

## COMPARISON OF SEDATIVE AND HAEMODYNAMIC EFFECTS OF INTRAVENOUS DEXMEDETOMIDINE AND MIDAZOLAM COMBINATION AND INTRAVENOUS DEXMEDETOMIDINE IN CHILDREN UNDERGOING MAGNETIC RESONANCE IMAGING

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### ABSTRACT

#### BACKGROUND

Sedation is a necessity for MR procedures conducted in children for adequate alleviation of anxiety, pain relief while securing IV access, and in order to avoid movements during the procedure. Dexmedetomidine, a selective alpha-2 adrenoceptor agonist is very useful for such procedures. We wanted to analyse and compare the sedative, hemodynamic effect of IV dexmedetomidine with IV dexmedetomidine and midazolam combination in children undergoing magnetic resonance imaging (MRI) examination in terms of, blood pressure before, and half an hour after the administration of sedation, and at the end of the procedure, onset of sedation, recovery from sedation for the initial drug administered, quality of MRI, need for supplementation.

#### METHODS

60 patients studied, were grouped in to two groups- group D and group DM with 30 patients in each group. In group D, inj. Dexmedetomidine at 2 mcg/kg was given IV and in group DM, inj. Dexmedetomidine at a dosage of 2 mcg/kg and inj. Midazolam at a dosage of 0.03 mg/kg were given. Onset of sedation and recovery from sedation were assessed by the Ramsay Sedation Scale and Quality of MRI was assessed using the 3-point scale. Hemodynamic parameters like blood pressure, and need for supplementation of sedation were recorded.

#### RESULTS

There was significant difference in onset time of sedation; mean values were  $6.3 \pm 2.28$  minutes and  $3.23 \pm 3.02$  minutes for D and DM group respectively ( $p < 0.05$ ). There was significant difference in the recovery from Sedation; the mean values were  $4.57 \pm 0.57$  and  $5.27 \pm 0.52$  for D and DM group ( $p < 0.05$ ). There was no significant difference in blood pressure values at various time periods between the two groups ( $p > 0.05$ ). There is a significant difference in the quality of MRI between the two groups ( $p < 0.05$ ), 4 patients in Group D received supplementation, whereas none in group DM received supplementation. This is statistically significant ( $p < 0.05$ ).

#### CONCLUSIONS

Usage of dexmedetomidine for the purpose of sedation is highly advocated and addition of midazolam to dexmedetomidine helped in decreasing the onset time for sedation and also offered a better quality of MRI study without any haemodynamic disturbances.

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#### BACKGROUND

Sedation is frequently necessary for children 1 to 10 years of age undergoing MRI. The different goals that we attain during the administration of general anaesthesia or sedation are highly variable and mainly dependent on the type of imaging procedure and the duration of that procedure. We mainly aim to attain anxiety relief, pain control and the restriction of excessive movement during the procedure.<sup>1,2</sup>

The American Academy of Pediatrics (AAP) defines the goals of sedation in the paediatric patient for diagnostic and therapeutic procedures as follows:

- To guard the patient's safety and welfare;
- To minimize physical discomfort and pain;
- To control anxiety;
- To minimize psychological trauma;
- To maximize the potential for amnesia;
- To control behaviour and/or movement to allow for the safe completion of the procedure;
- To return the patient to a state, in which safe discharge from medical supervision, as determined by recognized criteria, is possible.

The choice of drug that we administer depends on the type of sedation as well as the depth of sedation required. It may either be IV sedation or general anaesthesia. For CT

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Scanning, for instance, modern multi slice scanners allow for rapid image acquisition; therefore, moderate sedation can be employed. However, some children need to be asleep in order to tolerate complex or prolonged investigations such as MRI and nuclear medicine imaging, which may involve the child keeping still for up to 1 hour. Basic drugs such as (triclofos sodium) have been used for the purpose of procedural sedation such as ECHO and USG.<sup>3</sup> But the usage of such drugs cannot be extended onto other procedures that are of longer duration and noisier environment, where the disturbance from sedation is very high and that lead to interruptions in the procedure and also increasing the apprehensiveness of the child towards similar investigations.

Thus, we are completely dependent on drugs such as:

- Opioids - morphine sulphate, fentanyl.
- Benzodiazepines - midazolam, diazepam.
- Barbiturates - pentobarbital, methohexital, thiopental
- Other agents - nitrous oxide, ketamine, propofol, dexmedetomidine.

These drugs are able to provide a very good level of sedation such that even longer investigations such as MRI can be conducted in an orderly fashion without any form of interference or interruptions. The success of sedation for MRI depends on the safety of the sedation and the successful completion of the diagnostic examination. But the usage of these drugs such as thiopental, propofol, ketamine, morphine, diazepam, etc., is that they are also associated with some of the unwanted effects of hypoventilation, apnoea, sialorrhoea, airway obstruction, hyperventilation, hypotension or bradycardia. Interventions against such complications are difficult within the MRI procedural room since ferrous containing objects are not allowed within, because they can be converted into projectiles due to the electromagnetic discharges that develop within the MRI console. It is specifically needed for MRI compatible devices such as ECG monitors, pulse oximeters and other monitoring devices be used within the terminal for a proper continuous monitoring of the patient vitals. Due to the lack of immediate and easy access to the patients with instruments that would help

In securing the airway and stabilization of the circulatory function, it is necessary to utilize drugs such as dexmedetomidine, midazolam etc; so as to provide an adequate sedation level without severe adverse reactions.

Dexmedetomidine<sup>4</sup> is a potent, highly selective alpha-2 adrenoreceptor agonist having a distribution of 8 minutes and terminal t<sub>1/2</sub> of 3.5 hrs. At therapeutic doses, dexmedetomidine provides profound levels of sedation without affecting cardiovascular and respiratory stability. It also provides anxiolysis and analgesia.

The purpose of this randomized study is to compare between the effects of dexmedetomidine alone and its combination with midazolam and see if the combination would help in a faster induction and to know if the need for supplementation is reduced for the entire MRI study to be done without any interruptions and delay. This study also

looks into the probability of any adverse reactions to the cardiovascular and respiratory status of the patient on addition of midazolam to the initial drug administration.

### Aims and Objectives

To analyse and compare the sedative, hemodynamic effect of IV dexmedetomidine with IV dexmedetomidine and midazolam combination in children undergoing magnetic resonance imaging (MRI) examination. To assess, onset of sedation, recovery from sedation for the initial drug administered, quality of MRI and need for supplementation.

### METHODS

This study is a prospective randomized study, with double blind was undertaken in Andhra Medical College and King George Hospital, Visakhapatnam during the period October 2017 to May 2018.

The study was undertaken after obtaining ethical committee clearance as well as informed consent from all the guardians of the patients, since this study was conducted among children from ages 1 to 12 years. 60 children who were scheduled for magnetic resonance imaging study that was performed within the Department of Radiology, under IV sedation and belonging to ASA class I and 11 were included under this study.

### Inclusion Criteria

- a) Children under ASA I and ASA II.
- b) Age between 1-10 years
- c) Children who are posted for MRI
- d) Children whose Guardians have given consent for procedure.

### Exclusion Criteria

- a) All children of ASA III and IV.
- b) Known case of hypersensitive reaction to the drugs in study.
- c) Presence of Congenital Heart Disease, Gastroesophageal Reflux disease requiring treatment.
- d) Recent upper respiratory tract infection or pneumonia.
- e) Children whose Guardians have not given consent.
- f) Episode of acute asthma in the preceding month.
- g) Difficult airway that requires tracheal intubation or Laryngeal Mask Airway.
- h) Previous history of prolonged sedation.
  - i) Patient with history of trauma.
- j) Previous history of increased depth of sedation requiring assisted airway manipulation or active airway intervention.

Group D - Inj. Dexmedetomidine group (2 mcg/kg IV).

Group DM - Inj. Dexmedetomidine (2 mcg/kg) + inj. Midazolam (0.03 mg/kg).

Pre-anaesthetic evaluation was done the previous evening prior to the planned MRI procedure. A routine pre-anaesthetic examination was conducted, and routine investigations were done. The children were advised with a premedication of syrup Phenergan 0.5 mg/kg at night. They

were advised to maintain a nil per oral protocol as per 2-4-6 fasting rule.

Topical application of EMLA cream (5% emulsion preparation, containing 2.5% each of lidocaine and prilocaine) is done to the dorsum of the hand 1 hour prior to the procedure to facilitate the venous cannulation. Pre-sedation behaviour was assessed on a 4-point scale (81) by a senior anaesthesiologist who did not know which drug would be administered:

- 1 = calm, cooperative;
- 2 = anxious but assurable,
- 3 = anxious and not assurable;
- 4 = crying or resisting.

Categories 1 and 2 were called "undistressed behaviour," and categories 3 and 4 were defined as "distressed behaviour." Portable pulse oximeter is kept on continuous SPO<sub>2</sub> and PR monitoring. Baseline values were recorded upon the arrival of the unpremedicated children to the preparation room. A 24-gauge or 22-gauge intravenous cannula was inserted, depending on the venous access available. Children were allocated randomly using sealed envelopes containing the name of the group and the patient was asked to pick up the envelope. The envelope was opened by a senior anaesthesiologist who was not involved with the study. They were accordingly divided into two groups of D or DM, based on the envelop they open. Inj. Metoclopramide 0.3 mg/kg was injected 60 minutes prior to the start of the procedure and inj. Glycopyrrolate 0.005 mg/kg was injected 3 mins prior to the sedation of the patient. Solution of dexmedetomidine, 1 ml at a concentration of 100 mcg/ml, was diluted with 49 ml normal saline to a concentration of 2 mcg/ml. To group D children, the dose of dexmedetomidine at 2 mcg/kg is administered as a slow infusion over 10 mins. Solution of midazolam, 1 ml at a concentration of 1 mg/ml was diluted with 10 ml sterile water to a concentration of 100 mcg/ml. to the group DM children, the combined dose of dexmedetomidine at 2 mcg/kg and midazolam at 0.03 mg/kg is administered as a slow infusion over 10 mins.

The sedation level of the children was measured by the anaesthesiologist using the Ramsay sedation scale every 10 min. The Ramsay scale assigns a score of 1-6 based on the clinical assessment of the level of sedation as follows:

- 1 = anxious, agitated, restless;
- 2 = awake, but cooperative, tranquil, orientated;
- 3 = responds to verbal commands only;
- 4 = brisk response to loud noises or glabellar taps;
- 5 = sluggish response to loud noises or glabellar taps;
- 6 = no response to loud noises or glabellar taps.

Score 3 was accepted as onset level so as to start the procedure, whereas score 5 was accepted as level of deep sedation. The children were then transferred and positioned on the scanning table with a shoulder roll under the neck (either a rolled-up towel or a sheet) after both a Ramsay score of 5 was achieved and haemodynamic and respiratory stability was ensured. If a Ramsay score of 5 was not

achieved after the delivery of the study drug, then supplementary dose of inj. ketamine 1 mg/kg is given to the patient. If patient movements were observed in between the procedure, then the same supplementation (with dexmedetomidine 1 mcg/kg) is given depending on the duration of the procedure remaining. If in the case the procedure is interrupted repeatedly (cut off twice), then the procedure is cancelled and considered as a failure and it is then rescheduled with a deeper sedative along with active airway manipulation either with oropharyngeal airway, or intubation, depending on the inductive agent used. Inadequate sedation was defined as difficulty in completing the procedure as a result of the child's movement during MRI examination.<sup>5</sup>

Blood Pressure 5 minutes after the completion of the administration of drug was noted. Heart rate (HR), peripheral oxygen saturation (SPO<sub>2</sub>), blood pressure and respiratory rate (RR) were recorded continuously using MRI compatible monitors by Anaesthesiologist 1. If there was significant hypotension (SBP <20% of baseline), fluid at 10 ml/kg body weight would be administered. Patients were allowed to breathe spontaneously through a Hudson face mask with oxygen at 5 L/min without any artificial airway throughout the procedure. Ventilator function was continuously being assessed by the Anaesthesiologist 1 by observation of the child's respiratory function. If the SPO<sub>2</sub> level decreased below 95% for 30 seconds, the MRI procedure would be interrupted, and the child shifted out of the MRI tunnel. Then the airway patency will be assessed, the neck slightly extended and jaw thrust to be provided followed by an oral suction while actively supplementing oxygen via a Jackson Rees modification of the Ayre's T-piece (JRMATP) circuit with 100% O<sub>2</sub>, till the oxygen saturation picks up or else to actively intubate the child and ventilate till the child recovers for the unplanned apnoea and desaturation. The imaging study would then have been discontinued.

Quality of the MRI was evaluated by a radiologist, who is not a part of the study, using a three-point scale:

- 1 = no motion;
- 2 = minor movement;
- 3 = major movement necessitating another scan.

At the end of the procedure, the child was shifted from the imaging center to the post-anaesthesia recovery room in the left lateral position and then the vitals are continuously monitored until the child recovers completely from sedation and reaches a Ramsay Score of 2.

The onset of sedation time was defined as "the period of time between the beginning of study drug administration and reaching a Ramsay score of 5". Recovery time was accepted as the period of time taken for the patient to recover to the Ramsay score 2 from sedation. The patient was maintained in the nil per oral status for 6 hours while supplemented with IV fluid of plasmalyte-P at a maintenance rate based on the Holiday Segar formula of 4:2:1. Then the patient was started on sips of water followed by clear liquids. The criteria for discharge was the return of vital signs and

level of consciousness to baseline, absence of adverse effects and tolerating oral feeds.

Statistical analyses were made with SPSS® 24.0. Results are presented as mean (sd) or their confidence interval (CI). Analysis of variance for repeated measures was performed on hemodynamic and variables, with compensation for post hoc comparisons using the Bonferroni correction. Intergroup statistical analyses were performed using Student's t-test, and nonparametric data were analysed using chi<sup>2</sup> test. Statistical significance was considered at p value <0.05. The power of the study was calculated based on the onset of sedation time. Setting a significance level of P <0.05, it was calculated that a group size of 30 patients allowed detection of a difference of 4 min between groups with a power of 100%.<sup>6</sup>

**RESULTS**

Variable	Group D	Group DM	p Value
Age	6.57±2.62	7.07±2.61	0.4
Weight	20.08±8.89	2.49±7.87	0.12
Gender (M/F)	21/9	19/11	0.5

**Table 1. Demographic Characteristics of Study Population**

There were no statistically significant differences in the demographic profile of patients in either group in terms of age, weight and gender (p>0.05).

Variable	Group D	Group DM	p Value
Pre-Sedation Behaviour	2.33±0.55	2.1±0.71	0.16
Onset of Sedation	6.3±2.28	3.23±3.02	0.001
Recovery from Sedation	4.57±0.57	5.27±0.52	0.001

**Table 2. Comparison of Sedation Between D and DM Group**

Table 2 shows significance in the data between the two groups with regards to the time of sedation and the level of sedation (p<0.05).

Variable	Group D	Group DM	p Value
Baseline			
SBP	9207±6.96	94.8±9.96	0.22
DBP	58.47±5.65	6.73±4.87	0.1
Before Drug			
SBP	9587±7.43	98.47±8.43	0.21
DBP	59.73±4.45	6.27±3.43	0.6
5 Mins			
SBP	90.6±6.5	9287±9.26	0.28
DBP	58.47±4.22	59.6±4.28	0.3
Recovery			
SBP	96±7.86	99.67±10.58	0.13
DBP	59.6±4.28	59.47±3.48	0.8

**Table 3. Comparison of Blood Pressure at Various Time Points**

Table 3 shows that there was no significant difference in blood pressure values at various time periods between the two groups (p>0.05).

Quality of MRI	Group D	Group DM	p Value
1	26	30	0.04
2	4	0	
3	0	0	

**Table 4. Comparison of Quality of MRI Between D and DM Group**

There is a significant difference in the quality of MRI between the two groups. Group D and Group DM (p<0.05).

Quality of MRI	Group D	Group DM	Total	p Value
No	26	3	56	0.04
Yes	4	0	4	
Total	30	30	60	

**Table 5. Comparison of Supplementation Between D and DM Group**

Table 5 describes that 4 patients received supplementation in group D which is statistically significant (p=0.04).

**DISCUSSION**

The frequency of MRI scan in children has increased in recent years making its role crucial in diagnosis of various diseases. MRI scan takes about 30 minutes time, for optimum image quality enabling precise diagnosis, patients has to remain motionless, which is difficult for children. A deep level of sedation is required during MRI in children.<sup>1,2</sup> In our study pre-sedation behaviour in dexmedetomidine group (Group D) 2.33±0.55 and in Group DM (dexmedetomidine and midazolam group) is 2.1±0.71(p=0.16)which is nil significant. Which is similar to study of Jaydev Dave et al<sup>7</sup> In our present study interpretable MRI scans were obtained for all subjects in DM group adding midazolam 0.03 mg/kg to dexmedetomidine 2 mcg/kg is effective in completing MRI study with no interruption or need of supplementation in the form of pentazocine 0.3 mg/kg or ketamine 1-2 mg/kg with success rate of 100%. This study also showed that group D children who were given plain dexmedetomidine 2 mcg/kg IV bolus over 10 mins could provide an uninterrupted MRI only in 86% of cases.

In study conducted by Koroglu et al,<sup>5</sup> adequate sedation was obtained in 83% of children who received dexmedetomidine and 90% of the children who received propofol. The failure rate in dexmedetomidine group may be attributed to low dose of dexmedetomidine used by them. (loading dose of 1 mcg/kg over 10 mins followed by infusion of 0.5 mcg/kg/hr).

In other study by Koroglu et al<sup>8</sup> where dexmedetomidine was compared with midazolam for sedation during MRI in children, achieved adequate sedation

in 80% of children in dexmedetomidine group and only 20% in midazolam group.

In our study the mean onset of sedation is  $6.3 \pm 2.28$  mins in group D and  $3.23 \pm 3.02$  mins in group DM. This difference is highly significant. ( $p < 0.001$ ). Mean onset of sedation in K Kamal et al<sup>9</sup> is  $7.00 \pm 1.74$  in group D and  $3.42 \pm 1.34$  in group P. ( $P < 0.001$ ), In study of Koroglu et al<sup>8</sup> onset times were 19 mins in dexmedetomidine group and 34 mins in midazolam group as they used low doses compared to our present study.

In study conducted by Kirti Kamal et al<sup>9</sup> adequate sedation is obtained in 100% of patients in dexmedetomidine and propofol group.

In our study recovery from sedation in Group D  $4.57 \pm 0.51$  and in Group DM  $5.27 \pm 0.52$  ( $P < 0.001$ ).

In the study conducted by K Kamal et al<sup>9</sup> recovery from dexmedetomidine group is  $9.02 \pm 2.99$  and in propofol group is  $3.52 \pm 1.07$ . ( $P < 0.001$ ) these are similar to study of Arian and Ebert.<sup>10</sup> In another study conducted by Heard et al<sup>11</sup> the time of recovery of full responses after dexmedetomidine and midazolam infusion is significantly greater than propofol ( $p < 0.001$ ). In our study we noticed that there is no significant fall in heart rate, blood pressure and oxygen saturation throughout the study. By this study we have come to a interpretation that during an MRI study in paediatric age group, the use of dexmedetomidine is highly advocated and the addition of midazolam to dexmedetomidine helped in decreasing the time for onset of sedation and also offered a better quality of MRI study. This study presents a success rate of 100% with dexmedetomidine plus midazolam group of sedation for MRI. A single bolus dose of dexmedetomidine at 2 mcg/kg IV and midazolam 0.03 mg/kg IV over 10 mins allowed us to perform a complete test without any interruptions or postponements and without requirement of any additional supplementation. Also, the initial dose was not associated with any significant hemodynamic disturbances.

## CONCLUSIONS

The combination of dexmedetomidine to midazolam is safe without significant hemodynamic compromise in children, and it also provides adequate levels of sedation for the entire MRI study to be conducted without any interruption or requirement of additional supplementation.

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