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Original Research Article

Comparison of nebulised dexmedetomidine versus nebulised ketamine versus nebulised dexmedetomidine-ketamine as premedication in peadiatric surgery

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ABSTRACT

Aim and Objectives: The present study was undertaken to compare the efficacy of nebulized dexmedetomidine, nebulized ketamine and combination of nebulised dexmedetomidine and ketamine for premedication in pediatric patients.

Materials and Methods: Total 75 children aged between 3-6 years, ASA grade I and II, posted for elective surgery were enrolled and divided into three equal groups. Group D was premedicated with nebulized dexmedetomidine (2mcg/kg), group K was premedicated with nebulized ketamine (2 mg/kg), and group DK was premedicated with combined nebulized dexmedetomidine and ketamine (1 mcg/kg + 1 mg/kg). Primarily, patients were assessed for level of sedation, parental separation and mask acceptance at induction. Secondary assessments were hemodynamic parameters and immediate side effects if any.

Results: Studied groups were comparable as regards to demographic data and haemodynamic parameters. At all-time intervals except at 20 minutes, mean sedation scores were comparable among the three groups ($p>0.05$). At 20 minutes, group K had significantly higher sedation scores when compared to group D and group DK. The mean parental separation scores of group D, group DK and group K were 1.65 ± 0.48, 1.62 ± 0.49 and 1.37 ± 0.49 respectively, ($p>0.05$). The mean mask acceptance score of group D, group DK and group K were 1.73 ± 0.54, 1.73 ± 0.68 and 1.43 ± 0.66 respectively, ($p>0.05$). None of the patient had any immediate side effects.

Conclusion: Dexmedetomidine (2mcg/kg), Ketamine (2mg/kg) and combination of Dexmedetomidine and Ketamine (1mcg/kg and 1mg/kg) as premedication via nebulisation route in pediatric patients is efficacious and safe. Combination of dexmedetomidine and ketamine did not increase the success of premedication.

1. Introduction

The preoperative period can be a traumatic time for young children undergoing surgery. Pediatric anesthesiologists strive to minimize distress for children in the operating room environment and to provide a smooth induction of anesthesia.[1] Goals of premedication in pediatric anaesthesia are relieving pre and postoperative anxiety, allowing good parental separation, and facilitating smooth induction of anaesthesia.[2] Premedication can be given by various routes like parenteral, oral, rectal, nebulisation, etc.[3] Fear of needles is the most important reason for anxiety in children so it's preferable to have a route of drug administration which is free of needles. Medication administered without needle is more pleasant for the child, the family as well as the care team.[4]

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Various drugs usedGadkari Charuta for premedication are benzodiazepines barbiturates, phenothiazines, ketamine, opioids, alpha 2 agonists like clonidine, antihistamines, antichloniergics, etc.[4] Ketamine is widely used for pediatric premedication. Its efficacy through IM, IV route is established already. Its use by intranasal and oral routes is well studied.[5,6] Studies on nebulisation of ketamine for premedication are scarce. Dexmedetomidine is a potent and highly selective α-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties. It has been described as a useful and safe adjunct in many clinical applications.[7] Dexmedetomidine has been used by parenteral, oral and nasal routes. It has been used in pediatric patients for procedural sedation and premedication.[8] It is an attractive alternative, as premedication, to conventional drugs because of its non-interference with respiration.[9] Several reports are now available of dexmedetomidine for both noninvasive and invasive procedural sedation in infants and children.[7] However its use by nebulisation is reported in very limited number of studies.

Hence the present study was undertaken to compare the efficacy of nebulised dexmedetomidine, nebulized ketamine and nebulised dexmedetomidine-ketamine combination in paediatric premedication primarily in terms of level of sedation, parental separation and mask acceptance at induction and secondarily in terms of hemodynamic parameters and immediate side effects if any.

2. Materials and Methods

After obtaining Institutional Ethics Committee approval, this prospective randomized double blind trial was conducted in 75 children aged between 3-6 years, ASA physical status I and II, posted for elective surgery at Tertiary Care Hospital over a period of 2 years from November 2016 to October 2018. Children with known respiratory disease, cardiac arrhythmia or congenital heart disease, psychiatric disorder, history suggestive of allergy to study drugs, raised intracranial, intraocular pressure, parents' refusal and children with developmental delay were excluded from the study.

Pre-anesthetic assessment, investigations like complete blood picture, blood grouping, random blood sugar, urine analysis were done. Whenever indicated X-ray chest PA view, ECG and kidney function tests were also performed. Procedure to be performed was explained to the parents of children in their own language and their written consent was taken. A pre-operative visit was made one day prior to the elective surgery to gain the confidence of the child and the parents and to familiarize them with the procedure of nebulisation. Parents were instructed to make their children NPO for solids 6 hours prior to scheduled appointment and to give only clear liquids up to 2 hours prior to surgery. This helped us by improving childs compliance for nebulized premedication. Patients were allocated to either group D or group K or group DK by computer generated randomization table. Group allocation was concealed in sealed opaque envelopes which were shared with independent investigator 30 min before the proposed drug administration. All solutions were prepared in identical syringes with matching random codes by an independent investigator not involved in observation or the administration of anesthesia. The observer and patient were blinded to the drug administered.

Drugs were prepared in 3 ml of Normal saline (0.9%) for administration by a nebulizer via a facemask and were nebulised over 10 to 15 minutes (30 minutes before GA). Tools for administration of supplemental oxygen, ventilation support and resuscitation kept readily available. Group K patients were premedicated with nebulized Ketamine solution (2mg/kg), group D patients were premedicated with nebulized Dexmedetomidine solution (2 mcg/kg) and group DK patients were premedicated with combination of nebulised Dexmedetomidine and Ketamine (1mcg /kg +1 mg/kg). Nebulisation was stopped when the nebuliser began to sputter. The patient was transferred to operation room. Mask acceptance score was recorded when the child was induced on Sevoflurane in 100% Oxygen by mask. Patients were assessed every 5 min for the level of sedation till 30 minutes and for parental separation at 30 min. Hemodynamic parameters in terms of HR, Systolic BP, Diastolic BP, Mean Arterial Pressure and SpO2 were assessed at baseline, 5, 10, 15, 20, 25, 30 min after drug administration and in OT. Level of sedation was assessed using five-point sedation scale, parental separation was assessed using four-point parental separation anxiety scale (PSAS) and mask acceptance was scored using a four point likert scale.[2]

Incidence of bradycardia or hypotension defined as 30% decrease from baseline value[2] was noted. Hypotension was treated with fluid bolus administration. Bradycardia was treated with inj. atropineIV (0.03mg/kg) administration. Desaturation defined as SpO2< 95% was treated with oxygen supplementation by mask. Any immediate side effects like nausea and vomiting were recorded as yes /no survey. Nausea was defined as subjectively unpleasant sensation associated with urge to vomit. Vomiting was defined as forceful expulsion of gastric contents. Any of above side effects were treated with inj. Ondensetron 0.1mg/kg IV. Child agitated and crying and clinging to parents was considered as failure case and was administered injection ketamine 5 mg/kg intramuscularly as rescue premedication before shifting to OT. Further anesthesia management was done as per the discretion of the attending anesthesiologist.

2.1. Statistical analysis

The data was analyzed using Microsoft excel and SPSS Version 21. The qualitative variables were expressed in

terms of percentage and difference between two proportions was analyzed using chi-square test. The quantative variables were expressed in terms of mean and standard deviation and were analyzed using SNK test and student t test. Non parametric variables were analyzed by using kruskle Wallis test, Wilcoxons signed rank test. All the analysis was 2 tailed and the significance level was set at 0.05.

3. Observations and Results

Total 75 patients were enrolled in the study and divided into three groups of 25 patients in each groups. There were failure cases one in group D, two in group DK and one in group K. Thus data analysis was done with 24 patients in group D, 23 patients in group DK and 24 patients in group K. All the study subjects were of ASA grade I in all the three groups. The mean age of patients in group D, group DK and group K was 4.45 ± 1.25 years, 4.87 ± 1.1 years and 4.33 ± 1.23 years respectively. This difference was statistically non-significant (p>0.05). The mean weight of group D, group DK and group K was 15.48 ± 3.27kg, 16.65 ± 4.99kg and 14.56 ± 3.20kg respectively, (p>0.05). Majority of the study subjects in all the three groups were males as shown in Figure 1.

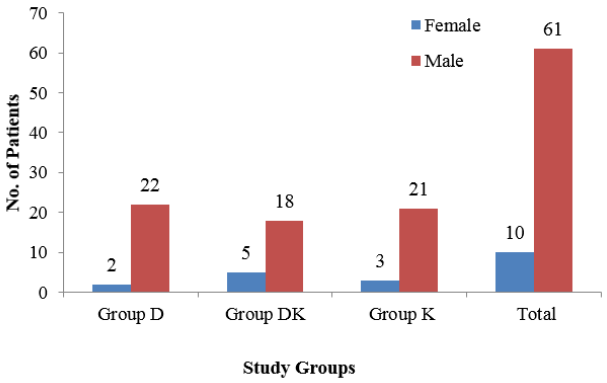

Fig. 1: Distribution of the study subjects based on gender

The mean sedation scores at 5 min were 1.58 ± 0.50, 1.39 ± 0.49 and 1.37 ± 0.49 in groups D, group DK and group K respectively. The average scores increased steadily among all the three groups to reach 2.83 ± 0.38, 2.96 ± 0.20 and 2.92 ± 0.40 respectively at 30 min. At all-time intervals except at 20 minutes, there was no significant difference between the three groups (p>0.05). At 20 minutes, group K had significantly higher sedation scores when compared to group D and group DK. However at 30 min mean sedation scores were comparable among the three groups, (Table 1).

The mean parental separation score of group D, group DK and group K was 1.65 ± 0.48, 1.62 ± 0.49 and 1.37 ± 0.49 respectively. This difference was statistically non-significant (p>0.05), (Table 2). The mean mask acceptance score of group D, group DK and group K were 1.73 ± 0.54, 1.73 ± 0.68 and 1.43 ± 0.66 respectively, (p>0.05), (Table 2).

The difference in baseline haemodynamic parameters was statistically non-significant (p>0.05). At all the time intervals the difference between heart rate (HR), systolic blood pressure (SBP) of three groups, was statistically non-significant (p>0.05). When compared group-wise, difference in SBP between baseline and 30 min was statistically significant (p<0.05) in all groups. Among all three groups DBP was maintained around the baseline and no significant changes occurred. When compared group-wise, difference in DBP between baseline and 30 min was statistically significant (p<0.05) in group D and group K, whereas it was statistically non-significant (p>0.05) in group DK. At all the different time intervals the difference in mean arterial pressure (MAP) was statistically non-significant (p>0.05) between the groups. When compared group-wise, difference in MAP between baseline and 30 min was statistically non-significant (p>0.05) in all groups, (Figure 2).

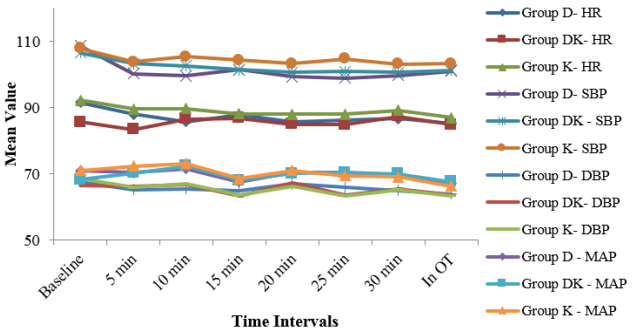

Fig. 2: Comparison of haemodynamic parameters among three groups

The oxygen saturation of all three groups was stable throughout at all different time intervals with the average changing around baseline and hence there was no significant difference among the three groups (p>0.05). When compared group-wise, difference in SpO2 between baseline and 30 min was statistically non-significant (p>0.05) in all groups, (Table 3). None of the patient had any immediate side effects like nausea, vomiting.

4. Discussion

Preoperative anxiety in children is a significant and challenging problem. If not managed in a considered and structured fashion, it can lead to distress for the child, parents, and the operating theatre staff involved. Preinduction techniques in paediatric anaesthesia are primarily focused on relieving the preoperative anxiety of the child, but consideration of parental anxiety is also important.[10] However, methods to reduce anxiety should be chosen accordingly to the age group of the child in

Table 1: Distribution of patients based on sedation score changes at different intervals

Sedation Score	Group D	Group DK	Group K	P value
5 min	1.58±0.49	1.39±0.45	1.37±0.49	0.283
10 min	1.87±0.45	1.87±0.34	1.75±0.44	0.505
15 min	2.04±0.62	2.17±0.49	2.33±0.48	0.177
20 min	2.41±0.50	2.56±0.51	2.92±0.28	0.001
25 min	2.83±0.38	2.91±0.29	3±0	0.119
30 min	2.83±0.38	2.96±0.20	2.92±0.40	0.462

Table 2: Distribution of patients based on parental separation score and Mask acceptance score

Parental separation anxiety score	Group D	Group DK	Group K	P value
1	15 (62.5%)	8 (34.8%)	9 (37.5%)	0.106
2	09 (37.5%)	15 (65.2%)	15 (62.5%)	
Mean	1.65±0.48	1.62±0.499	1.37±0.499	0.110
Mask acceptance score	**Group D**	**Group DK**	**Group K**	**P value**
1	15 (62.5%)	7 (30.4%)	9 (37.5%)	
2	7 (29.2%)	15 (65.2%)	12 (50%)	0.064
3	2 (8.3%)	1 (4.4%)	3 (12.5%)	
Mean	1.73±0.54	1.73±0.68	1.43±0.66	0.135

Table 3: Distribution of the study subjects based on SpO2 changes at different intervals

SpO2	Group D	Group DK	Group K	P Value
Baseline	99.58±0.50	99.60±0.49	99.41±0.58	0.431
5 min	99.37±0.71	99.43±0.66	99.58±0.58	0.52
10 min	99.45±0.77	99.43±0.66	99.45±0.83	0.994
15 min	99.41±0.88	99.43±0.84	99.45±0.83	0.985
20 min	99.45±0.83	99.56±0.89	99.50±0.78	0.899
25 min	99.50±0.72	99.65±0.77	99.29±0.99	0.31
30 min	99.45±0.88	99.60±0.78	99.50±0.78	0.803
In OT	99.45±0.83	99.43±0.89	99.50±0.88	0.964
P value	0.251	0.5	0.33	-

consideration. We chose children between age group of 3yrs to 6yrs, an age group where sedative premedication is most appropriate. Majority of patients were male, however, gender has not been found to be a factor involved in preoperative anxiety or in postoperative behavioral problems in prepubescent children.[11] Commonly used route for premedication in children are oral, rectal, intramuscular, intravenous, intranasal, sublingual route.[12–14] We have used nebulisation as a route to administer premedication. A nebulizer may be paired with either a facemask or a mouthpiece to deliver aerosols and in general, a mouthpiece is preferred due to improved drug delivery to the lungs.[15] However, developmentally, children cannot maintain a seal around a mouthpiece until about age 4, thus necessitating the use of a facemask for the youngest patients. A large leak in a facemask will lead to ambient air being inspired, rather than medication from the Valved Holding Chamber (VHC); thereby diminishing the effective inhaled dose.[15] Hence we have used appropriate sized facemask in our study population.

The dosage of study drugs were decided based on previous studies.[2,3,16–18] Drugs were prepared in 3 ml of Normal saline (0.9%) to minimize wastage of drug. Water was avoided as it may cause bronchoconstriction.[19] The present study did not include control group because control group with no premedication in pediatric age group would result in great distress to patient and would be unethical. In the pre-operative room childrens were nebulised with study drug 30 minutes prior to anticipated induction with parents around. We used preoperative visit to be friendly with the child and allowed tidal breathing during nebulisation. Distraction methods like toys, drawing etc were employed to ensure compliance of child with procedure of nebulisation.

Adequately sedated children are found to be less anxious and calm. Previous studies [2, 3 and 16] reported adequate sedation levels at 30 min. Studies by Jia et al[17] and Narendra et al[18] have reported still earlier onset of sedation. Hence, the present study compared sedation scores every 5 min till 30min amongst the study groups. The average sedation scores increased steadily from 5 min to 30 min among all the three groups. At all-time intervals except at 20 minutes, there was no significant difference between the three groups ($p>0.05$). At 20 minutes, group K had significantly higher

sedation scores when compared to group D and group DK. After assessing sedation scores at 30min, all the patients were shifted to OT. At this time we assessed separation scores. The mean value of parental separation scores was comparable among three group and difference was not statistically significant (p>0.05). The premedication makes acceptance of face mask by child easier, resulting in smooth induction. The mean value of mask acceptance score also comparable among three groups and found no significant difference (p>0.05). All the above results are similar to the study done by Bhat et al,[2] Zanaty et al,[3] Mostafa et al[5] and Abdel-Ghaffar et al.[20]

The baseline haemodynamic parameters (HR, SBP, DBP and MAP) and mean values of all these parameters at 30 min were comparable among the groups. At all the different time intervals the difference in HR, SBP, DBP and MAP was not statistically significant between the groups (p>0.05). If we consider group wise haemodynamic parameters at 30 min compared to baseline, there was no significant change in HR and MAP whereas SBP was significantly less among all three groups (p<0.05) while DBP was significantly lowering among group D (p=0.03) and group K (p=0.04), in group DK the change was not significant (p=0.20). Though ketmaine is known to raise HR and blood pressure, however nebulized ketamine in dose of 2mg/kg did not result in rise in HR and blood pressure in our study population. Lower mean HR and blood pressure at 30 min is likely due to sedation resulting from ketamine. Dexmedetomidine is known to result in hypotension and decrease in heart rate which is generally dose dependent. With doses we used (2μg/kg) HR and blood pressure remained stable in present study. The oxygen saturation for all the three groups was stable throughout at all-time intervals with the average changing around the baseline and hence there was no significant difference among the three groups (p>0.05). All above findings of haemodynamic variables and oxygen saturation are correlated well with the study done by Bhat et al,[2] Zanaty et al[3] and Abdel-Ghaffar et al.[20]

In current study, none of the patients experienced bradycardia, hypotension or episodes of desaturation. All the patients were hemodynamically stable. It indicates that our nebulised study drug used in dose that are safe. There was no any incidence of nausea or vomiting noted. This study had failure cases, one in group D, two in group DK and one in group K. Those who were scored to have unsatisfactory separation score were given rescue sedation in the form of inj. Ketamine 5mg/kg intramuscularly. Thus adequate sedation was ensured before shifting the children to OT. They were labeled as failure and these patients were excluded from the statistical analysis. All of these children accepted nebulisation well. Dose calculation was done meticulously. Methodology was same for patients still we had failure in all three study groups. Interestingly all of them had acceptable sedation scores. However did not attain satisfactory PSAS scores. These children were agitated at separation, so reason behind failure could be inter patient variability.

5. Limitation of the Study

The present used dexmedetomidine for preoperative sedation till date FDA has approved dexmedetomidine for ICU sedation only. However it has been used by various routes for a wide spectrum of clinical application by researchers. Many studies are going on to establish its other uses. A potential weakness of the study is the choice of scoring system to assess the patients' co-operation (sedation score, parental separation anxiety score, and mask acceptance score). Although these scoring systems have been used in several published studies, it has been formally validated, and the intra- and inter-rater variability has not been established.

6. Conclusion

Dexmedetomidine (2 mcg/kg), Ketamine(2mg)kg) and combination of Dexmedetomidine and Ketamine (1mcg/kg and 1mg/kg) as premedication via nebulisation route in pediatric patients were comparable in terms of sedation and parental separation and mask acceptance at induction of anaesthesia and resulted in stable haemodynamic parameters without immediate adverse effects thus were efficacious and safe. Combination of dexmedetomidine and ketamine did not increase the success of premedication.

As seen in present study, nebulization route is easily accepted by children for premedication. However, it is noted that nebulization route for premedication in children is underutilized and further studies using drug combinations and dose should be undertaken.

7. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

8. Source of Funding

None.

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