 mins	98.2 ± 1.54	98.01 ± 1.43	0.41
	5 mins	97.54 ± 1.63	96.63 ± 2.35	0.08
	10 mins	96.92 ± 2.1	96.23 ± 2.71	0.26
	15 mins	96.72 ± 2.14	95.96 ± 2.28	0.34
	20 mins	96.72 ± 1.85	96.21 ± 2.09	0.36
	25 mins	97.04 ± 1.34	96.44 ± 1.69	0.03
	30 mins	97.34 ± 1.14	97.04 ± 1.17	0.1
	35 mins	97.64 ± 1.06	97.38 ± 0.96	0.12
	40 mins	97.78 ± 1.17	97.48 ± 1.05	0.14

4 patients in group B) were observed more often in group A. Hypoxia and bradycardia were observed in 2 patients from group B. Flushing occurs in 4 patients from group B and 3 patients from group A. The difference between the incidence of minor complications in the groups was statistically insignificant. A total of 35 patients (35.7%) developed

complications during the recovery such as dizziness, agitation, emergence reaction, double vision. Agitation was the most frequent complication (14 patients, 14.2%). complication rate in group A was 46% while in group B was 25%. Although the incidence of complications during recovery was statistically insignificant between the groups.

Mean heart rate values were found to be similar between the groups. Patients in both groups have been found to have a reduction in respiratory rate recorded in 5-minute intervals. Although the difference in respiratory rate reduction between both groups was not statistically significant. In our study, although there was a decrease in mean arterial pressure in both groups, none of the patients had hypotension. The difference in mean arterial pressure between two groups was not significant. In our study, both groups have been found to have reduction in oxygen saturations. Mean peripheral arterial oxygen saturations fluctuated between 96% and 98%. At 25 min, the mean peripheral oxygen saturation in group B was statistically less than Group A ( $97.04 \pm 1.34$  v/s  $96.44 \pm 1.69$ ;  $p=0.03$ ).

## Discussion

Our study aimed to compare the effects of Midazolam-Ketamine and Propofol for sedative effect, hemodynamic parameters, and complications in children undergoing sedation for MRI. There were no comparative study evaluating the Midazolam Ketamine combination versus Propofol in children undergoing sedation for MRI.

In our study, 100 patients were randomized into 2 groups (Group A and Group B). Group A received Midazolam and Ketamine combination and group B received Propofol. 2 patients were excluded from group B because of the failure of induction. The two groups were similar in our study in terms of demographic profile (Age, gender, weight and height, ASA Physical status, indication, and duration of MRI). The quality of MRI evaluated in the study by us using a three-point scale -namely no movement, minor movement, and major movement. 26% patients in group A and 20.8% patients in group B had no movement during the examination while 74% patients in group A and 79.2% patients in group B had minor movement. No patient had major movement necessitating another scan. While compared Midazolam Ketamine (M-K) and Midazolam Propofol (M-P) and evaluated the quality of MRI on basis of Subjective quality of the Scans and found that MRI scanning quality was very good in 70% and moderately good in 30% of patients in the M-K group, whereas the scanning quality was very good in 45% and moderately good in 55% of patients in the M-P group [12].

In our study, mean induction dose of Propofol administered to the patients of group B was Significantly higher than the dose of Ketamine administered to group A. Though MRI could be completed with both regimes. 24% of patients in group A and 75% patients in group B needed additional sedation during the procedure and the need of additional sedation was significantly higher in group B than group A while Cho et al reported that 4 (5%) out of 80 patients in the group who received single-dose Propofol required additional sedation during the examination [13]. Although they used a higher

induction dose (2 mg/kg) and they excluded the patients from the study when the MRI duration was prolonged (>30 min). In contrast, no patient needed additional sedation throughout the procedure in a study done [12] on 40 patients although most of the studies in literature used Propofol infusion in long procedures like MRI [1,6,8,14].

To facilitate ambulatory radiological procedures in children, the anesthetic agent should facilitate rapid recovery. We observed that Propofol group had a rapid awakening compared to Midazolam - Ketamine. Hasan et al [14] in their study on Deep sedation with Propofol for children undergoing ambulatory magnetic resonance imaging of the brain also reported that the recovery time of Propofol was rapid. No patients in our study developed major complications such as cardiac arrest, apnea or laryngospasm during the procedure. Similar results were found in a study by Akbulut et al. [15] on endoscopy comparing Midazolam Ketamine and Propofol Fentanyl that 28.6% of patients developed minor complications. Complications were comparable in both groups except for in the occurrence of bradycardia which was significantly higher in the latter group. Among minor complications increased oral secretions occurred in 10% of patients. Although an increase in secretion is associated with risk of aspiration and laryngospasm, these complications were observed in none of our patients while 4% of patients (2 patients in both groups) had nausea during recovery which relieved after 1 dose of intravenous antiemetic. Although we noticed a decrease in mean arterial pressure in both groups, none of our patients had hypotension while Christopher et al [16] in their study found more hypotension in the Propofol group, but they used a high dose (250-300 mcg/kg/min) of Propofol infusion. Sebe et al [1] compared Midazolam and Propofol in pediatric diagnostic imaging and reported that patients in both the group experience a significant decrease in systolic and diastolic BP, although the difference in systolic BP was not significant but a change in diastolic BP was significant between the groups. In our study, we analyzed mean arterial pressure and the difference of MAP between 2 groups was not significant.

In our study, the difference in heart rate between both groups was not significant. Although Sebe et al [1] in their study experienced a slight decrease in HR in both groups but that reduction also did not have clinical or statistical significance ( $P=0.060$ ). In our study both groups have been found to have a reduction in Respiratory rate and oxygen saturation however the difference in Respiratory rate reduction between the groups was not statistically significant. Mean Peripheral arterial oxygen saturations fluctuated between 96 % and 98% from the starting of the procedure to recovery. Although at 25 minute the mean peripheral oxygen saturation in group B was statistically less than Group A. These findings are attributed to the predictable effects of the drugs [17] In another study comparing midazolam and ketamine

in pediatric Procedural sedation and analgesia, 12% of the patients experienced a temporary but significant decrease in oxygen saturation. Machata et al [18] in their study on Propofol-based sedation regimen for 500 infants and children undergoing ambulatory magnetic resonance imaging found respiratory adverse events in five patients (1%). All of these patients suffered from oxygen desaturation ( $SpO_2 < 92\%$ ). Three children in their study experienced partial airway obstruction, which was treated immediately with slight neck extension and chin support. Two other children required short time assistance of spontaneous respiration via bag-valve-mask ventilation and afterward further reposition of neck and shoulders. We observed that a total of 35 (35.7%) patients developed complications during the recovery. Agitation in form of excessive crying was the most frequent complication. The complication rate in group A was higher than group B; Although the incidence of complications during recovery was comparable between the groups. However, Ulas E. Akbulut et al [15] reported that the rate of complications during the recovery was significantly higher in the Midazolam-Ketamine group than the Propofol-Fentanyl group. Agitation and emergence reactions were significant side effects observed during recovery in Ketamine-based sedation. The incidence of emergence reaction increases, especially when Ketamine is used at high doses, when a fast injection ( $< 1$  minute) is administered, and when excessive visual or verbal stimuli exist during the recovery [19,20]. Propofol reduces the incidence of emergence reactions. In our study, similarly, none of the patients administered Propofol combination developed emergence reactions.

## Conclusion

Midazolam-Ketamine is found to be better than single-dose Propofol in children undergoing magnetic resonance imaging. Although Propofol has rapid awakening as the recovery time of Midazolam Ketamine is significantly higher than Propofol but Propofol needs more induction dose. Maintenance of sedation is a problem with single-dose Propofol and patients might need additional doses during MRI. However the results revealed no significant difference between the two groups in terms of quality of MRI, complications during and after the procedure and hemodynamic parameters.

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