Intravenous Dexmedetomidine versus Dexmedetomidine and Midazolam Combination for Paediatric Sedation in MRI Room: A Randomized Study

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Abstract

Background: Sedation is a necessity for MRI (Magnetic Resonance Imaging) procedures in children for alleviating anxiety and to avoid movements during the procedure. Dexmedetomidine a selective alpha-2 adrenoreceptor agonist is very useful for such procedures. *Aims and Objectives:* To analyze and compare the sedative, hemodynamic and respiratory effect of Intravenous (IV) dexmedetomidine with IV dexmedetomidine and midazolam combination in children undergoing magnetic resonance imaging (MRI) examination. *Material and Methods:* Total of 60 patients were studied, 30 in each group, group D and group DM. Group D received inj. Dexmedetomidine 2mcg/kg, Group DM received dexmedetomidine 2mcg/kg and inj. Midazolam 0.03 mg/kg intravenously. The level of sedation was assessed by the Ramsay sedation scale and quality of MRI was assessed using the 3 point scale. During the procedure, respiratory rate, heart rate, oxygen saturation and blood pressure were continuously monitored and recorded using MRI compatible monitors. The data were analysed using SPSS version 24.0. *Results:* There was significant difference in onset of sedation; the mean values ranged 6.3±2.28 minutes (mins) and 3.23±3.02 minutes for D and DM group respectively (p < 0.05). There was significant difference in the Level of sedation; the mean values ranged 4.57±0.57 and 5.27±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. The quality of MRI is better in Group DM than group D. There was no significant difference in heart rate, respiratory rate, oxygen saturation values at various time periods between the two groups. 4 patients in Group D received supplementation, whereas none in group DM received supplementation. *Conclusion:* Addition of midazolam to dexmedetomidine for sedation helped in decreasing the onset of sedation and also offered a better quality of MRI study without any haemodynamic or respiratory disturbances.

Keywords: Dexmedetomidine; Hemodynamic; Midazolam; MRI; Respiratory; Sedation.

Introduction

Sedation is frequently necessary for children less than 10 years of age undergoing MRI. We mainly aim to attain anxiety relief, pain control and the restriction of excessive movement during imaging procedures without compromising patient safety [1]. The choice of drug that we administer depends on the type of sedation as well as the depth of sedation required. For CT Scanning, for instance, modern multislice scanners allow for rapid image acquisition; therefore, moderate sedation can be employed. Children need deeper levels of sedation to stay still in noisier environments like MRI room. We have opioids, benzodiazepines, barbiturates, ketamine, propofol and alpha2 adrenergic agonists as options. These drugs are able to provide a very good level of sedation [2].

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 associated with some of the unwanted effects like hypoventilation, apnea,

sialorrhea, airway obstruction, hyperventilation, hypotension or bradycardia [3]. 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 [4].

Dexmedetomidine an alpha-2 adrenergic agonist at therapeutic doses provides profound levels of sedation without affecting cardiovascular and respiratory stability [5,6]. It also provides anxiolysis and analgesia [7]. 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 without compromising patient safety.

Material and Methods

This prospective randomised study was undertaken in tertiary care medical college hospital, during the period November 2015 to May 2017 after obtaining ethical committee clearance as well as informed consent from all the guardians of the patients. 60 children who were scheduled for magnetic resonance imaging study under IV sedation and belonging to ASA class I and II were included under this study. All children of ASA III and IV, children with congenital heart disease, gastroesophageal reflux disease and respiratory tract infection were excluded from the study. The study population was randomly divided into two groups group D and group DM, with 30 patients in each group using sealed envelope technique. The envelope was opened by a senior anaesthesiologist who was not involved with the study. Group D received Inj. Dexmedetomidine (2mcg/kg IV), Group DM received Inj. Dexmedetomidine (2mcg/kg) + inj. Midazolam (0.03 mg/kg). A routine pre-anaesthetic examination was done in all the participants.

All the children were premedicated with 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 [8]. Topical application of EMLA cream is done to the dorsum of the hand 1 hour prior to the procedure to facilitate the venous cannulation. Pre-sedation behavior was assessed on a 4 point scale 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. After obtaining IV access inj. Metoclopramide 0.3 mg/kg and inj.Glycopyrrolate 0.005 mg/kg were given 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 by a blinded anaesthesilogist.

Ramsay sedation scale was used to measure sedation levels by a blinded anaesthesiologist. The Ramsay scale assigns a score of 1-6 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 [8,9]. Score 3 was accepted as a level to start the procedure, whereas score 5 was accepted as level of deep sedation. The children were then transferred after both a Ramsay score of 5 was achieved and haemodynamic and respiratory stability was ensured. 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. Inadequate sedation was defined as difficulty in completing the procedure as a result of the child's movement during MRI examination [8,9].

Blood Pressure 5 minutes after the completion of the administration of drug was noted. Heart rate (HR), peripheral oxygen saturation (SpO_2), blood pressure and respiratory rate (RR) were recorded continuously using MRI compatible monitors. 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 4 L/min. Ventilator function was continuously being assessed by the blinded anaesthesiologist by observation of the child's respiratory function. If the SpO_2 level decreased

below 95% for 30 seconds, the MRI procedure would be interrupted and the child shifted out of the MRI tunnel for stabilization.

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" [8,9]. 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 [10]. Statistical analyses were made using 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 respiratory 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 analyzed using chi^2 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%.

Results

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). (Table 1).

There was no significant difference in baseline Pulse Rate and respiratory rate between two groups. (Table 2).

There was significant earlier onset of sedation and level of sedation in group DM compared to group D. (p value – 0.001) (Table 3).

There was no significant difference in blood pressure values at various time periods between the two groups (p > 0.05) (Table 4).

There was no significant difference in Heart Rate values at various time periods between the two groups (p > 0.05) (Table 5).

There was no significant difference in Respiratory Rate values at various time periods between the two groups (since p > 0.05) (Table 6).

There was no significant difference in SpO_2 values at various time periods between the two groups (p > 0.05) (Table 7).

Table 8 describes that 4 patients received supplementation in group D which is statistically significant. (p = 0.04) (Table 8).

This showed that there were no untoward effects in both the groups, both group D and group DM. (Table 9).

The quality of MRI was significantly better in Group DM compared to Group D. (p < 0.05). (Table 10).

Table 1: Demographic Characteristics of study population

Variable	Group D	Group DM	P value
Age	6.57 ± 2.62	7.07 ± 2.61	0.4
Weight	20.08 ± 8.89	23.49 ± 7.87	0.12
Gender (M/F)	21/9	19/11	0.5

Table 2: Comparison of Baseline Measurements in both groups

Variable	Group D	Group DM	P value
Pulse Rate	102.7 ± 9.09	99.27 ± 19.47	0.38
Respiratory Rate	22.9 ± 3.52	21.03 ± 5.88	0.14

Table 3: Comparison of Sedation between D and DM group

Variable	Group D	Group DM	P value
Pre sedation Behavior	2.33 ± 0.55	2.1 ± 0.71	0.16
Time Sedation	6.3 ± 2.28	3.23 ± 3.02	0.001
Level of sedation	4.57 ± 0.57	5.27 ± 0.52	0.001

Table 4: Comparison of Blood Pressure at various time points

Variable	Group D	Group DM	P value
Baseline			
SBP	92.07 ± 6.96	94.8 ± 9.96	0.22
DBP	58.47 ± 5.65	60.73 ± 4.87	0.1
Before drug			
SBP	95.87 ± 7.43	98.47 ± 8.43	0.21
DBP	59.73 ± 4.45	60.27 ± 3.43	0.6
5 Mins			
SBP	90.6 ± 6.5	92.87 ± 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 5: Comparison of Heart Rate (mins) in both groups over the time

Heart Rate	Group D	Group DM	P Value
0 Min	126.8 ± 9.35	124 ± 20.18	0.49
5 Mins	116.2 ± 9.19	113.6 ± 20.2	0.52
10 Mins	109.5 ± 8.97	107.1 ± 19.36	0.54
15 Mins	105.83 ± 8.96	101.93 ± 18.93	0.31
20 Mins	103.1 ± 9.98	97.3 ± 18.54	0.13
25 Mins	99.93 ± 9.25	93.37 ± 18.04	0.08
30 Mins	98 ± 9.46	90.7 ± 17.97	0.15
35 Mins	95.53 ± 8.39	89.6 ± 17.88	0.1
40 Mins	93.06 ± 9.47	89.21 ± 18.44	0.43
45 Mins	94.83 ± 11.5	82 ± 20.2	0.23

Table 6: Comparison of Respiratory Rate (mins) in both groups over the time

RR	Group D	Group DM	P Value
0 Min	24.47 ± 6.66	24.87 ± 4.24	0.78
5 Mins	22.07 ± 6.07	22.27 ± 4.05	0.88
10 Mins	20.8 ± 5.79	21.37 ± 3.76	0.66
15 Mins	20.43 ± 5.64	19.83 ± 4.14	0.64
20 Mins	20.43 ± 5.98	19.03 ± 4.07	0.29
25 Mins	19.57 ± 5.43	18.07 ± 4.33	0.24
30 Mins	19.23 ± 5.24	17.8 ± 4.39	0.25
35 Mins	18.58 ± 5.09	17.43 ± 3.92	0.36
40 Mins	19.67 ± 5.19	17.36 ± 4.19	0.16
45 Mins	17.5 ± 4.73	18.25 ± 4.59	0.79

Table 7: Comparison of SPO_2 (mins) in both groups over the time

SPO_2	Group D	Group DM	P Value
0 Min	99.83 ± 0.53	99.8 ± 0.66	0.83
5 Mins	99.9 ± 0.3	99.9 ± 0.4	0.99
10 Mins	99.93 ± 0.25	100	0.15
15 Mins	99.93 ± 0.25	100	0.15
20 Mins	99.93 ± 0.3	100	0.32
25 Mins	99.97 ± 0.18	100	0.32
30 Mins	99.97 ± 0.18	100	0.32
35 Mins	99.88 ± 0.33	100	0.14
40 Mins	99.89 ± 0.32	100	0.14
45 Mins	99.71 ± 0.49	100	0.22

Table 8: Comparison of Supplementation between D and DM group

Supplementation	Group D	Group DM	Total	P
No	26	30	56	0.04
Yes	4	0	4	
Total	30	30	60	

Table 9: Comparison of untoward effects between D and DM group

Un toward Effects	Group D	Group DM	Total
No	30	30	60
Yes	0	0	0

Table 10: Comparison of Quality of MRI between D and DM group

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

Discussion

Sedation is seen as a depressed state or level of consciousness of a patient. It can vary from various stages. It can exist from a very light plane of sedation to a very deep plane of sedation. The level or plane of sedation that is required for any particular investigation or procedure mainly depends on the type of procedure, the location where it is being held, the duration of the procedure and if any interference is present during the undergoing investigation. At concious sedation we find that the patient is able to retain the ability to independently and consciously maintain a patent airway and is also able to respond properly to verbal commands. The patient might have ante grade amnesia, but the protective airway reflexes are normal or minimally altered.

A variety of drugs have been used for MRI sedation. Pentobarbital has been used very frequently for MRI sedation due to being a short acting barbiturate. Rooks, et al conducted a study comparing pentobarbital and chloral hydrate among 498 children and found no significant differences between the two groups [10]. The common side effects associated with pentobarbital were respiratory depression, cardiovascular depression and need for active airway interventions. Lower doses were associated with no sedation or lighter planes of sedation leading to repeated interruptions or delay of the imaging study and even postponement of the scan [12]. Chloral hydrate was also associated with the stimulation of nausea and vomiting in children due to its property of gastric irritation [13]. No intrinsic analgesic effect was appreciated with this drug. Chloral hydrate can also cause respiratory depression [14].

Barbiturates such as thiopental were also in usage. Filner BF et al found that 5 mg/kg IV of thiopental in normovolemic patients caused a transient and mild decrease in blood pressure of 10- to 20- mm Hg and was followed with a rise of heart rate around 15- to 20- beats per minute [15]. It also resulted in a dose related depression of medullary and pontine ventilatory centers. These cases required active airway management in the form of laryngeal mask airway or intubated with an endotracheal tube along with active ventilation till spontaneous breathing occurred. These facilities are difficult to manage in the MRI settings and hence active management of the patient in response to drug induced ventilatory depression is cumbersome and dangerous. Methohexital a potent sedative is not recommended by Pomeranz et al as a rectal route due to the high frequency of apnea or desaturation [16].

Propofol, administered at 1.5 – 2.5 mg/kg in < 15 seconds, produces unconsciousness in 30 seconds. Awakening is also rapid when compared with other drugs [17]. But large doses reduce the SBP significantly. It also decreases the cardiac output and systemic vascular resistance [18]. Baroreceptor reflex of the heart is also depressed as seen by Deutschman CS et al [19]. Bradycardia and asystole was observed in many cases requiring active airway management and assisted ventilation. Tidal volume and frequency of breathing is also decreased

Dexmedetomidine, an alpha-2 agonist, is a drug with safe therapeutic window in relation to respiratory depression [20,21,22]. This is a very positive point with respect to its usage for procedural sedation. In case of MRI study, it has an advantage over the other medications due to the child not being immediately accessible to the medical team. Many studies demonstrate dexmedetomidine as a good option for procedural sedation [8,9,23,24]. Previous studies show that low dose dexmedetomidine of rates 0.1 – 0.7 mcg/kg/min as an safe and effective sedation dose [3,25]. But, this dosage will not be sufficient in conducting MRI sedation as higher levels are required for children. There have been several trials clinically to compare between dexmedetomidine and propofol usage for IV sedation in pediatric age groups during

MRI studies [8,9,26]. 83% sedation with dexmedetomidine and 90 % sedation with propofol, was observed in a study conducted among 60 children undergoing MRI [26]. Shorter means were noticed in the propofol group with respect to onset, recovery and discharge time. Studies evaluated the safety and efficacy of dexmedetomidine during noninvasive radiological procedures [27]. Use of high dose dexmedetomidine as a sole sedative was found to provide higher quality radiological imaging and lesser use of rescue medications [5,28]. But there were incidences of bradycardia during these studies. In our study, we have compared the advantage of adding midazolam in combination with dexmedetomidine in hope to further prolong the time as well as improving the quality of the MRI. It is seen that, adding midazolam (0.03mg/kg) to dexmedetomidine (2 mcg/kg) is effective in completing a MRI study with no interruptions or need for supplementation in the form of pentazocine 0.5 mg/kg or ketamine 1-2 mg/kg and with a success rate of 100%. This study also showed that plain dexmedetomidine 2 mcg/kg IV bolus over 10 mins could provide an uninterrupted MRI study in 86% of cases.

In our study, there was no significant fall in the heart rate from baseline during sedation. It could be explained also by the fact that the anxiolytic action of dexmedetomidine was countered by the prophylactic administration of glycopyrrolate in both groups at the dose of 0.005 mg/kg IV. Other studies showed the heart rate to decrease to a value < 20% from baseline, which is considered to be insignificant [3,24]. In this study, the incidence of bradycardia is 0% of the total, which is less than 4% as noticed by Mason et al [24] or 3.9% as reported by Ahmed et al [28]. Our study, it was noticed that the blood pressure and oxygen saturation was maintained in the normal range throughout the entire MRI study period. One study showed that there was a fall in blood pressure immediately after stopping the dexmedetomidine infusion at the end of the MRI procedure which reverted to the baseline without any intervention [28]. Such infusion can be avoided by adding midazolam at 0.03 mg/kg to the dexmedetomidine drug at 2 mcg/kg.

The limitation of our study was the absence of recording the recovery time and duration of sedation for the two groups, group D and group DM. It has been reported in a previous study, the average recovery time of 38 minutes with dexmedetomidine [29]. By this study, we have come to the interpretation that during an MRI study within the pediatric age group, the usage of dexmedetomidine for the purpose of sedation is highly advocated and that addition of midazolam to dexmedetomidine helped in decreasing the time for the onset of sedation and also offered a better quality of MRI study. Thus, we come to the final conclusion that the combination of dexmedetomidine and midazolam is better and equally safe from the respiratory and haemodynamic perspective when compared with plain dexmedetomidine for the successful completion of MRI study in the pediatric age group.

Conclusion

Thus with this study, we have come to the findings that during an MRI study within the pediatric age group, the usage of dexmedetomidine for the purpose of sedation is highly advocated and that addition of midazolam to dexmedetomidine helped in decreasing the onset time for sedation and also offered a better quality of MRI study. It was also noted that 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 the complete test without any disturbance or break and without requiring any additional supplementation.

Also the initial dose was not associated with any significant hypotension or bradycardia. Thus, by this study, we come to the final conclusion that the combination of dexmedetomidine and midazolam is safe without any haemodynamic or respiratory compromise in children, and it also provides adequate level of sedation for the entire MRI study to be conducted without any interruptions or requirements of additional supplementation.

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