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## Comparison of dexmedetomidine-ketamine and propofol-midazolam in children undergoing MRI: A prospective randomised study

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### Abstract

**Background:** Deep sedation required for magnetic resonance imaging (MRI) in paediatric age group is a challenge. This study is done to compare the sedative and hemodynamic effects of dexmedetomidine with ketamine (DK) in comparison to propofol with midazolam (PM) in children undergoing MRI. The primary objective is to compare the recovery time and recovery characteristics between the drug combination and secondary objectives were to compare the efficacy and adverse events between the two groups.

**Methods:** This is a double blind randomised controlled study involving 100 patients posted for MRI in a tertiary care hospital between 01 Jan 2017 to 31 Dec 2018. Statistical analysis tests performed to compare the results between the two groups.

**Results:** The average time to achieving the Aldrete score of 10/10 in DK group was 25.43 min as compared to 13.7 min in PM group which is statistically significant. Also, time to achieve Ramsay Sedation Scale (RSS) scale of 5 was significantly higher in the DK group (12.20min) in comparison to PM group (6.30 min). There was no significant difference between heart rate, respiratory rate, systolic blood pressures or oxygen saturation during the procedure.

**Conclusion:** Combination of propofol with midazolam provided statistically significant rapid rates of anaesthetic induction as well as recovery when compared with dexmedetomidine ketamine group.

**Keywords:** Ketamine-dexmedetomidine, propofol-midazolam, paediatrics, magnetic resonance imaging

### Introduction

The number of diagnostic and therapeutic procedures done outside the operating room has increased dramatically in recent years. In children, most of these procedures require sedation, analgesia, or both to achieve optimal immobilization.

Anaesthetic intervention done during these procedures can be associated with higher safety issues than the procedure itself. This may be particularly relevant for magnetic resonance imaging (MRI), that could frighten the child and therefore call for deep sedation<sup>[1, 2]</sup>

Multiple drugs and drug combinations have been used in the past for adequate sedation during the procedure. Search for a perfect combination of drug that causes rapid induction and emergence with least side effects continues.

### Aims and Objectives

The aim of this study was to compare the sedative and hemodynamic effects of dexmedetomidine with ketamine in comparison to propofol with midazolam in children undergoing MRI. The primary objective was to compare the recovery time and recovery characteristics of combination of dexmedetomidine with ketamine as compared to propofol with midazolam combination. Secondary objectives included were firstly to compare the efficacy and adverse events associated with use of dexmedetomidine with ketamine as compared to propofol with midazolam combination in terms of decrease in heart rate, blood pressure, oxygen saturation and respiratory rate and secondly to compare the need to supplement sedation during the scan in both the drug groups.

### Material & Methods

This double blind randomised controlled prospective study was carried out at the MRI Centre of a large teaching hospital from 01 Jan 2017 to 31 Dec 2018 after obtaining

clearance from the hospital ethical committee. 100 patients were enrolled on the basis of sample calculation of the previous studies for the procedure with 50 in each group, as calculated from the power of previous studies. Group "PM" was receiving midazolam and propofol combination and group "DK" was receiving dexmedetomidine and ketamine combination. Inclusion criteria was to have American Society of Anaesthesiologists (ASA) physical status I and II children between 1 month to 12 years. Exclusion criteria included congenital heart disease, a recent upper respiratory tract infection, pneumonia, or episode of acute severe asthma in the proceeding 4 weeks, recent use of digoxin, alpha-2 agonist or psychotropic medications, allergy to the study drugs, predicted difficult airway, active, uncontrolled gastroesophageal reflux disease, recent use of study drugs in the last 30 days and small duration scans (less than 30 min). Randomization was done using the sealed envelope technique. After explaining the procedure and with written informed parental consent, the parent/guardian picked a pre-sealed envelope before the procedure. After opening the envelope secretly, the patient was allocated to either the "PM" or the "DK" group.

Children, their parents, clinical and study staff involved in recruitment, sedation, or patient care remained blinded. A trained nurse, who was not involved in patient care, prepared the study medication.

Patient arrived at the hospital after having fasted according to ASA guidelines. Intravenous access was obtained using 24- or 26-gauge cannula in the right hand, or feet in the ward 30 minutes prior to taking the patient to the MRI Complex. It was planned that if the procedure was delayed for more than an hour, intravenous fluids (Ringer Lactate with 2% Dextrose) will be administered in the pre-anaesthesia care unit at the MRI Centre at the rate of 2ml per kilogram of body weight. The patients entered the MRI room where MRI compatible non-invasive blood pressure, and pulse oximetry monitors, were applied. Supplemental oxygen was administered at a rate of 4 L/min through a facial mask with a ferromagnetic piece removed. All the patients were administered IV glycopyrrolate 10 mcg/kg before receiving their initial loading doses of sedatives. Sedation level was measured by the anaesthesiologist as per Ramsay sedation scale. The closed chit containing the drug group was opened by the anaesthesiologist administering the drug. This anaesthesiologist was not involved in data collection or the observation. Additionally, the infusion syringe and line was covered in an opaque sheet. Group DK (dexmedetomidine plus ketamine), patients received 1.5 mg/kg of intravenous ketamine followed by loading dose of intravenous dexmedetomidine as 1 mcg/kg over 10 minutes. During the maintenance of sedation maintenance infusion of dexmedetomidine 0.5mcg/kg/h was continued to maintain Ramsay sedation scale 5. Infusion was given with MRI compatible infusion pump.

In group PM (propofol plus midazolam) IV midazolam 70mcg/kg was administered as loading dose. This was followed by loading dose of propofol 2mg/kg to achieve Ramsay sedation scale 5. Infusion of propofol as 50mcg/kg/min was initiated following the loading dose. Heart rate, respiratory rate, SpO<sub>2</sub> was recorded at every 5 min during the procedure.

#### **Maintenance of Sedation and Rescue Sedation**

During the maintenance of sedation, in DK group, the

infusion rate of dexmedetomidine was controlled up and down by 0.2mcg/kg/h depending on any mild movement or any features suggestive of decreasing saturation like decreased depth of respiration, decreased rate of respiration or apnoea. Inadequate sedation was defined as difficulty in completing the procedure because of the child's movement during MRI examination. Movement was graded as mild (image acquisition not interrupted, intervention not required), moderate (intervention, ie, rescue bolus and/or increased propofol infusion rate required), or severe (image acquisition interrupted or repetitive events requiring intervention more than twice). Sedation quality was independently evaluated by the MRI technician, and the quality of MR images was assessed by a radiologist not involved in image acquisition. If patient movements were observed during the imaging process, dexmedetomidine was increased to 0.7 mcg/kg/min in Group DK. In group PM, propofol in the range of 0.5-1mg/kg was given as bolus dose to control the movement.

During sedation, airway interventions were performed when patients presented with apnea (>30 seconds), oxygen desaturation (SpO<sub>2</sub> <93%), and/or airway obstruction.

These interventions included airway repositioning, chin lift/jaw thrust manipulation, and positive pressure ventilation using bag and mask in sequential manner. If there was no improvement, artificial airway devices such as oral or nasal airways, laryngeal mask airways, or endotracheal tubes (ET) were sequentially applied.

Bradycardia was defined as fall of the heart rate below normal to less than 20% of the baseline recording. If heart rate remained low (<20% of the baseline) for 30s, the procedure was stopped, patient was taken out of the suite and the study drug was discontinued immediately. If there was no increase in heart rate in next 30s or the heart rate fell further, atropine was administered in a dose of 10 mcg/kg.

Blood Pressure was measured using MRI compatible non-invasive blood pressure monitor. Hypotension was defined as decrease in the systolic blood pressure more than 20 percent of baseline measurement.

Time to onset of sedation was defined as the period between the start of sedative administration and prior to the MRI scans, which corresponds to the sum of the time to reach a Ramsay sedation scale 5 and the airway optimization time. The time interval from the termination of the anaesthetic until spontaneous eye opening, recovery of full responsiveness (based on a modified Aldrete score of 10/10) were recorded.

The data collected included patient demographics, anesthetic variables (including total doses of propofol or dexmedetomidine and infusion rates of propofol and dexmedetomidine), use of artificial airway devices during MRI, hemodynamic parameters, recovery data, and sedation-related adverse events.

#### **Observations and Results**

Nominal data (number of subjects with apnoea, saturation, and rescue medication etc) were presented as number (N) and percentage (%). Continuous variables (e.g. age, weight, heart rate, respiratory rate etc) were expressed as mean and standard deviation (SD). Chi-Square test was applied for comparison of nominal data. For continuous variable, unpaired t test was applied to compare between groups (Propofol Vs Dexmedetomidine). Paired t test was applied to compare within group findings (Pre Vs Post) with p value

of <.005 as significant. The analysis of the data was performed using Microsoft excel and SPSS. In total, 100 patients were enrolled and randomised between the study period. As shown in Table 1, the mean age in the

DK group was 4.8 years in comparison to the PM group where it was 4.08 years. The gender distribution was uniform and clinically insignificant.

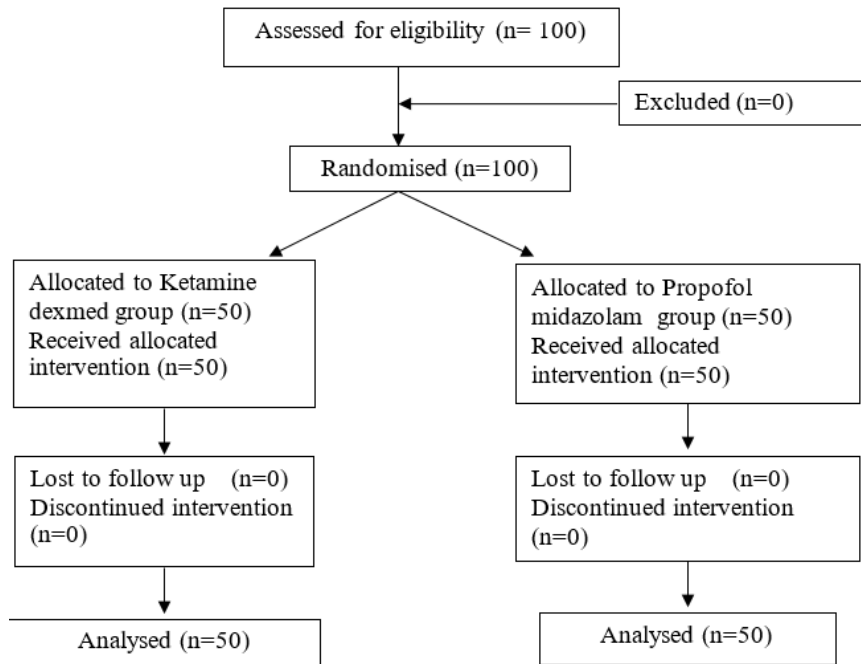


Fig 1: Consort Diagram

Table 1: Comparison of demographic variables between Group PM & Group DK.

Parameter	Group PM (n=50)		Group DK (n=50)		Significance (P value)
	Mean	SD	Mean	SD	
Age	4.08	3.26	4.88	2.83	0.56
Weight	17.23	6.00	19.33	5.84	0.22

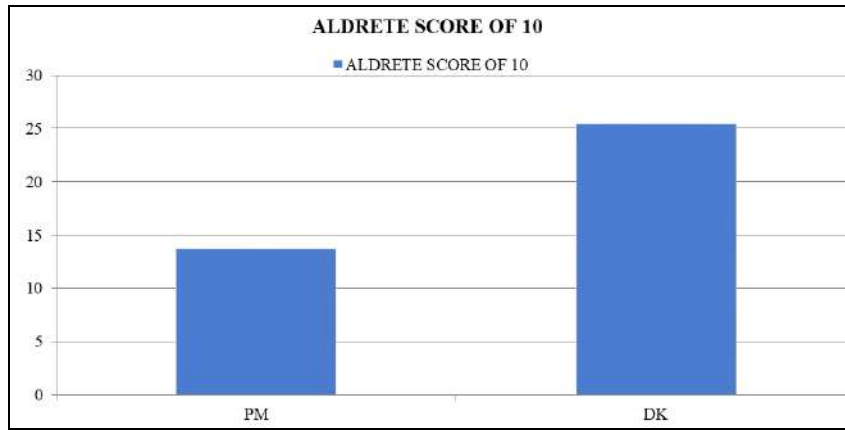
Un-paired t test is applied. P value is significant if < 0.05. In addition to this the average weight in DK group and PM group was 17.23kg and 19.33 kg respectively. Both the values were found to be statistically insignificant. The patients enrolled for the study had diagnosis ranging from involvement of central nervous system to gastrointestinal system as shown in Table 2.

Table 2: Comparison of Diagnosis of patients between Group PM & Group DK

Diagnosis	DK (n=50)	PM (n=50)	Grand Total
Arnold Chiarri Malformation	1	1	2
B/L SNHL( Sensorineural Hearing Loss)	4	3	7
Cerebellar Ataxia	0	1	1
Cerebral Palsy	2	2	4
Congenital Hearing Loss	2	1	3
Congenital Short Stature	1	2	3
Facial Nerve Palsy	4	2	6
Floppy Infant	12	10	22
Haemangioma - Thorax &Abdomen	4	3	7
Hemiplagia	0	1	1
Hydrocephalus	1	3	4
Impaired Hearing	1	3	4
Meduloblastoma	1	2	3
Meningomyocoele	4	3	7
Obstructive Jaundice	1	1	2
Ophthalmic Neuritis	1	1	2
Post Meningitis Sequae	0	1	1
Precocious Puberty	3	2	5
Short Stature,Failure to Thrive	7	7	4
Undescended Testis	1	1	2
Grand Total	50	50	100

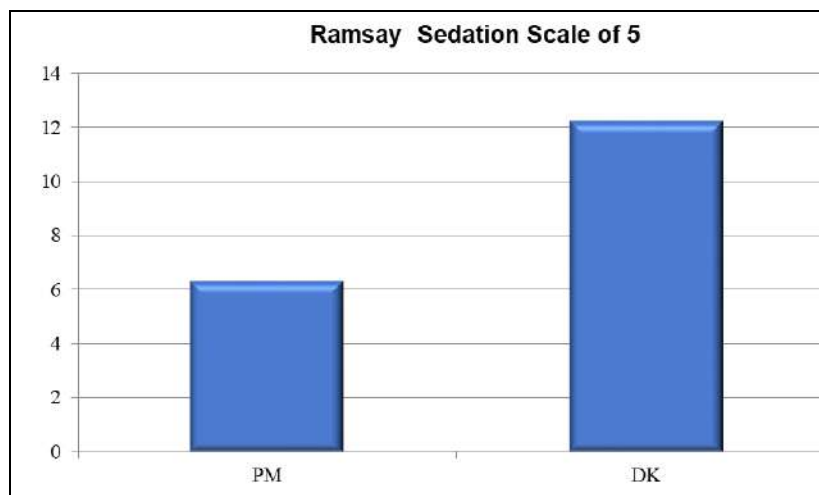
The primary objective of this study was to compare the recovery time between DK and PM group in terms of achieving Aldrete scoring of 10/10 after stopping of the

infusion. The average time to achieving the Aldrete score of 10/10 in DK group was 25.43 min as compared to 13.7 min in PM group (Fig2) with p value < 0.05.



**Fig 2:** The time to achieve the desired Aldrete Score of 10/10 prior to discharge was significantly higher in the dexmedetomidine+ketamine group (Group DK) as compared to the propofol+midazolam group (Group PM) (time in min)

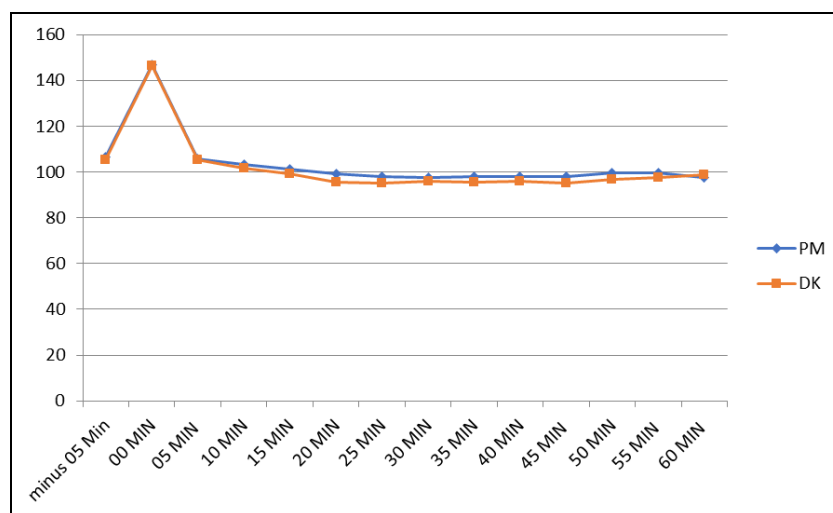
It was found that time to achieve RSS scale of 5 was also significantly higher in the DK group (12.20min) in comparison to PM group (6.30 min) as shown in Fig.3



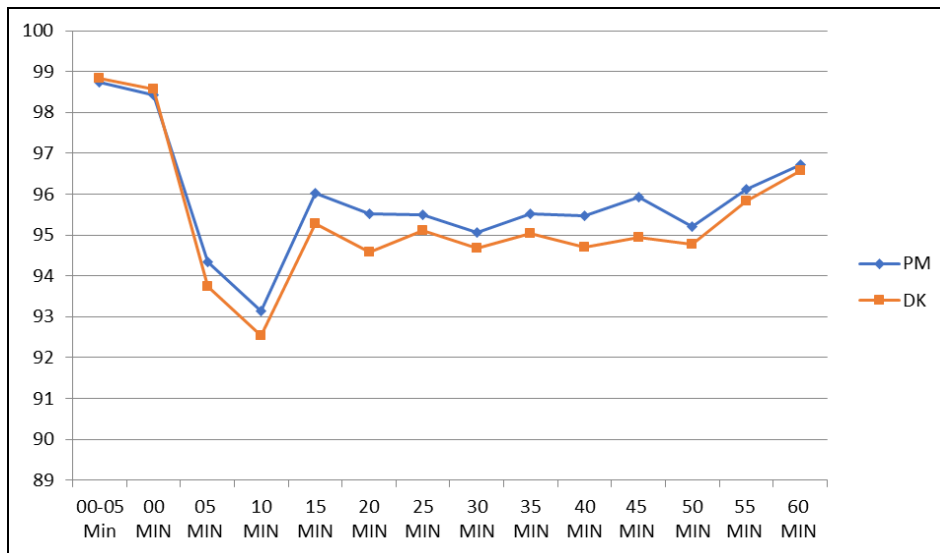
**Fig 3:** The time to achieve a desired Ramsay Sedation Scale of 5 was significantly higher in the Group DK as compared to Group PM (time in min)

Secondary objectives of the study included hemodynamic parameters. There was no significant difference between heart rate, respiratory rate, systolic blood pressures or

oxygen saturation during the procedure. The rescue sedation for both the studies were comparable and statistically insignificant.



**Fig 4:** There was no significant difference in the heart rate of both the groups throughout the MRI (heart rate in beats per min vs time in min)



**Fig 5:** Comparison of oxygen saturation between Group PM & Group DK (percent oxygen saturation vs time in min)

### Discussion

The results of our study suggest that the drug combination of propofol and midazolam cause faster onset of sedation as well as recovery from sedation in comparison to dexmedetomidine and ketamine. Both groups had adequate procedural sedation (RSS=5) for MRI scan and 100% of the children in both the groups completed their scan without any interruption, interference, or complications.

Despite excellent onset of sedation and rapid recovery<sup>3</sup>, propofol continued to have dose dependent risks of loss of airway reflexes<sup>[4]</sup> and propofol infusion syndrome in rare cases. For this purpose, midazolam was added in PM group to be able to reduce propofol infusion rate during maintenance in MRI.

Dexmedetomidine in comparison to propofol have an excellent combination of sedation, analgesia, preservation of airway reflexes and anti-sialagogue property, making it an excellent agent for procedural sedation especially in children who are prone to have collapsible airway<sup>[5-8]</sup>.

In previous studies, it was found that the onset of sedation time was 19 minutes for dexmedetomidine in MRI sedation. In this study, the faster onset of sedation time (Mean=12.20 minutes, SD=2.01 minutes) could be attributed to use of two drugs dexmedetomidine and ketamine simultaneously and also explained by the fact that the Ramsay sedation score of 5 was accepted as the time to onset of sedation as opposed to the accepted Ramsay sedation score in the previous study<sup>[9]</sup>.

Previous studies indicate that infusion doses of Dexmedetomidine (0.2-0.7 mcg/kg/min) have provided effective procedural sedation (RSS=5) although with some scan failure rates<sup>[10, 11]</sup>.

Like previous studies, no incidence of inadequate sedation was noted with dexmedetomidine in this study. However, unlike previous studies, loading dose of dexmedetomidine (1mcg/kg/min) was started which was followed by higher doses of continuous infusion of 0.5 mcg/min/kg instead of a lower dose used in the previous few studies (starting does 0.2mcg/kg/min, titrated to effect) that too with or without a loading dose of dexmedetomidine.

Similarly, propofol infusion (50-100 mcg/kg/min) with midazolam premedication (70 mcg/kg IV stat) was also found to have provided effective and adequate procedural sedation (RSS=5) which corroborates with previous studies<sup>[12, 13]</sup>.

In both the groups there was requirement of supplemental sedation and increasing the infusion rate, however it remained within the limits of doses as planned earlier.

Decreases in heart rate have been reported over time with dexmedetomidine in children. The results are consistent with those data, with heart rate falling significantly. However, there were no instances of bradycardia requiring any intervention in this study. Like previous studies, propofol also has been shown to cause a decrease in heart rate in this study. However, this fall in heart rate was never of clinical magnitude requiring intervention or interruption of the scan. Respiratory events make up a large population (5.5%) of complications of sedation in children<sup>[14]</sup>. Some authors have reported that dexmedetomidine did not affect RR and SpO<sub>2</sub><sup>[15, 16]</sup>. However, though rare, some respiratory complications have been reported with large and rapid initial loading doses<sup>[17, 18]</sup>. In comparison to dexmedetomidine, propofol may depress ventilation, suppress pharyngeal and laryngeal reflexes, and cause transient apnoea<sup>[19, 20]</sup>.

No other side effects or complications were attributed to either anaesthetic in this study.

There were minor limitations noted in the study. The MRI scans with a longer duration (approximately > 45 minutes) were chosen. Use of ketamine had been a matter of debate due to potential effect on increase in Intra cranial pressure, especially in pathology involving brain.

### Conclusion

Both dexmedetomidine with ketamine (DK) and the combination of propofol with midazolam (PM) provided adequate conditions for MRI without failures in this study or any requirement of supplemental sedation. Respiratory indices were similar in both the groups. There were no episodes of bradypnea, apnoea or desaturation in either group. Heart rate changes were transient and of limited clinical importance at the doses of anaesthetic treatments studied. There were no significant blood pressure changes through the study period in both the groups.

Combination of propofol with midazolam provided statistically significant rapid rates of anaesthetic induction when compared with dexmedetomidine ketamine group. Recovery to full responsiveness after dexmedetomidine ketamine was significantly prolonged.

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