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A COMPARISON OF CARDIAC AND RESPIRATORY EFFECTS OF DEXMEDETOMIDINE VERSUS PROPOFOL + MIDAZOLAM IN CHILDREN UNDERGOING MRI: A PROSPECTIVE RANDOMISED TRIAL

Pharmacology

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ABSTRACT

Background: The number of diagnostic and therapeutic procedures done outside the operating room has increased dramatically in recent years. Despite local anaesthesia, reassurance and distraction techniques (young) children are often unable to undergo these procedures without being physically restrained.

Objective: To compare the cardiac effects (heart rate) and respiratory effects (respiratory rate and saturation) of Dexmedetomidine in comparison to Propofol+Midazolam in children undergoing MRI.

Materials and methods: A prospective, randomized, single blinded comparative study between two anaesthetic agents in a teaching hospital. A sample size of 30 patients in each group, as calculated from the power of previous studies was taken, setting a significance level of P = 0.05, it was calculated that a group of 30 patients allowed the power of the study to be 95 %.Group "P": Patients receiving Midazolam+Propofol combination. Group "D": Patients receiving Dexmedetomidine alone

Results : Both groups showed statistically significant fall in heart rate, respiratory rate and SpO2 at and after 15 min as compared to the baseline values (P value=0.001,P value significant if <0.05).

Conclusion: Dexmedetomidine is a newer drug with fewer side effects and has potential to become a suitable alternative for Propofol+Midazolam combination in children undergoing MRI

KEYWORDS

MRI, Dexmedetomidine, Propofol, Midazolam, Rescue Sedation

Background: 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 the degree of cooperation or immobilization. While most of these procedures themselves pose little risk to the child, the administration of sedation or analgesia may add substantial risk. This may be particularly relevant for procedures, such as magnetic resonance imaging (MRI), that could frighten the child and therefore call for deep sedation. [1]MRI requires specially designed equipment that can function within a powerful magnetic field, that does not degrade the image by interference, and that does not cause injuries from currents induced by strong magnetic fields. Although such specialised equipment is expensive, this should not be a significant consideration when safety is of paramount importance. Respiratory events make up a large population (5.5%) of complications of sedation in children [2][3]

Objective: To compare the cardiac effects (heart rate) and respiratory effects (respiratory rate and saturation) of Dexmedetomidine in comparison to Propofol+Midazolam in children undergoing MRI.

Study Design: A prospective, randomized, single blinded comparative study between two anaesthetic agents in a teaching hospital. The study was carried out at the MRI Centre of a large teaching after obtaining clearance from the hospital ethics committee. Children between the age groups 1 Month - 12 Yrs undergoing elective MRI under anaesthesia at a tertiary level hospital.

Inclusion Criteria

1. Written and informed consent
2. 1 Month – 12 Yrs
3. ASA physical status I or II

Exclusion Criteria

1. Age <1 Month & > 12 Yrs
2. Congenital Heart Disease
3. A recent Upper Respiratory Tract Infection, Pneumonia or episode of Acute Severe Asthma in the proceeding 4 weeks
4. Recent use of Digoxin,Alpha 2 Agonist or Psychotropic medications
5. Allergies to the study drugs
6. Predicted difficult airway
7. Active, uncontrolled GERD
8. Recent use of study drugs in the last 30 days
9. Small duration scans < 50 minutes

Sample Size: It was calculated from the power of previous studies as 30 in each group setting a significance level of P = 0.05, it was calculated that a group of 30 patients allowed the power of the study to be 95 %. Group "P": Patients receiving Midazolam+Propofol combination. Group "D": Patients receiving Dexmedetomidine alone. Randomization was done using the sealed envelope technique; the subject/guardian picked a pre-sealed envelope before the procedure. The envelope was not opened in the presence of subjects/guardians. After opening the envelope secretly the patient was allocated to either the "P" or the "D" group. The parents/guardians of the patient were not aware of the group allocation.

Methodology: Parents/Guardian were briefed and written informed consent obtained.

1. Intravenous access was obtained in the ward.

2. Pre-procedural Baseline Monitoring was done with HR,SpO2,RR.

3. NPO Guidelines which were followed prior to MRI are: Child > 3 Yrs – NPO for Solid & Milk X 08 Hrs Child < 3 Yrs – NPO for Solids & Milk X 06 Hrs Water & Clear liquids to allowed upto 2 Hrs before the procedure. If the procedure was delayed IV fluids will administered in the Pre Anaesthesia Care Unit at the MRI Centre.

4. Drugs were administered on the scan table as follows :
a. Premedication :
I. Inj Glycopyrolate 10 mcg/kg
ii. Inj Midazolam 70 mcg/kg (only in Group P)

b. Group D-Dexmedetomidine
I. Loading Dose - 1 mcg/kg over 10 min
ii. Maintenance Infusion – 0.5 mcg/kg
c. Group P-Propofol
i. Loading Dose – 2 mg/kg over 10 min
ii. Maintenance Infusion – 50 mcg/kg/min

5. Patients were allowed to breathe spontaneously without an artificial airway throughout the procedure. Ventilatory function was assessed by

observation of respiratory activity by anaesthesiologist. If the SpO2 level decreased below 93% for 30 s the imaging process was interrupted and the patient was taken out of the MRI tunnel. After airway patency was assessed, the neck was extended slightly and oxygen was administered via facemask, and the study drug infusion was discontinued temporarily.

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

7. The observer recorded the heart rate, respiratory rate, SpO2, every 5 min during the procedure. The observer also recorded all complications and side effects during or after the anesthetic.

8. The anesthetic was continued for upto 60 min and stopped. Care was taken to include patients with a scan duration approximating 60 minutes. This was for ease of the study. The smaller duration scans were excluded from this study.

Statistical analysis: The information was collected using a structured questionnaire and information entered in computer software. Cross checking and data cleaning was done

- Nominal data (no 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).
- Additional parametric as well as non parametric analysis of the data was performed as deemed essential. p value of < 0.05 was considered as statistically significant. The analysis of the data was performed using Microsoft excel and SPSS.
- A total of 60 patients were included in the study and randomised into two groups viz Propofol (Group P) and Dexmedetomidine (Group D). No patient was excluded in the study. Final analysis of 60 patients was done. (Fig 1)

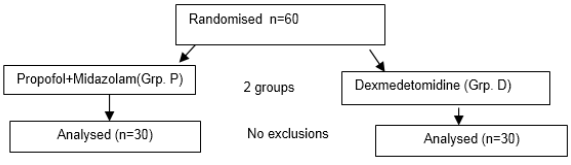

Table 1: Comparison of demographic variables between Group P & Group D. Un-paired t test is applied.

Parameter	Group P (n=30)		Group D (n=30)		Significance (P value)
	Mean	SD	Mean	SD	
Age	4.64	3.16	4.88	2.83	0.76
Weight	17.62	6.00	19.33	5.84	0.27

Table 2: Comparison of heart rate between Group P & Group D. Un-paired t test is applied.

Parameter	Time points	Group P (n=30)		Group D (n=30)		Significance (P value)
		Mean	SD	Mean	SD	
HEART RATE	minus 05 Min	107.10	10.41	105.10	9.89	0.45
	00 MIN	114.63	10.74	112.86	12.10	0.55
	05 MIN	106.10	8.55	104.87	9.41	0.60
	10 MIN	103.30	7.63	101.67	9.26	0.46
	15 MIN	101.53	8.92	99.10	8.37	0.28
	20 MIN	99.07	7.63	95.77	9.68	0.15
	25 MIN	98.03	6.54	95.30	8.98	0.18
	30 MIN	98.43	7.33	96.03	9.33	0.27
	35 MIN	97.70	6.78	95.87	8.79	0.37
	40 MIN	98.07	6.94	95.57	9.39	0.25
	45 MIN	98.00	7.09	95.30	9.67	0.22
	50 MIN	97.97	7.07	96.67	9.56	0.55
	55 MIN	99.57	8.40	97.60	9.39	0.40
	60 MIN	99.70	7.56	98.40	9.64	0.56

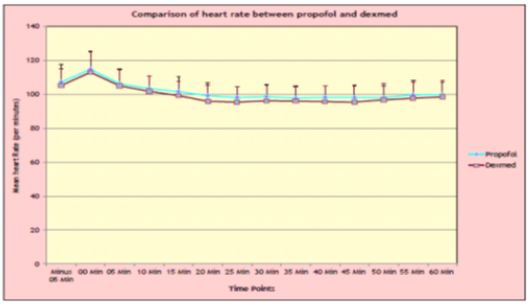

Fig 2: There was no significant difference in the heart rate of both the groups throughout the MRI.

Table 3: Comparison of saturation between Group P & Group D.

Parameter	Time points	Group P (n=30)		Group D (n=30)		Significance (P value)
		Mean	SD	Mean	SD	
	00-05 Min	99.10	0.88	98.83	1.02	0.28
	00 MIN	98.67	1.03	98.57	1.10	0.72
SATURATION	05 MIN	94.33	16.23	94.00	16.21	0.94
	10 MIN	93.07	16.77	93.00	16.79	0.99
	15 MIN	95.57	1.59	95.40	1.81	0.71
	20 MIN	95.20	1.81	95.10	1.77	0.83
	25 MIN	95.17	1.95	95.37	2.06	0.70
	30 MIN	94.87	1.98	95.00	2.15	0.80
	35 MIN	95.47	1.78	95.63	1.99	0.73
	40 MIN	95.47	1.89	95.43	1.81	0.94
	45 MIN	95.47	1.91	95.27	1.93	0.69
	50 MIN	94.80	1.65	95.17	1.95	0.43
	55 MIN	95.97	1.54	96.17	1.60	0.62
	60 MIN	96.40	1.50	96.70	1.29	0.41

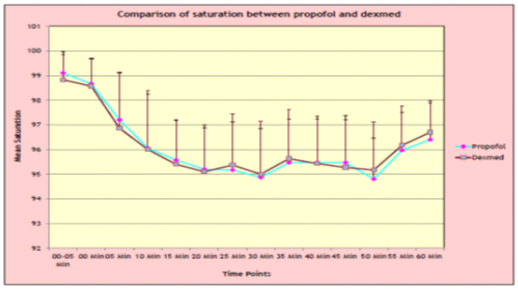

Fig 3:There was no significant difference between the saturation of both the groups throughout the MRI.

Table 4: Comparison of respiratory rate between Group P & Group D. Un-paired t test is applied.

Parameter	Time points	Group P (n=30)		Group D (n=30)		Significance (P value)
		Mean	SD	Mean	SD	
RESPIRATORY RATE	00-05 Min	20.97	2.98	19.93	2.85	0.18
	00 MIN	22.43	2.86	21.80	3.93	0.47
	05 MIN	20.17	2.93	19.90	3.74	0.76
	10 MIN	18.50	3.16	17.70	3.82	0.38
	15 MIN	16.67	3.34	19.27	17.66	0.43
	20 MIN	16.00	3.83	15.37	4.27	0.55
	25 MIN	15.93	3.68	15.33	3.86	0.54
	30 MIN	15.90	3.37	15.27	3.67	0.49
	35 MIN	16.20	2.31	15.63	2.76	0.39
	40 MIN	16.40	2.14	15.93	2.30	0.42
	45 MIN	16.47	2.49	16.10	3.06	0.61
	50 MIN	16.57	2.40	16.63	2.47	0.92
	55 MIN	17.40	2.49	17.43	2.49	0.96
	60 MIN	18.13	2.15	18.13	2.34	1.00

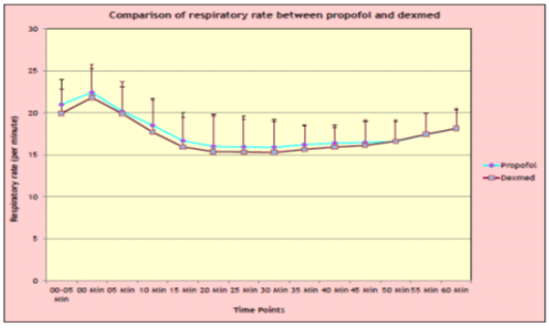

Fig 4 : There was no significant difference between the respiratory rates of both the groups.

Table 5: Comparison of apnoea between propofol and dexmed. Chi-Squared test is applied

Parameter	Time points	Group P (n=30)		Group D (n=30)		Significance (P value)
		No Apnoea (n)	%	No Apnoea (n)	%	
	00	30	100 %	30	100 %	1.00
APNOEA	05 MIN	30	100 %	30	100 %	1.00
	10 MIN	30	100 %	30	100 %	1.00
	15 MIN	30	100 %	30	100 %	1.00
	20 MIN	30	100 %	30	100 %	1.00
	25 MIN	30	100 %	30	100 %	1.00
	30 MIN	30	100 %	30	100 %	1.00
	35 MIN	30	100 %	30	100 %	1.00
	40 MIN	30	100 %	30	100 %	1.00
	45 MIN	30	100 %	30	100 %	1.00
	50 MIN	30	100 %	30	100 %	1.00
	55 MIN	30	100 %	30	100 %	1.00
	60 MIN	30	100 %	30	100 %	1.00

Table 6: Comparison of desaturation between Group P & Group D. Chi-Squared test is applied

Parameter	Time points	Group P (n=30)		Group D (n=30)		Significance (P value)
		No Desaturation(n)	%	No Desaturation(n)	%	
	00 MIN	30	100 %	30	100 %	1.00
Desaturation	05 MIN	30	100 %	30	100 %	1.00
	10 MIN	30	100 %	30	100 %	1.00
	15 MIN	30	100 %	30	100 %	1.00
	20 MIN	30	100 %	30	100 %	1.00
	25 MIN	30	100 %	30	100 %	1.00
	30 MIN	30	100 %	30	100 %	1.00
	35 MIN	30	100 %	30	100 %	1.00
	40 MIN	30	100 %	30	100 %	1.00
	45 MIN	30	100 %	30	100 %	1.00
	50 MIN	30	100 %	30	100 %	1.00
	55 MIN	30	100 %	30	100 %	1.00

Table 7: Change in heart rate within Group P & Group D. Paired t test is applied

Parameter	Time points	Group P (n=30)			Group D (n=30)		
		Mean	SD	Paired t test	Mean	SD	Paired t test
	-05 Min	107.10	10.41	-	105.10	9.89	-
Heart Rate	00 MIN	114.63	10.74	0.001	112.86	12.10	0.001
	05 MIN	106.10	8.55	0.50	104.87	9.41	0.87
	10 MIN	103.30	7.63	0.01	101.67	9.26	0.02
	15 MIN	101.53	8.92	0.001	99.10	8.37	0.001
	20 MIN	99.07	7.63	0.001	95.77	9.68	0.001
	25 MIN	98.03	6.54	0.001	95.30	8.98	0.001
	30 MIN	98.43	7.33	0.001	96.03	9.33	0.001
	35 MIN	97.70	6.78	0.001	95.87	8.79	0.001
	40 MIN	98.07	6.94	0.001	95.57	9.39	0.001
	45 MIN	98.00	7.09	0.001	95.30	9.67	0.001
	50 MIN	97.97	7.07	0.001	96.67	9.56	0.001
	55 MIN	99.57	8.40	0.001	97.60	9.39	0.001
	60 MIN	99.70	7.56	0.001	98.40	9.64	0.001

Table 8: Change in saturation within propofol and dexmed groups. Paired t test is applied

Parameter	Time points	Propofol (N=30)			Dexmed (n=30)		
		Mean	SD	Paired t test	Mean	SD	Paired t test
SATURATION	00-05 Min	99.10	0.88	-	98.83	1.02	-
	00 MIN	98.67	1.03	0.03	98.57	1.10	0.20
	05 MIN	94.33	16.23	0.12	94.00	16.21	0.11
	10 MIN	93.07	16.77	0.06	93.00	16.79	0.07
	15 MIN	95.57	1.59	0.001	95.40	1.81	0.001
	20 MIN	95.20	1.81	0.001	95.10	1.77	0.001

	25 MIN	95.17	1.95	0.001	95.37	2.06	0.001
	30 MIN	94.87	1.98	0.001	95.00	2.15	0.001
	35 MIN	95.47	1.78	0.001	95.63	1.99	0.001
	40 MIN	95.47	1.89	0.001	95.43	1.81	0.001
	45 MIN	95.47	1.91	0.001	95.27	1.93	0.001
	50 MIN	94.80	1.65	0.001	95.17	1.95	0.001
	55 MIN	95.97	1.54	0.001	96.17	1.60	0.001
	60 MIN	96.40	1.50	0.001	96.70	1.29	0.001

Table 9: Change in respiratory rate within Group P & Group D. Paired t test is applied

Parameter	Time points	Propofol (n=30)			Dexmed (n=30)		
		Mean	SD	Paired t test	Mean	SD	Paired t test
	00-05 Min	20.97	2.98	-	19.93	2.85	-
Respi. Rate	00 MIN	22.43	2.86	0.002	21.80	3.93	0.01
	05 MIN	20.17	2.93	0.08	19.90	3.74	0.95
	10 MIN	18.50	3.16	0.001	17.70	3.82	0.01
	15 MIN	16.67	3.34	0.001	19.27	17.66	0.85
	20 MIN	16.00	3.83	0.001	15.37	4.27	0.001
	25 MIN	15.93	3.68	0.001	15.33	3.86	0.001
	30 MIN	15.90	3.37	0.001	15.27	3.67	0.001
	35 MIN	16.20	2.31	0.001	15.63	2.76	0.001
	40 MIN	16.40	2.14	0.001	15.93	2.30	0.001
	45 MIN	16.47	2.49	0.001	16.10	3.06	0.001
	50 MIN	16.57	2.40	0.001	16.63	2.47	0.001
	55 MIN	17.40	2.49	0.001	17.43	2.49	0.001
	60 MIN	18.13	2.15	0.001	18.13	2.34	0.001

Result and Discussion: The patients' demographic were not statistically different between groups. (Table 1) Both the groups had comparable heart rate, respiratory rate and saturation throughout the study. P value > 0.05 (P value significant if <0.05). (Table 2, 3, 4) Both groups showed statistically significant fall in heart rate, respiratory rate and SpO2 at and after 15 min as compared to the baseline values (P value=0.001,P value significant if <0.05).However these never went below the normal acceptable value for that age group and were not any significant magnitude so as to warrant any interruption or intervention. Decreases in heart rate have been reported over time with dexmedetomidine in children.[8,9,10]. Our results are consistent with those data, with heart rate falling significantly. (Table 2, 7) However, there were no instances of bradycardia requiring any intervention in this study. Some studies have also shown contradictory results with no significant fall in heart rate [9]. Similar to previous studies propofol has been shown to cause a decrease in heart rate in our study [9].(Table 2,7) 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 [1].Some authors have reported that dexmedetomidine did not affect RR and SpO2[11,12].However, some respiratory complications have been reported with large and rapid initial loading doses (4,5,6). Propofol may depress ventilation, suppress pharyngeal and laryngeal reflexes, and cause transient apnoea (4,7).In our study respiratory rate and SpO2 fell significantly (P=0.001) at and after 15 minutes however this was not clinically insignificant and required no intervention during the two treatments. This, together with the absence of any episodes of apnoea, bradypnoea or desaturation suggests that neither dexmedetomidine nor propofol depresses respiration excessively in children when used in the dose range and manner used in this study.(Table 2,3,4,5,6,7). 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. Moreover the infusion was given for exact 60 minutes duration only after which it was stopped. This was done for the convenience of the analysis. This lead to exclusion of scan which were deemed to have smaller duration. This might have lead to a selection bias. Another limitation was that we did not monitor the blood pressure before, during or after the scan. Paediatric patients are more dependent on heart rate than on blood pressure to maintain cardiac output, hence monitoring of blood pressure would have been inconsequential. Moreover adding another parameter would have made the statistical analysis more complex.

Conclusion:

- Both Dexmedetomidine alone (Group D) & the combination of Propofol+Midazolam (Group P) provided adequate conditions for MRI without failures in our study or any requirement of supplemental sedation.
- Respiratory indices were similar in both the groups.There were no episodes of bradypnoea, apnoea or desaturation in either group.
- Heart rate changes were transient and of limited clinical importance at the doses of anaesthetic treatments studied.Recovery to full responsiveness after Dexmedetomidine was statistically significantly prolonged.
- Although time required for induction and recovery are higher with Dexmedetomidine, the better therapeutic index of Dexmedetomidine gives it an advantage over combination of Propofol+Midazolam.
- "Dexmedetomidine is a newer drug with fewer side effects and has potential to become a suitable alternative for Propofol+Midazolam combination in children undergoing MRI."

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