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Original Research Article

Comparative efficacy of three different doses of intranasal dexmedetomidine for premedication in children

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ABSTRACT

Background: Preoperative emotional distress in children should be addressed properly for better anesthetic experience. The present study was a Prospective randomized double-blind study to evaluate comparative efficacy of three different doses of intranasal dexmedetomidine for premedication in children.
Materials and Methods: Sixty children were then randomly allocated to one of the three groups of 20 each by a computer generated table. The drug was administered 45 minutes prior to induction of anesthesia intra-nasally. Following intra-nasal drug administration, anxiety was assessed at 0 minutes -baseline, 30 minutes, 45 minutes and at parental separation in the preoperative area just before shifting in operation theater using the mYPAS (modified Yale Preoperative Anxiety Scale). At induction, induction compliance was assessed using the induction compliance checklist and heamodynamic response to definitive airway was assessed.
Results: It was observed that intranasal dexmedetomidine in lower doses of 0.5 and 1μg/kg was effective in reducing anxiety from baseline values but was not sufficient for providing anxiolysis at the most stressful time - at parental separation and shifting to OR (Operating room). The dosage of 1.5μg/kg was found to be the most effective dose for allaying preoperative anxiety without any adverse effect. However, this dose was insufficient for optimizing induction as it is mainly anxiolytic and higher doses having additional sedative action may be required to make the child more compliant for induction of anesthesia.
Conclusions: Based on our findings, we recommend that intranasal dexmedetomidine in the dose of 1.5μg/kg can be used for allaying preoperative anxiety, without any adverse events.
Key Points Summary: • Question: To evaluate and compare the efficacy of three different doses of intranasal dexmedetomidine for premedication in children for preoperative anxiety using the mYPAS scale. • Findings: Dose of 1.5μg/kg can be used for allaying preoperative anxiety, without any adverse events. • Meaning: Optimum dose of intranasal dexmeditomedine which is efficient to allay preoperative anxiety in children.

1. Introduction

Preoperative anxiety in children is a major concern to the pediatric anesthesiologist. Approximately 60% of pediatric patients suffer preoperative anxiety.[1] Children may become overtly uncooperative at the time of separation from parents, venipuncture, or mask application.

Pre-induction techniques, aimed at reducing preoperative anxiety, consist of: (i) sedative premedication, (ii) parental presence at induction of anesthesia, and (iii)

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behavioral intervention. While parental presence has a questionable role, there are many upcoming research on non pharmacological interventions but anesthesiologist still has preferences for time tested pharmacological interventions.

Therefore, despite many advances in non pharmacologic interventions, practitioners still rely on sedative premedicants.[2]

Dexmedetomidine is a selective alpha-2 adrenoceptor agonist that provides sedation that parallels natural sleep, analgesia, sympatholysis and an anesthetic sparing effect without causing respiratory depression.[3] Recently, it has been explored extensively in the pediatric population. It has also been demonstrated to effectively reduce opioid requirements and to potentiate analgesia.

Recent studies on use of intranasal dexmedetomidine for premedication have shown variable results.[4–8] Thus we planned to undertake this study to evaluate and compare the efficacy of three different doses of intranasal dexmedetomidine for premedication in children for preoperative anxiety using the mYPAS (modified Yale Preoperative Anxiety Scale).

2. Materials and Methods

It is a prospective randomised double-blind study was conducted in a tertiary hospital, New Delhi after taking institutional review board approval (IRB approval no. : F. No./11/IEC/MAMC/201736; clinical trial was registered before enrollment of patient in study principal investigator Dr Neelam Prasad (professor) Clinical trial number and registry URL: CTRI/2018/05/014305) dated 31/5/2018. Where American Society of Anaesthesiologists (ASA) physical health status grade I and II patients of age 1-6 years, of either sex, scheduled to undergo elective surgery under general anesthesia were enrolled.written informed consent was taken from legal gaudians of all subjects. While all patient with known allergy to dexmedetomedine, with any obvious aberrant nasal deformity, acute or chronic nasal trauma that may preclude adequate intranasal delivery of drug and patients with anticipated difficult airway were excluded.

All patients accompanied by parents, were taken to preoperative room approximately 1 hour before surgery and baseline measurement of heamodynamics vitals was done. Non invasive blood pressure, Heart rate, oxygen saturation were recorded. Children were randomly allocated, to one of the following three groups: D1- 0.5 1μg/kg, D2- 1μg/kg and D3- 1.5 μg/kg.

The study drug was prepared in a 1ml syringe by an anesthetist not involved in observing or administering anesthesia to the child. The drug was administered intra-nasally with the child in lap of mother 45mins prior to shifting the patients to OR. Following intra-nasal drug administration, anxiety was assessed: T1- 0min (baseline), T2- 30min, T3- 45min and T4- parental separation while shifting in OR (Operating room) using the mYPAS (modified Yale Preoperative Anxiety Scale) in the preoperative area.

Continues vital monitoring was done at 5, 10, 15, 30 and 45 minutes after drug administration in the pre-operative period till the airway was secured following induction of general anesthesia. The child was transferred to operation theatre after 45 min of premedication.

At the time of induction, induction compliance was assessed using the induction compliance checklist which is classified as perfect score=0, moderate score=1-3, poor score ≥4. Thereafter, inhalation induction of general anesthesia was carried out using sevoflurane 2-6% in 100% oxygen and surgery was conducted under standard general anesthesia.

This manuscript adheres to the applicable CONSORT (Consolidated Standard of Reporting Trials) guidelines.

2.1. Statistical analysis

The quantitative variables in the three groups were expressed as median-interquartile range and compared using Kruskal Wallis and Mann-whitney test between groups and paired t-test within each group at various follow-ups. The qualitative variables were expressed as frequencies/percentages and compared using Chi-square test. A p-value of < 0.05 was considered statistically significant. Statistical Package for Social sciences (SPSS) was used for statistical analysis.

3. Results

Each groups consists of 20 patients had 18 female and 42 males divided into three groups with a p value 0.777 statistically not significant.

The demographic profile of patient in terms of age, weight and height in three different groups are comparable to each other and statistically not significant, with a p value of age(p-0.474), weight(-0.128) and height-(0.075) respectively.

3.1. Types of surgeries patient underwent

Of all the surgeries patient underwent ophthalmic surgery were the most common.

mYPAS- modified Yale Preoperative Anxiety Scale:

Preoperative anxiety was compared using mYPAS scale at-T1- baseline, T2- 30min after drug, T3- 45 min after drug and T4- assessed at parental separation(Table 1).

Induction compliance of the children was studied using ICC-induction compliance checklist with results as shown in Figure 1. Optimum induction compliance was seen in 23.8% in group D3 while it was seen in only 10% and 4.8% patients in D1 and D2 respectively. However, p value was not statistically significant.

Table 1: Mean value of anxiety scores of different groups at T1, T2, T3 and T4 (Inter-group).

	Groups						
	D1	D2	D3	P Value	D1 V/S D2	D1 V/S D3	D2 V/S D3
	Mean ± SD	Mean ± SD	Mean ± SD				
T1	12.35± 5.06	10.05± 4.91	8.52 ± 2.91	0.025	0.381	0.018	0.544
T2	7.95 ± 2.89	8.14 ± 3.69	6.81 ± 2.48	0.322	0.997	0.458	0.445
T3	7.20 ± 2.73	6.52 ± 2.87	5.57 ± 1.12	0.095	0.828	0.060	0.426
T4	13.6 ± 4.1	12.76± 5.22	8.38 ± 3.81	0.001	0.920	<0.001	0.011

At T1 group D1 has Mean ± SD of 12.35 ± 5.06 while D2 has 10.05 ± 4.91 and D3 has 8.52 ± 2.91 with a p value of 0.025 that is statistically significant. Later comparing the anxiety levels group D1 vs D3 have a significant p value of 0.018.

At T2 and T3 no statistically significant results are found.

At T4 group D1 have Mean ± SD of 13.6 ± 4.1, group D2 have 12.76 ± 5.22 and D3 have 8.38 ± 3.81 with a p value of 0.001 is statistically significant. efficacy of three different groups D1 vs D3 have a p value of 0.001 and D2 vs D3 have a p value of 0.011 both of these are statistically significant.

Table 2: Mean values of SBP (Systolic blood pressure) in three groups at different time intervals.(inter group)

Groups						
D1	D2	D3	P Value	D1 V/S D2	D1 V/S D3	D2 V/S D3
Mean ± SD	Mean ± SD	Mean ± SD				
92.05± 8.94	95.8± 11.17	96.52± 9.38	0.309	0.457	0.322	0.970
92.55±0.18	96.25±0.84	97.24± 8.22	0.282	0.460	0.283	0.944
90.6 ± 7.39	95.95± 10.9	95.81± 7.76	0.098	0.142	0.150	0.999
89.79± 6.54	91.90 ± 8.8	94.14± 7.66	0.215	0.673	0.187	0.625
89.85± 6.96	89.4 ± 7.23	92.33± 7.55	0.382	0.979	0.521	0.404
86.15± 6.97	86.9 ± 7.77	89.81± 8.05	0.273	0.948	0.281	0.445

None of the mean SBP value comes out to be statistically significant in intergroup comparison.

Table 3: Mean values of DBP (Diastolic blood pressure) in three groups at different time intervals.(inter group)

	Groups						
DBP	D1	D2	D3	P Value	D1 V/S D2	D1 V/S D3	D2 V/S D3
	Mean ± SD	Mean ± SD	Mean ± SD				
Baseline	59.85 ± 7.84	59.05 ± 6.47	56.57 ± 5.91	0.277	0.926	0.276	0.475
1-Min	55.95 ± 7.90	57.35 ± 7.78	56.43 ± 6.90	0.837	0.827	0.977	0.919
3-Min	57.00 ± 6.51	58.05 ± 6.81	58.05 ± 6.55	0.845	0.871	0.869	1.000
5-Min	56.70 ± 5.97	54.20 ± 7.39	59.19 ± 7.51	0.083	0.500	0.494	0.066
7- Min	57.20 ± 5.70	52.80 ± 5.85	59.76 ± 5.22	0.001	0.041	0.314	0.001
10-Min	54.75 ± 6.12	51.50 ± 6.05	56.10 ± 4.75	0.035	0.174	0.728	0.031

At 7min- Group D1 has Mean ± SD 57.20 ± 5.70, D2 has 52.80 ± 5.85 and D3 has 59.76 ± 5.22 with a p value of 0.001 which is statistically significant. While comparing groups D1 vs D2 have a p value of 0.041 and D2 vs D3 have a p value of 0.001 are statistically significant.
At 10min- group D1, Mean ± SD 54.75 ± 6.12, D2 has 51.50 ± 6.05 and D3 has 56.10 ± 4.75 with a p value of 0.035.
While comparing groups D1 vs D3 has a p value of 0.031 which is statistically significant.

Table 4: Mean values of MBP (Mean blood pressure) in three groups at different time intervals. (inter group)

	Groups						
MBP	D1	D2	D3	P Value	D1 V/S D2	D1 V/S D3	D2 V/S D3
	Mean ± SD	Mean ± SD	Mean ± SD				
Baseline	67.42 ± 7.65	70.75 ± 8.01	67.90 ± 7.33	0.342	0.370	0.978	0.465
1- Min	65.32 ± 7.23	68.85 ± 9.76	69.57 ± 6.99	0.220	0.366	0.228	0.956
3- Min	66.53 ± 4.84	70.1 ± 8.30	70.86 ± 6.64	0.111	0.234	0.117	0.932
5- Min	64.84 ± 5.75	66.45 ± 7.18	68.90 ± 6.82	0.157	0.730	0.138	0.467
7- Min	65.37 ± 5.74	64.55 ± 6.42	69.71 ± 4.50	0.009	0.891	0.044	0.012
10-Min	63.37 ± 4.54	62.4 ± 5.21	66.95 ± 3.98	0.006	0.788	0.044	0.007

At 7 min group D1 has Mean ± SD 65.37 ± 5.74, D2 has 64.55 ± 6.42 and D3 has 69.71 ± 4.50 with a p value of 0.009 which is statistically significant. While comparing groups D1 vs D3 has a p value of 0.044 and D2 vs D3 has a p value of 0.12 both of them are statistically significant.
At 10 min group D1 has Mean ± SD 63.37 ± 4.54, D2 has 62.4± 5.21 and D3 has 66.95 ± 3.98 with a p value of 0.006 which is statistically significant. While comparing groups D1 vs D3 has a p value of 0.044 and D2 vs D3 has a p value of 0.007. Both of them are statistically significant.

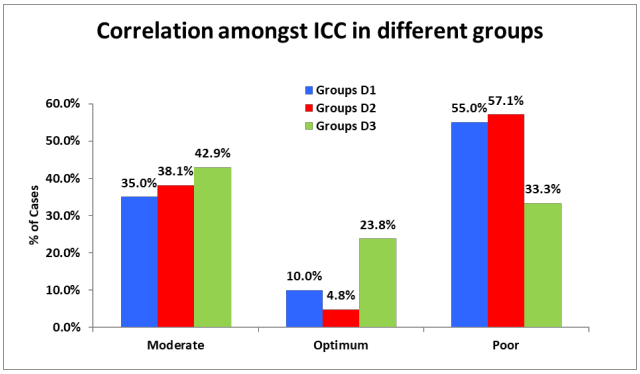

Fig. 1: Correlation amongst ICC (induction compliance checklist) in different groups

Hemodynamic monitoring to definitive airway insertion:

Heart rate: None of the mean HR values comes out to be statistically significant in intergroup comparison.

4. Discussion

In this study preoperative anxiety was assessed using mYPAS (modified Yale Preoperative Anxiety Scale) after using three different doses of intra nasal dexmeditomedine.

In group D1 and D2, at time T1, the baseline mean mYPAS anxiety score were 12.35±5.06 and 10.05± 4.91 respectively which reduced at T2 and T3. This decrease in anxiety score is because of onset of anxiolytic effect of dexmedetomidine which starts at around 25 minutes. Jun et al. in meta analysis of 13 study concluded that intranasal dexmedetomidine provides more satisfactory sedation at parent separation than other intranasal or oral premedicants (midazolam, ketamine, clonidine) with an additional advantages of decreased incidence of postoperative nausea and vomiting, nasal irritation, and the need for rescue analgesics.[9] However at T4, mean mYPAS increased to 13.6±4.1 and 12.76±5.22 respectively. The probable reason for this increase may be that parental separation while shifting child to OR (Operating room) is the most stressful time and these doses are not adequate enough for anxiolysis during this time. Yuen et al[6] in 2007 conducted a study comparing two doses of dexmedetomidine 0.5μg/kg and 1ug/kg with midazolam and concluded that 0.5μg/kg dose was not very effective, similar to our study. 1μg/kg dose was found to be better in terms of sedation at the time of parental separation. However, we did not find intranasal dexmedetomidine in the dose 1μg/kg effective to allay preoperative anxiety. This difference could be because of different types of preoperative anxiety assessment scales. Yuen et al[6] have used a four point likert scale which is not a validated scoring system, while we have used mYPAS which is a structured instrument that consists of five domains of anxiety. It is much more sensitive to changes in anxiety levels than other global instruments.

Ghali et alstudied 1μg/kg intranasal dexmedetomidine and compared it with oral midazolam 0.5mg/kg.[7] In contrast to our study, they found dexmedetomidine in dose of 1μg/kg to be associated with better sedation levels, lower anxiety levels and easier child-parent separation at the time of transferring patients to OR. This difference could be because of different time interval for shifting patients to OR, we shifted patient at approximately 45 minutes while their shifting time was around 60 minutes. It is possible that the anxiolytic effect of dexmedetomidine is better achieved at 60 min rather than at 45 minutes. In another study, conducted by Segovia BL. et al. also found 1μg/kg of dexmedetomidine to be effective in contrast to our study.[4] This difference can again be attributed to time difference in shifting the patient to the OR as previously stated. Li-Qun Li et al also compared effects of different doses of intranasal dexmedetomidine on preoperative sedation and postoperative agitation in children. They found that the time of intranasal administration of drug was an important factor affecting preoperative sedation.[10]

In our study, group D3 had mean mYPAS anxiety scores 8.52±2.91 at time T1, mYPAS score at T2 and T3 are comparable with D1 and D2. However, the scores remained similar to baseline during parental separation and shifting the child to OR (T4) unlike other groups. This may be due to a better anxiolytic effect of dose used in this group. In intergroup comparison, on comparing group D1 vs D2 mean mYPAS scores were found to be comparable at all time intervals. When comparing D1 vs D3, baseline anxiety as assessed by mYPAS scales was lower in D3 which is because preoperative anxiety is a multifactorial parameter affected by variables such as situational anxiety of the mother, temperament of the child, age of the child and quality of pervious medical encounters.[11]

Intergroup comparison D1 vs D3 and D2 vs D3, there was significant statistical difference. This is because in both group D1 and D2, the doses used as anxiolytic (0.5μg/kg and 1μg/kg respectively) may not be optimum as compared to that in group D3 (1.5μ/kg).

In a similar study by Yuen et al in 2012, they compared two intranasal doses of dexmedetomidine i.e. 1μg/kg and 2μg/kg and found 2μg/kg to be more effective for sedation. Both the doses produced satisfactory sedation in children aged 1-4 years. In children aged 5-8 years, 2μg/kg was associated with a higher proportion of satisfactory sedation than 1μg/kg without causing any adverse hemodynamic effects.[8]

Similarly Pavithra et al[12] found 2μg/kg to be a better dose in terms of sedation & behavioral scores and intra-operative hemodynamics in comparison to 1μg/kg. This 2μg/kg dose is associated with significant hypotension (fall in BP more than 30% from baseline). There was no such event with the highest dose of 1.5μg/kg used in our study.

It has been found that the induction of anesthesia is the most stressful phase of the entire preoperative period for the children and their families.To assess the behavior of the child during the induction, we have used ICC- induction compliance checklist.[11] However, we did not get any statistically significant results with any of the doses.This is probably because the doses of intranasal dexmedetomidine used in our study (0.5 μg/kg, 1μg/kg and 1.5μg/kg) are mainly anxiolytic. Higher doses having additional sedative action may be required to make the child more compliant for induction of anesthesia.

We also observed hemodynamic responses to definitive airway insertion. Decrease in HR, SBP, DBP and MAP were statistically significant at 10 min in group D1; at 5, 7 and 10 minutes in group D2 and at 10 minutes in group D3. HR had statistically significant fall in all the three group at 5, 7 and 10 minutes, and at 3 minutes in group D2.

This reflects the effect of dexmedetomidine on hemodynamics (i.e. HR and BP) combined with pharmacokinetics actions of other drugs and inhalation agent used at the time of induction.

Similar modest reduction in HR and BP was observed by Yuen et al 2012 in their study at around 45 minutes.[8]

In intergroup comparison no statistically significant results were obtained while comparing SBP and HR. While for DBP, we found statistically significant results in intergroup comparison at 7 minutes in D1 vs D2 and D2 vs D3; at 10 minutes in D2 vs D3.

For MAP, results were found to be significant at 7 and 10 min both while comparing D1 vs D3 and D2 vs D3.

Pavithra et al[12] did not find any difference in SBP, DBP and HR values to be statistically significant while comparing two groups. Similar results were found by Wang et al. while using a dose of 2μg/kg compared to a dose of 1μg/kg.[13]

5. Limitations of Study

1. Preoperative anxiety is a multifactorial parameter affected by variables such as situational anxiety of the mother, temperament of the child, age of the child and quality of pervious medical encounters should be considered.
2. Administration of intranasal drugs by atomizer could have been a better technique.

We concluded

1. Intranasal dexmedetomidine in lower doses of 0.5 and 1μg/kg reduces anxiety from baseline values but is not sufficient for providing anxiolysis at the most stressful time –i.e. parental separation. The dose 1.5μg/kg is the most effective dose for allaying preoperative anxiety. Stable hemodynamics and prevented sympathetic response to definitive airway insertion, without causing any adverse effects such as hypotension or bradycardia.
2. The dosage of 1.5μg/kg is however insufficient for optimizing induction scores (ICC).

Thus, we recommend that, intranasal dexmedetomidine in the dose of 1.5μg/kg can be used for allaying preoperative anxiety, without any adverse events. Further, studies on preoperative anxiety can include psychosocial factors which may have effect on anxiety. Further, studies with a larger sample size and population sub-group based on age should be undertaken to get better conclusions and results.

6. Abbreviation

1. **mYPAS:** modified Yale Preoperative Anxiety Scale; **OR :** Operating room; **IRB:** Institutional review board; **CTRI:** Clinical Trial Registry - India; **ASA:** American Society of Anaesthesiologists; **CONSORT:** Consolidated Standard of Reporting Trials; **SD:** Standard deviation; **ICC:** Induction compliance checklist; **SBP:** Systolic blood pressure; **DBP:** Diastolic blood pressure; **MBP:** Mean blood pressure; **HR:** Heart rate

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None.

8. Conflict of Interest

None.

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