

# The Effect Of Two Doses Of Nebulised Dexmedetomidine For Premedication Of Pediatric Patients: A Randomised Study

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## Abstract

**Background:** Pre-operative anxiety is common in pediatric population. Fear of parental separation, fear of strange hospital environment and painful procedures contribute to preoperative anxiety. Preoperative anxiety in children is associated with several adverse postoperative outcomes, such as increased distress in the recovery phase, and postoperative regressive behavioural disturbances, such as nightmares, separation anxiety, eating disorders, and bedwetting. Preoperative anxiety in paediatric patients is therefore an important concern for anaesthesiologist. Dexmedetomidine nebulisation is an attractive option as paediatric premedication. However, the effective dose is not well established in paediatric patients. So, in our study, we want to compare the doses of 2 mcg/kg and 3mcg/kg and study their effects.

**Methodology:** This prospective randomised study included 78 patients between 1-8 years. Patients were divided into two groups as A and B. Group A received 2 mcg/kg of nebulised dexmedetomidine, and the Group B received 3mcg/kg of nebulised dexmedetomidine preoperatively. Parental separation anxiety scale score noted 30 minutes after end of nebulisation. In operating room Mask acceptance score noted before induction. All the patients received general anaesthesia. Hemodynamic variables, emergence agitation and sedation score compared between two groups. Statistical analysis done using Mann Whitney U test and chi square test. A p-value <0.05 accepted as significant.

**Results:** Parental separation anxiety score ( $p < 0.003$ ) and mask acceptance score ( $p < 0.014$ ) was significantly better in group B when compared to group A. All hemodynamic parameters were comparable between group A and group B. Vital signs were maintained within normal range in both the groups during perioperative period, with no significant statistical difference between two groups.

**Conclusion:** Nebulised dexmedetomidine in a dose of 3mcg/kg provides better parental separation and mask acceptance.

**Keywords:** Dexmedetomidine, paediatric patients Nebulised dexmedetomidine, premedication, separation anxiety.

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## I. Introduction

Pre-operative anxiety is common in pediatric population. Fear of parental separation, fear of strange hospital environment and painful procedures contribute to preoperative anxiety. This leads to stress, tachycardia, agitation, or excessive crying which make management of such patients difficult during induction of anaesthesia. Preoperative anxiety in children is associated with a number of adverse postoperative outcomes, such as increased distress in the recovery phase, and postoperative regressive behavioural disturbances, such as nightmares, separation anxiety, eating disorders, and bedwetting. Preoperative anxiety in paediatric patients is therefore an important concern for anaesthesiologist. Various nonpharmacological means to minimize child's anxiety are used like preadmission visits showing videos and preoperative clinic visits by the anaesthesiologist to establish rapport with the child. Despite the many advances in nonpharmacologic interventions, practitioners

still rely on sedative premedicants. Most of young unpremeditated children resist application of face mask during induction or become uncooperative on venepuncture. Effective premedication often permits a less traumatic separation of the child from parents and can facilitate smooth induction of anaesthesia. Premedication can be given by various routes like oral, rectal and transmucosal or parenteral route. Transmucosal route including intranasal, sublingual and buccal are effective way to administer premedication as it is relatively easy, non-invasive route with high bioavailability and rapid onset of action comparable to that of intravenous administration because of rich blood supply of the airway mucosa and bypassing the first pass hepatic metabolism. The sensation of burning and nasal irritation is a disadvantage of the nasal route, and sneezing or coughing caused by the nasal irritation could reduce the effects of nasal premedication. Inhalation of nebulized drug is an alternative method of administration that is relatively easy to set up, does not require venipuncture, and is associated with high bioavailability of the administered drug. Dexmedetomidine, a selective alpha-2 agonist with central sedative and anxiolytic, has been tried as preoperative anxiolytic via nasal and inhalational routes in paediatric patients. Dexmedetomidine nebulisation is an attractive option as paediatric premedication. However, the effective dose is not well established in paediatric patients. The aim of the present study was to compare the efficacy of two doses of dexmedetomidine as premedication for parental separation anxiety and mask acceptance scores.

## **II. Methods and Materials**

This prospective study was conducted in the Department of Anaesthesiology and Critical care, Gauhati Medical College and Hospital, Guwahati in a span of 1 year with prior permission and approval from the institutional ethical committee, after fulfilling the norms (Institutional Ethics Committee, Gauhati Medical College and Hospital clearance no. MC/190/2007/Pt-11/July 2021 /TH-31). This trial was prospectively registered under Clinical Trials Registry- India (Registration no. CTRI/2022/02/040637).

**Study Design:** Single centre, prospective, randomized study.

**Study Location:** The study was carried out in the pre-operative holding area, operation theatre, and recovery rooms of Department of Paediatric surgery, general surgery, and ENT, GMCH.

**Study Duration:** 1<sup>st</sup> August 2021 to 31<sup>st</sup> July 2022

**Sample size:** 78 patients.

**Sample size calculation:** The sample size calculations were done based on a previous study which showed a Parental Separation Anxiety Scale (PSAS) of 1 in 60% of the patients and a Mask Acceptance Score (MAS) of 1 in 15% of the patients. The power of the study was taken as 80% with a 5% level of significance. 31 patients were needed to detect a 30% increase in the PSAS score and 35 patients were needed to detect a 30% increase in the MAS score after increasing the dose of dexmedetomidine. Considering the larger number, we considered 35 patients will be needed in each group. Further, to account for a 10% dropout rate, 39 patients will be needed per group with a fixed sample size of 78 patients.

### **Subjects & selection method**

Patients aged between 1 and 8 years belonging to the American Society of Anesthesiologists (ASA) physical status I and II of either sex posted for elective surgery were included in the study. Patients with a history of cardiac disease, asthma, seizure disorders, mental retardation, developmental delay, congenital malformation and allergy were excluded from the study. A written and informed consent was taken from parents/ guardians of all patients, who met the inclusion criteria, after explaining the procedure involved.

## **III. Methodology**

Parents/guardians of the patients, who gave consent to participate in the study were divided into two groups, A and B (39 each) by a computer-generated list of random numbers, with group allocation concealed in sealed opaque envelopes.

**Group A:** received 2mcg/kg of dexmedetomidine diluted with 0.9% normal saline to total volume of 3ml in nebulisation mask chamber.

**Group B:** received 3 mcg/kg of dexmedetomidine diluted with 0.9% normal saline to total volume of 3 ml in nebulisation mask chamber.

On the day of surgery, patients were taken to the pre-operative holding area with one parent and monitors were connected- baseline SpO<sub>2</sub> and Heart Rate and MAP values were recorded. A designated resident, who was not involved in the data collection or anaesthetic management of the patients; opened the sealed envelopes- that allocated the patients into two groups. After allocation, the resident also prepared the drugs to be used in the study. At 30 minutes before induction nebulisation of the drugs were started via a nebuliser with a proper fitting face mask with continuous flow of 100% oxygen at 6L/min for 10-15mins. Spo<sub>2</sub>, Heart Rate (HR), non-invasive

blood pressure(NIBP)were monitored every 5 minutes from the start of nebulisation. Separation anxiety score was noted 30 minutes after the end of nebulization, while shifting the patient to the operating room (OR) room based on Parental Separation Anxiety Scale(PSAS).After shifting the patient to OR, standard monitors such as SpO<sub>2</sub>, NIBP(MAP), electrocardiogram (ECG) were connected. In the OR, mask acceptance by the child was assessed using Mask Acceptance Score (MAS), just before induction of anaesthesia.The primary outcome of this study was to compare PSAS while shifting patient to OR ,30 min after the end of nebulization .The separation score was monitored as per Parental Separation Anxiety Scale (PSAS), with a 4-point scale as: 1=easy separation; 2=whimpers, but is easily reassured, not clinging; 3=cries and cannot be easily reassured, but not clinging to parents and 4=crying and clinging to parents<sup>9</sup> and to compare MAS score before induction. Mask Acceptance Score (MAS) was noted according to a 3-point scale: 1=patient allows mask over his face without any resistance; 2=patient allows mask over his face with some resistance that can be overcome by the person holding the mask and 3=patient allows mask over his face with significant resistance that cannot be overcome by the person holding the mask alone and requires additional help<sup>10</sup>. All patients were made to undergo general anaesthesia with the similar protocol. Pre oxygenation with 100% Oxygen was done for 3 minutes with a proper fitting face mask. IV premedication was done simultaneously with Inj Glycopyrrolate 10 µg/kg and Inj Fentanyl 1 µg/kg. Induction was started with 8% Sevoflurane dial concentration which was incrementally lowered to reach a final concentration of 2%, with 100% O<sub>2</sub> via a face mask. Tracheal intubation was done under muscle paralysis with Inj Atracurium 0.5mg/kg and the ET tube placement was confirmed with 5-point auscultation and capnography, before the tube was fixed. Hemodynamic parameters were recorded at every 5 minutes after intubation. Anaesthesia was maintained with O<sub>2</sub>:N<sub>2</sub>O in the ratio 2:4, with Sevoflurane dial concentration adjusted to maintain age specific MAC of 0.9 to 1.2. Muscle relaxation was maintained with intermittent doses of 0.1 mg/kg Inj Atracurium. Patients were ventilated with an initial tidal volume of 6 to 8 ml/kg and age specific respiratory rate; which was later adjusted to keep the end tidal carbon dioxide (EtCO<sub>2</sub>) within 35 to 45 mmHg. Intraoperative fluid was given as per Holliday-Segar formula. MAP,HR and SpO<sub>2</sub> were monitored throughout the procedure.Sevoflurane inhalation was stopped at the commencement of skin closure. Patients were reversed with Inj Neostigmine 0.05 mg/kg and Inj Glycopyrrolate 0.01 mg/kg. Oropharyngeal suctioning was done and trachea was extubated when the patient's gag reflex had returned and was breathing spontaneously and making purposeful movements. Duration of surgery was noted.

Emergence Agitation Score <sup>10</sup>noted just after extubation according to a 3-point scale: grade 1-calm and easily arousable, grade 2-restless but calms to verbal instructions and grade 3-combative and disoriented . Patients were then transferred to the PACU. Post Operative sedation was assessed just after shifting the patient to PACU using Ramsay Sedation Score according to 6 point<sup>12</sup> scale :1- Anxious or restless or both,2-Cooperative, oriented and tranquil,3- Responding to commands ,4- Brisk response to stimulus,5- Sluggish response to stimulus,6- No response to stimulus.

#### **Statistical analysis**

After completion of the study, data was entered in MS Excel spreadsheet. Chi square test or Fisher's exact test was used to evaluate association between categorical variables. Data was checked for normality using Kolmogorov-Smirnov test and Shapiro-Wilk test. Independent t test was used to compare mean difference between two groups depending on fulfilment of normality assumption for continuous variables. For non-normal data, Mann Whitney test was used. All data was analysed using SPSS version 2.1.

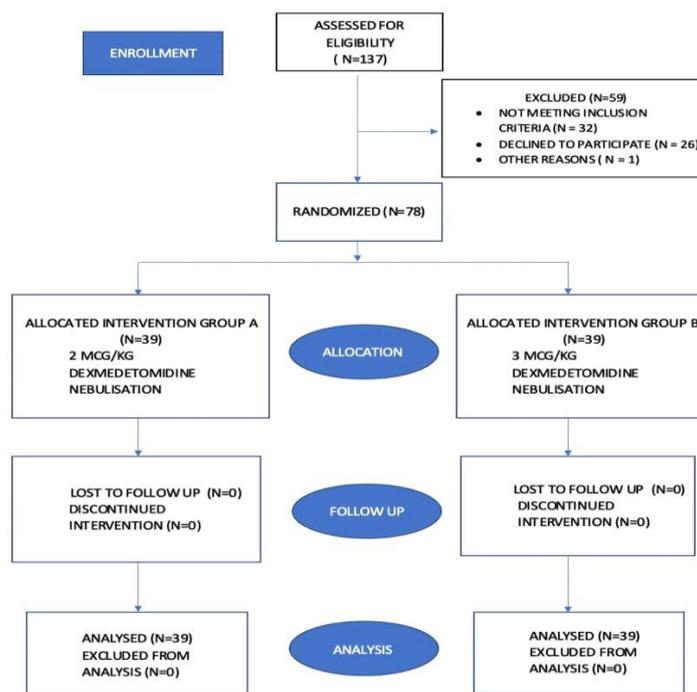
Statistical significance between the two groups were interpreted as follows-

- p- value > 0.05 – not significant
- p-value < 0.05 – significant
- p-value < 0.001 – highly significant

#### **IV. Result**

A total of 137 patients were screened for inclusion criteria for this study. 32 patients were excluded from the study due to not meeting the inclusion criteria. 26 patients' parents refused to participate in the study and hence were excluded. One patient was excluded because of non-standardized nebulization protocols. Data from the rest of 78 patients were analysed. All patients belonged to ASA physical status I and II. Patients were randomly divided into two equal group (Group A and B)

Figure I: Consort Flow Diagram



PSAS	Mean	SD	Median (IQR)	p value
Group A	1.54	0.643	1 (1-2)	0.003
Group B	1.15	0.366	1 (1-1)	

Table 1: Comparison of Mean Parental Separation Anxiety Scale scores between both groups

Table 1 shows that the mean PSAS in Group B 0.366, was lesser than 0.643, the mean score in Group B; with a statistically significant difference.

PSAS	Group A	Group B	Total	p value
1	21(53.8%)	33(84.6%)	54(69.2%)	0.009
2	15(38.5%)	6(15.4%)	21(26.9%)	
3	3(7.7%)	0(0%)	3(3.8%)	
4	0(0.0%)	0(0.0%)	0(0.0%)	
Total	39(100%)	39(100%)	78(100%)	

Table 2: Comparison of individual PSAS scores in both groups

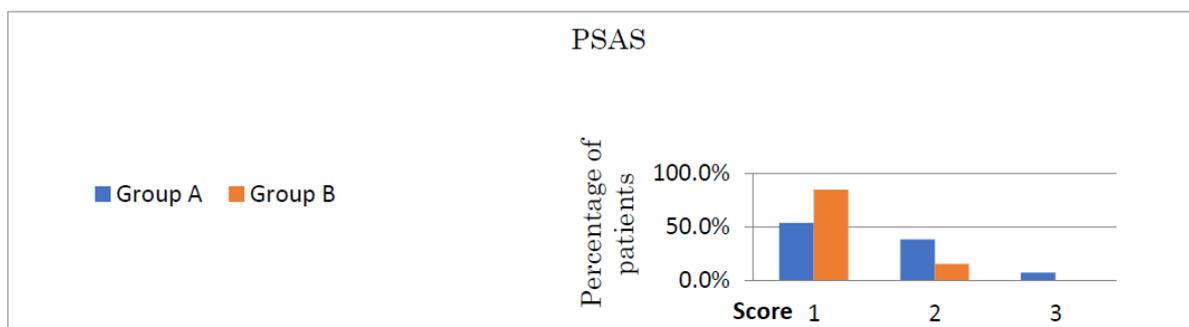


Figure II: Comparison of individual PSAS scores in both groups

It can be seen from table 2 and figure 1 that number of patients with scores 1 and 2 are more in Group B; and that of scores 3 are more in Group A with a statistical significant difference.

**Mask Acceptance Score (MAS)**

TABLE 3: Comparison of mean MAS scores in both groups

MAS	Mean	SD	Median (IQR)	p value
Group A	1.9	0.821	2 (1-3)	0.013
Group B	1.46	0.682	1 (1-2)	

Table 3 shows Mean MAS score in Group A and Group B. This difference was highly significant  $p < 0.013$ .

TABLE 4: Comparison of individual MAS scores in both groups

MAS	Group A(Number of Patients )	Group B(Number of Patients )	Total(Number of Patients )	p value
1	15(38.5%)	25(64.1%)	40(51.3%)	0.046
2	13(33.3%)	10(25.6%)	23(29.5%)	
3	11(28.2%)	4(10.3%)	15(19.2%)	
Total	39(100%)	39(100%)	78(100%)	

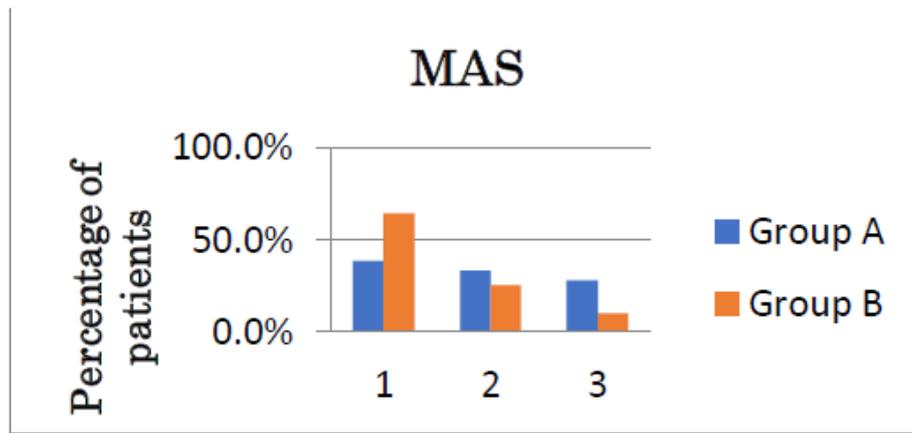


Figure III: Comparison of individual MAS scores in both groups

Table 4 and Figure II shows a comparison of individual MAS scores in both groups with a higher number of children with score 2 (unacceptable) in Group A as compared to Group A with a statistically significant difference.

**Emergence Agitation Score (EAS)**

TABLE 5: Comparison of mean EAS scores in both groups

EAS	Mean	SD	Median (IQR)	p value
Group A	1.87	0.62	2(1-2)	0.578
Group B	1.79	0.62	2(1-2)	

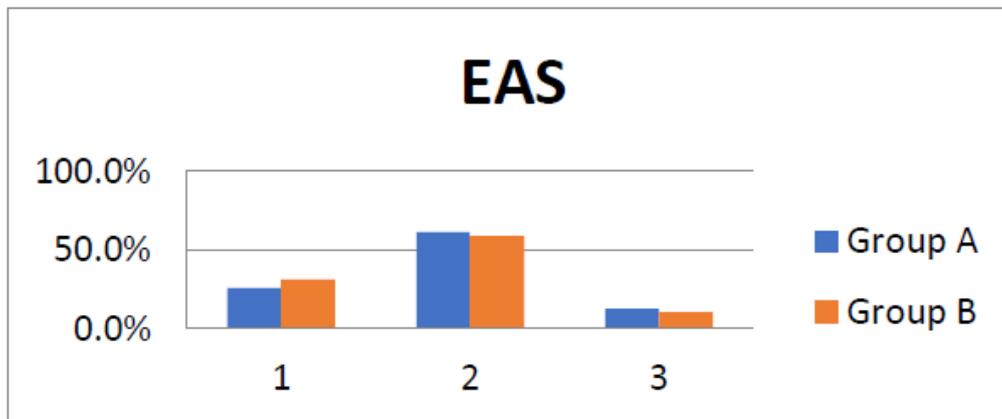


Figure IV: Comparison of individual EAS scores in both groups

Table 5 shows Mean EAS score in Group A was  $1.87 \pm 0.62$  and in Group B was  $1.79 \pm 0.62$ . This difference was not significant.

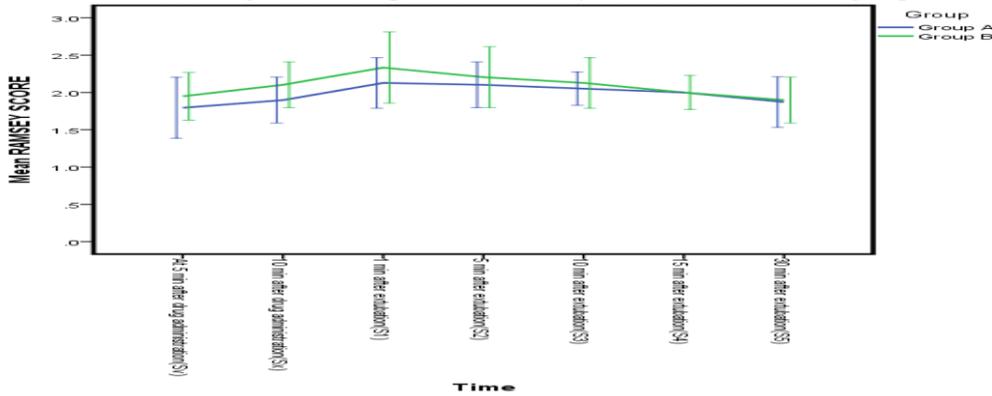
A comparison of individual EAS scores in both groups show a higher number of children with score 2 in both groups without any statistical significance (figure IV).

**Ramsay Sedation Scores**

Table 6: Comparison of Ramsay sedation scores in both groups

	Group A		Group B		
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
At 5 min after drug administration(Sv)	1.79±0.409	2(2-2)	1.95±0.32	2(2-2)	0.071
10 min after drug administration(Sx)	1.9±0.307	2(2-2)	2.1±0.307	2(2-2)	0.005
1 min after extubation(S1)	2.13±0.339	2(2-2)	2.33±0.478	2(2-3)	0.033
5 min after extubation(S2)	2.1±0.307	2(2-2)	2.21±0.409	2(2-2)	0.212
10 min after extubation(S3)	2.05±0.223	2(2-2)	2.13±0.339	2(2-2)	0.238
15 min after extubation(S4)	2±0	2(2-2)	2±0.229	2(2-2)	1.00
30 min after extubation(S5)	1.87±0.339	2(2-2)	1.9±0.307	2(2-2)	0.725

Figure V : Comparison of Ramsay sedation scores in both groups



In table 7 and figure V, the mean RSS scores at all time points were found to be higher in Group B than in Group A, with no statistically significant difference except at 10 minutes after nebulisation.

Figure VI: Comparison of individual Ramsay sedation scores in both group

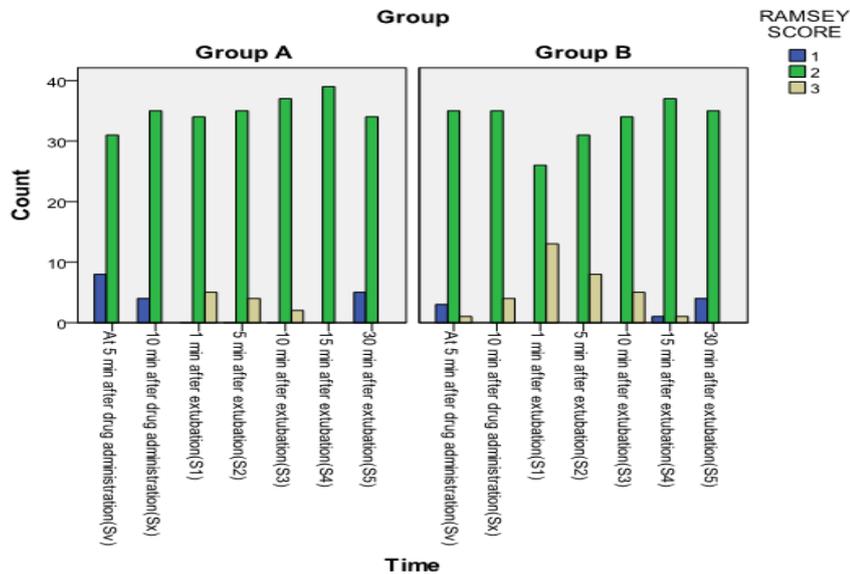


Figure VI shows individual RSS scores at different time points for both the groups .No. of children with score 2 is much higher in Group B than in, at all points of time except 10 mins after drug administration. The difference was not found to be statistically significant in any point of time. In neither group was a RSS score of  $\geq 4$  seen at any given time point.

**Hemodynamic Variables**

Figure VII: Comparison of heart rate in both groups

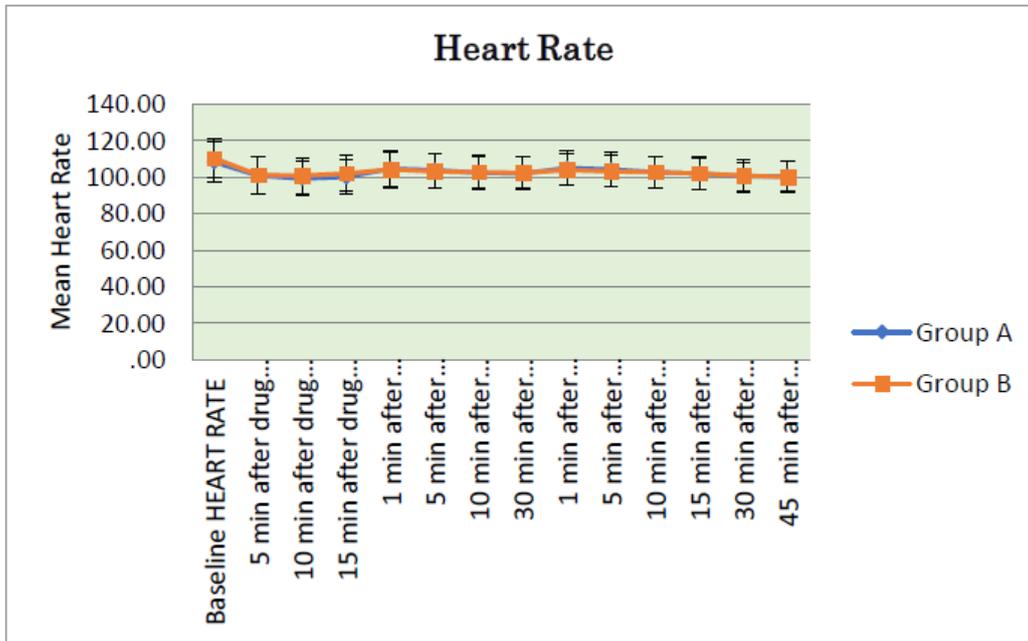


Figure VII shows comparison of the HR trends between the groups, it was found that there was a mean decrease after administration of the drug in Group B. This difference was not statistically significant.

**Mean Arterial Pressure (MAP)**

Figure VIII: Comparison of MAP in both groups

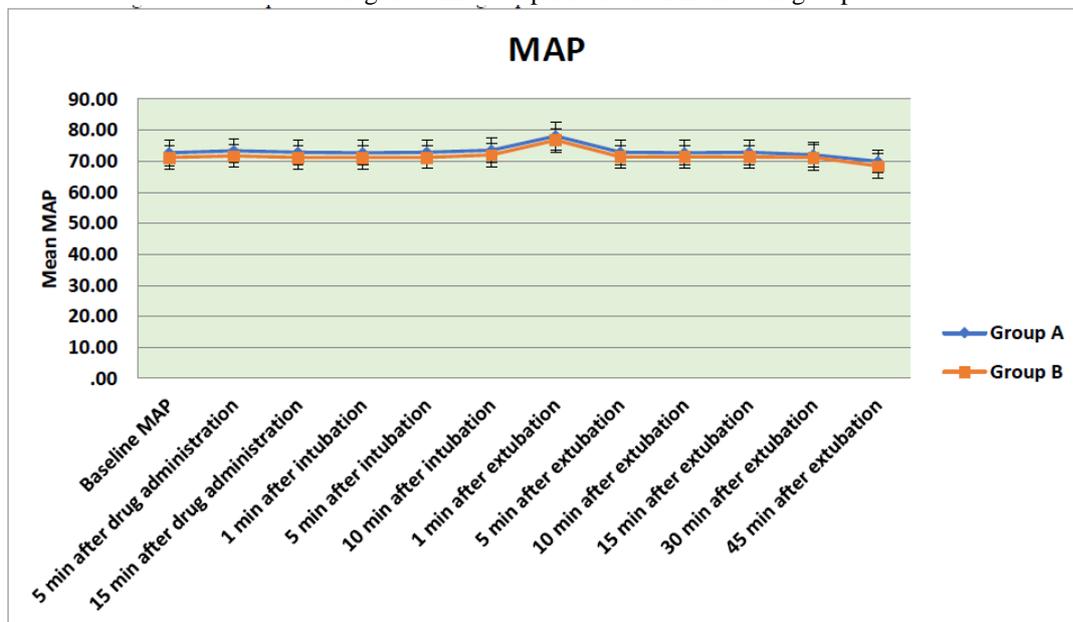


Figure VIII shows Comparison of the mean MAP in both groups. There was a decrease in mean MAP in Group B compared to Group A, however this difference was not found to be statistically significant. No episodes of hypotension were recorded in any of the groups.

### Oxygen Saturation (SpO<sub>2</sub>)

Figure IX: Comparison of SpO<sub>2</sub> in both groups

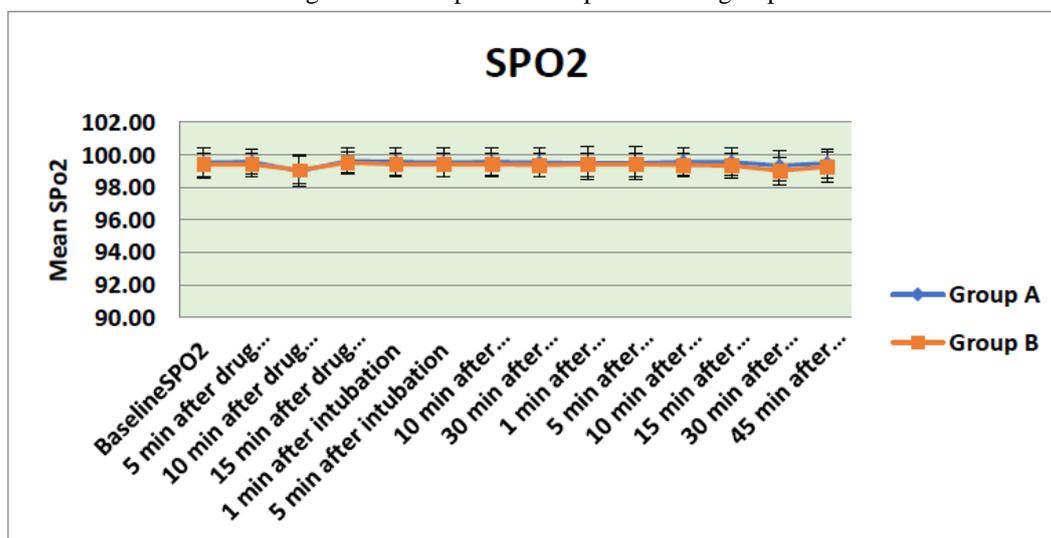


Figure IX compares SpO<sub>2</sub> in both groups. No statistically significant difference was seen at any time point and no episode of desaturation was recorded in either group at any time points. No incidence of adverse effects like hypotension, bradycardia, desaturation, laryngospasm were seen in either group.

### V. Discussion

The demographic characteristics of the patients in the study groups in terms of age, sex, ASA category, weight, and duration of surgery were comparable and statistical tools did not show any significant difference.

In our study we compared the effect of two doses of nebulised dexmedetomidine (2 mcg/kg and 3 mcg/kg) for premedication in pediatric patients. The primary outcome of our study was to compare the PSAS and MAS between both the groups. In our study, comparing the mean PSAS, we observed a lower value in group B (3mcg/kg) compared to group A (2mcg/kg) which was statistically significant. We found that 84.6% of patients in group B and 53.8% of patients in group A had score of 1, 15.4% of patients in group B and 38.5% of patients in group A had a score 2. Only 7.7% of patients in group A had score 3 whereas no patients in both the groups had score 4.

Similar to our study, Abdel-Ghaffar et al. found lower PSAS scores in patients receiving 2mcg/kg nebulised dexmedetomidine. Consistent with our findings, Anupriya et al. found better parental separation with a dose of 3mcg/kg of nebulised dexmedetomidine in pediatric patients of age group 1-3 years, compared to a dose of 2mcg/kg nebulised dexmedetomidine, with a statistical significance, which is within our study group age limits. However, contrary to our findings, Ali and Mahmoud found higher scores in group receiving 3mcg/kg nebulised dexmedetomidine. This discrepancy might be attributed to the lower sample size used in their study.

In our study Mask acceptance score (MAS) was assessed using a 3-point scale. Scores 1 and 2 were considered acceptable. We found that 64.1% of patients in group B (3mcg/kg) and 38.5% of patients in group A (2mcg/kg) had score 1, 25.6% of patients in group B and 33.3% of patients in group A had score 2. In group B, 10.3% of patients and 28.2% of patients in group A had score 3. Thus, we found more acceptable mask acceptance score in group B which was statistically significant. Our findings are consistent with Anupriya et al. study, who also reported a better MAS in group receiving 3 mcg/kg.

In our study EA was noted using 3-point scale. EA scores were comparable between both groups. Our findings are comparable with study done by Ali and Mahmoud in patients receiving 3mcg/kg. Similarly, Anupriya et al. did not find any statistically significant difference in EA score between the two groups receiving 2mcg/kg and 3mcg/kg respectively.

Thus, both the doses 2mcg/kg and 3 mcg/kg of nebulized dexmedetomidine can offer acceptable results in preventing emergence agitation.

We compared the sedation of children in both groups using Ramsay Sedation Score (RSS). RSS is a validated 6-point scale with higher scores corresponding to more sedation. Scores 1-3 has been considered to be lightly sedated and 4-6 as deeply sedated. We found comparable sedation score between both the groups. After extubation number of children with score 3 was higher in Group B compared to group A. We evaluated the sedative action of dexmedetomidine up to 30 mins post-operatively as elimination half-life of dexmedetomidine is 2 hours. Dexmedetomidine has been reported in earlier studies to offer better post operative sedation when compared to ketamine via intranasal route. Elshafeey et al., found median (IQR) of RSS assessed post operatively as 3(3-4), 3(2-3) and 2(2-2) at 10 minutes, 20 minutes and 30 minutes respectively in intranasal dexmedetomidine group. We observed a similar trend of sedation in both the groups. Post operatively, no statistically significant difference was found between Mean RSS of both the groups at any point of time. Deep sedation was not noted in either group. However, no study has been done earlier which compared sedation in any scale using two doses of dexmedetomidine as of ours.

When comparing Heart rate (HR) and Mean arterial pressure (MAP) changes after nebulisation, we observed that at the baseline before giving the drug there was no statistically significant difference ( $p > 0.05$ ) between both groups. There was a decrease in HR and MAP following administration of drug in both the groups preoperatively. The Mean HR and Mean MAP at various intervals, were comparable between both the groups. Anupriya et al. found a 10.3% incidence of hypotension in Group D2 (2mcg/kg nebulised dexmedetomidine) and 13.3% in group D3 (3mcg/kg nebulised dexmedetomidine). One patient in Group D3 had developed bradycardia which was managed conservatively. In contrast, our results showed no episodes of bradycardia or hypotension both pre and post operatively. Abdel-Ghaffar et al. in their study found that the patients who received nebulised dexmedetomidine showed lower HR and BP mean values preoperatively and lower mean HR at 10 min intraoperatively. However, these haemodynamic changes were not clinically significant and required no intervention. There was no significant difference in oxygen saturation values in both the groups. Our findings are in par with the the study done by Anupriya et al.

After an extensive literature search we found 4 studies which used doses of dexmedetomidine for nebulisation comparable to our study. All of these studies were conducted in pediatrics population. Abdel-Ghaffar et al. used a dose of 2mcg/kg dexmedetomidine for nebulization and found that nebulised dexmedetomidine at this dose had more satisfactory outcome with respect to sedation, parental separation anxiety score, mask acceptance score, emergence agitation score, with no incidence of significant side effects. Similarly, Zanaty and El Metainy compared 2 mcg/kg of nebulized dexmedetomidine with nebulized ketamine and combination of dexmedetomidine with ketamine. When in combination with ketamine they used a dose of 1mcg/kg of nebulized dexmedetomidine. They found combination of low dose ketamine and dexmedetomidine produced more satisfactory sedation than nebulised ketamine or dexmedetomidine alone. No side effects were reported in their study at this dose of dexmedetomidine when used alone or in combination. Anuriya et al. used doses of 2mcg/kg and 3 mcg/kg of nebulised dexmedetomidine which is similar to our study and found satisfactory results in the higher dose used without any major side effects which did not respond to any pharmacological intervention. Similarly, Ali and Mahmoud compared two doses of nebulized dexmedetomidine (3mcg/kg and 4mcg/kg) and concluded that a dose of 3mcg/kg was associated with a lesser incidence of adverse effects such as hypotension and bradycardia. At a dose of 4mcg/kg nebulization of dexmedetomidine was associated with higher rates of bradycardia and hypotension. Hence, we chose to use the dose of 2mcg /kg and 3 mcg/kg.

Adverse events in the form of laryngospasm, hypotension and bradycardia were not seen in any of the groups, in consistence with results of other studies<sup>1,8</sup>

## VI. Conclusion

Dexmedetomidine with a dose of 3 mcg/kg provided better parental separation and better mask acceptance. Acceptable sedation was seen in both the groups. In perioperative period, patients in both the groups remained hemodynamically stable. No side effects were seen in both the groups.

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