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Randomised Comparison between the Efficacy of Two Doses of Nebulised Dexmedetomidine for Premedication in Paediatric Patients

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Abstract

Objective: Nebulised dexmedetomidine can be an easy alternative for preoperative sedation in paediatric patients, but data regarding its efficacy are very limited.

Methods: This prospective, randomised, double-blind study included 66 patients aged between 1 and 8 years. Patients were divided into two groups as D2 and D3. The D2 group received 2 μg kg^{-1} of nebulised dexmedetomidine, and the D3 group received 3 μg kg^{-1} of nebulised dexmedetomidine preoperatively. All the patients received general anaesthesia and caudal epidural analgesia with 0.75 mL kg^{-1} of 0.2% ropivacaine. Parental Separation Anxiety Scale at 30 min after the end of nebulisation, Mask Acceptance Score (MAS) during induction, haemodynamic variables, emergence agitation and duration of caudal analgesia were compared between the groups. Statistical analysis was done using Mann-Whitney U test and chi-square test. A p-value <0.05 was accepted as significant.

Results: All the parameters were comparable between the D2 and D3 groups; however, significantly more number of younger children was observed in the D3 group. Hence, further analysis was done after division into the lower age (1-3 years) and higher age (4-8 years) groups. In lower age group children, satisfactory parental separation was achieved in 100% of the patients in the D3 group compared to 20% of those in the D2 group (p=0.00). MAS was significantly better in the D3 group in both the lower (p=0.019) and higher (p=0.036) age groups.

Conclusion: We conclude that nebulised dexmedetomidine in a dose of 3 μg kg^{-1} provides better parental separation and mask acceptance in younger children.

Keywords: Dexmedetomidine, epidural analgesia, haemodynamic variables, paediatric patients, separation anxiety

Introduction

Preoperative anxiety is seen in 50%-70% of the paediatric patients posted for surgery. Fear of parent separation, fear of strange hospital environment and painful procedures contribute to preoperative anxiety (1). Children with high preoperative anxiety have high incidence of postoperative pain, emergence delirium, delayed discharge and maladaptive and behavioural changes that can last for weeks in the postoperative period (2). Various pharmacological and non-pharmacological methods are in practice with variable success rate. Drugs, such as midazolam and ketamine, have been tried for this frequently via oral, nasal and parenteral routes, but each one has its limitations (3). Inhalation of nebulised drug is an easy alternative for preoperative sedation in children as it avoids needle puncture necessary for intravenous (IV) or intramuscular (IM) route. However, the systemic absorption of the nebulised drug depends on multiple factors, such as dosages of the drug, properties of the drug and the nebuliser used.

Dexmedetomidine, which is a selective alpha-2 agonist with central sedative and anxiolytic properties, has been tried for preoperative anxiolysis in children via nasal and inhalational routes. It is well absorbed systemically through per-

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oral and buccal routes due to bioavailability as high as 82%. Previous study has suggested that nebulised dexmedetomidine can provide a clinically relevant, non-invasive alternative to the invasive IV or IM route of administration (4). There are only a few studies on the efficacy of nebulised dexmedetomidine. Those studies have used dexmedetomidine in the doses of 2 μg kg^{-1} and found that it was effective in achieving calm parental separation in approximately 60%-70% of children (5, 6). Dexmedetomidine in a dose of 3 μg kg^{-1} via parenteral route has produced satisfactory procedural sedation without any haemodynamic adverse events (7, 8). Studies on the efficacy and safety of nebulised dexmedetomidine in a dose of 3 μg kg^{-1} are not available.

Data regarding the efficacy of nebulised dexmedetomidine are very limited, and none of the studies has seen the adjuvant effect of nebulised dexmedetomidine on caudal epidural analgesia. We hypothesised that a higher dose of nebulised dexmedetomidine can cause significantly more reduction in parental separation anxiety and provide prolonged analgesia compared to 2 μg kg^{-1}. The aim of the present study was to compare the efficacy of two doses of dexmedetomidine as premedication for parental separation anxiety and as an adjuvant for caudal epidural analgesia.

Methods

This prospective, randomised, double-blind study was conducted from November 2017 to October 2018. The study was approved by the institutional human ethics committee. (IEC No: 2017/342)The trial was registered prior to enrolment of patients in the clinical trial registry of India (CTRI/2017/10/010276). 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 surgeries, such as circumcision and herniotomy and were planned under caudal analgesia, were included in the study. Patients with a history of cardiac disease, asthma, seizure disorders, mental retardation, developmental delay, prematurity and allergy were excluded from the study. Patients who had any contraindication to caudal analgesia were also excluded. The study protocol was explained. Written informed consent was obtained from the parents of the patients.

Patients were randomly divided into two equal groups (33 each) by a computer-generated list of random numbers, with group allocation concealed in sealed opaque envelopes. For the D2 group, 2 μg kg^{-1} of dexmedetomidine diluted with 0.9% normal saline to total volume of 3 mL and for the D3 group, 3 μg kg^{-1} of dexmedetomidine diluted with 0.9% normal saline to total volume of 3 mL were added to the nebulisation mask chamber. The preparation of the nebulised drug was done by an investigator who was not participating in the monitoring of the patients. All patients were kept fasting according to the ASA guidelines. The D2 group patients received 2 μg kg^{-1} of nebulised dexmedetomidine, and the D3 group patients received 3 μg kg^{-1} of nebulised dexmedetomidine. With the child in the mother's lap, nebulisation was started via mask by Accusure piston compressor nebuliser (Mfd by Microgene Diagnostic Systems Pvt Ltd, India). After applying pulse oximeter, the time of the start of nebulisation was noted. Oxygen saturation (SpO_2) and pulse rate (PR) were monitored every 5 min. Then, 30 min after the end of nebulisation, separation anxiety score was noted during shifting of the patient to the operative room (OR). 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 (9).

After shifting the patient to the OR, standard monitors, such as SpO_2, non-invasive blood pressure (NIBP), electrocardiogram and end-tidal carbon dioxide ($EtCO_2$), were connected and were monitored continuously. Then, 100% oxygen with 8% sevoflurane was started through mask for induction via a Jackson Rees breathing circuit. 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 (10). IV cannula was placed after induction of anaesthesia, and fluid was started. Patients then received IV glycopyrrolate 5 μg kg^{-1}, IV fentanyl 2 μg kg^{-1} and IV propofol 2 mg kg^{-1}, and a laryngeal mask airway (LMA) of suitable size was inserted. Anaesthesia was maintained with sevoflurane in 50% oxygen/nitrous oxide mixture. Spontaneous breathing was maintained during the procedure. Thereafter, patients were positioned in a lateral decubitus, and under complete aseptic precautions, caudal injection was done using a 22 G caudal needle. After proper placement of the needle with negative aspiration for blood or cerebrospinal fluid, all patients had 0.75 mL kg^{-1} of 0.2% ropivacaine (Ropin 0.2%; Neon Laboratories Ltd, India).

Mean arterial blood pressure (MAP), heart rate (HR), SpO_2, $EtCO_2$ and respiratory rate were monitored every 10 min throughout the procedure. By the end of surgery, inhalational anaesthesia was discontinued, and the LMA was removed. Duration of anaesthesia was recorded in minutes. Emergence agitation (EA) was noted 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 (10). When the patient started responding to verbal

commands, they were transferred to the postanaesthesia care unit (PACU); all care givers, anaesthesiologist, surgeon and PACU nurse, as well as patient's parents, were unaware of the dose used for nebulisation. In the PACU, pain scores were evaluated by the face, leg, activity, cry, consolability (FLACC) pain scale every 1 h (11). The scale is scored in a range of 0-10, with 0 representing no pain, whereas 10 is the worst pain. Acetaminophen suppository 30 mg kg^{-1} was given if pain score was ≥4 and subsequent doses of 20 mg kg^{-1} with minimum interval of 6 h between two doses. The time of first rescue analgesia was noted.

NIBP, HR and SpO_2 were monitored every 10 min intraoperatively and postoperatively every 1 h for the first 4 h then every 4th hourly till the need of first rescue analgesia. The incidence of hypotension (decrease in MAP of 20% from baseline), bradycardia (20% decrease from baseline in HR) and respiratory depression (SpO_2 <92%) was noted. Time between caudal injection and rescue analgesic demand was taken as the duration of analgesia. Time of first analgesic requirement was the endpoint of the study. The primary outcome of our study was to compare PSAS while shifting to the operation theatre, 30 min after the end of nebulisation. The secondary outcomes were to compare mask acceptance score, to compare haemodynamic variables, EA scores and to compare the adjuvant effect on caudal epidural with respect to time of first rescue analgesic.

Statistical analysis

Sample size calculations were done based on previous study with a separation anxiety score of 1 in 60% of the patients (5). A sample size of 29 patients per group was needed to achieve a PSAS score of 1 in 90% of the patients by increasing the dose of dexmedetomidine with significance of 5% and 80% power of the study. A total of 33 patients per group were included in the study to allow for possible dropouts. The statistical analysis was done using Statistical Package for Social Sciences for Windows (Microsoft, version 23, 2015; IBM Corp., Armonk, NY, USA). Distribution of data was analysed using Shapiro-Wilk test. Non-normally distributed continuous parameters were compared using Mann-Whitney U test, and data were expressed as median ± interquartile range. Categorical data were compared using chi-square test and were expressed as number and percentage. A p-value <0.05 was accepted as significant for a two-sided test.

Results

Among the 80 patients who were screened for eligibility, 66 were enrolled into two groups. Of the 66 patients, 59 were subjected to statistical analysis as 29 in the D2 group and 30 in the D3 group. Seven patients were excluded from the analysis due to various reasons (Figure 1). Three patients in the D2 group and two patients in the D3 group did not allow nebulisation. Overall, 92% of children accepted mask and nebulisation with ease.

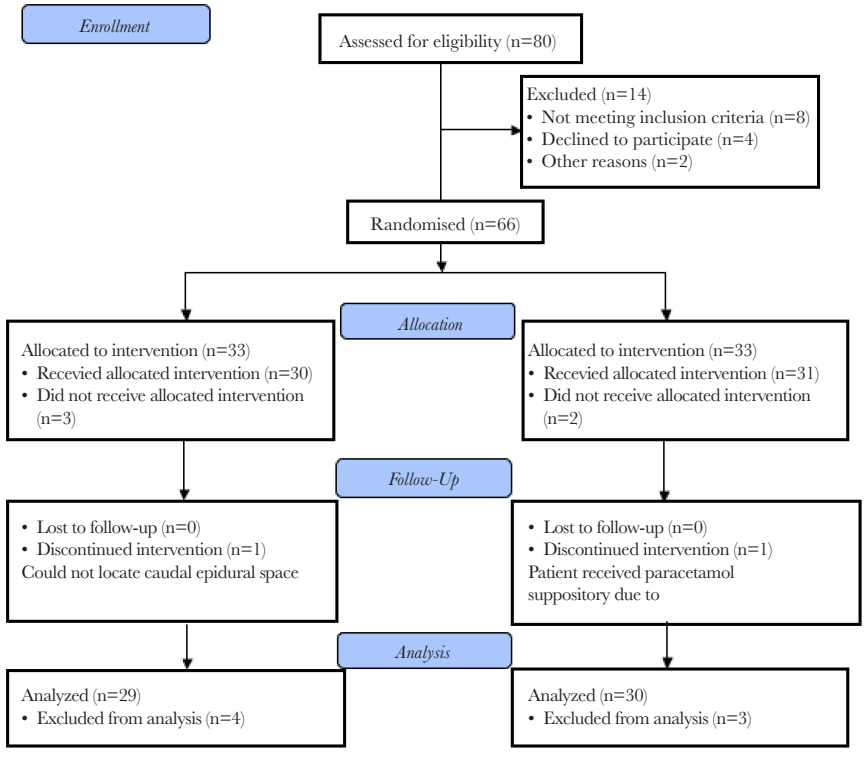

Figure 1. CONSORT flow diagram

Patient's characteristics and clinical data are shown in Table 1. There were a significantly higher number of younger children in the D3 group than those in the D2 group. Weight of the children in the D3 group was statistically lower than that in the D2 group (p=0.018). Duration of anaesthesia and analgesia was comparable between both the groups. The number of children having PSAS 1 was almost similar in both the groups (Table 1). Ten patients in the D3 group and six patients in the D2 group had a PSAS of 2. Four patients in the D2 group and only one patient in the D3 group had a PSAS of 3. These differences in PSAS between the groups were statistically insignificant (Table 1). MAS was comparable between the groups and statistically insignificant (Table 1). EA scores were comparable between the groups. EA score 1

Table 1. Patient characteristics and clinical data

Parameter	D2 group (n)	D3 group (n)	p
Age (year)	7±2.75 (1-8)	4±4.13 (1-8)	0.004
Weight (kg)	21±7 (8-28)	13.75±6.75 (7-35)	0.018
Gender (male/female)	26/3	22/8	
ASA status (I/II)	19/10	16/14	
Duration of anaesthesia (min)	50±42.5 (20-120)	50±26.25 (25-90)	0.193
PSAS[a] 1	19 (65.5%)	19 (63.3%)	0.861
PSAS 2	6 (20.7%)	10 (33.3%)	0.156
PSAS 3	4 (13.8%)	1 (3.3%)	0.149
MAS[b] 1	16 (55.2%)	16 (%)	0.887
MAS 2	6 (20.7%)	8 (%)	0.590
MAS 3	7 (24.1%)	6 (20%)	0.701
Duration of analgesia (min)	640±960 (300-1440)	690±1031 (300-1440)	0.595
Emergence Agitation Score	2±2 (1-3)	2±2 (1-3)	0.594
Incidence of hypotension	3 (10.3%)	4 (13.3%)	0.723
Incidence of bradycardia	0 (0%)	1 (3%)	0.321
Decrease in SpO_2	0	0	

Expressed as median±interquartile range (minimum-maximum) and number (%). [a]Parental Separation Anxiety Scale. [b]Mask Acceptance Score. ASA: American Society of Anesthesiologists

Table 2. PSAS, MAS and duration of analgesia after age stratification

Age group	Parameter	Score	D2 group n (%)	D3 group n (%)	p
Low age group (1-3 years)	PSAS[a]	1	1 (20%)	6 (46.2%)	0.308
		2	0	7 (53.8%)	0.036
		3	4 (80%)	0	0.000
	MAS[b]	1	0	0	0.063
		2	0	8 (61.5%)	0.019
		3	5 (100%)	5 (38.3%)	0.019
	DOAL[c] (min)		720±555 (330-1440)	632±673 (345-1440)	0.390
High age group (4-8 years)	PSAS	1	18 (75%)	13 (76.5%)	0.914
		2	6 (25%)	3 (17.5%)	0.575
		3	0	1 (5.9%)	0.229
	MAS	1	16 (66.7%)	16 (94.5)	0.036
		2	6 (25%)	0 (0%)	0.026
		3	2 (8.3%)	1 (5.9%)	0.767
	DOAL[c] (min)		615±982 (435-1440)	780±850 (300-1440)	0.079

Expressed as number (%). aParental Separation Anxiety Scale. bMask Acceptance Score. cDuration of analgesia is expressed as median±interquartile range (minimum-maximum)

was seen in 37% of the patients in the D2 group and 26% of the patients in the D3 group. Score 2 was seen in 34% of the patients in the D2 group and 46% of the patients in the D3 group. Score 3 was seen in eight patients in both the groups. Duration of analgesia was 640 min in the D2 group and 690 min in the D3 group. This difference in analgesia duration was statistically insignificant.

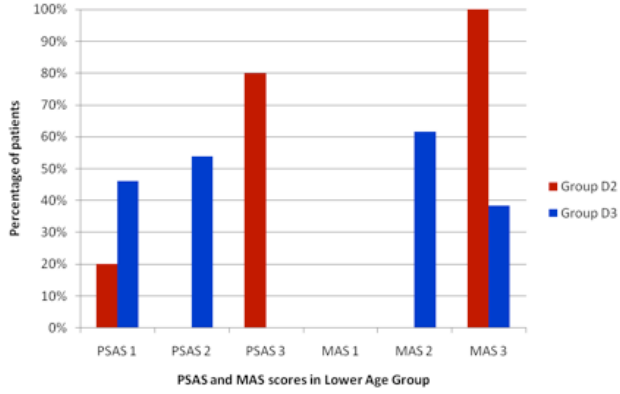

Figure 2. Parental separation and mask acceptance scores in the lower age group

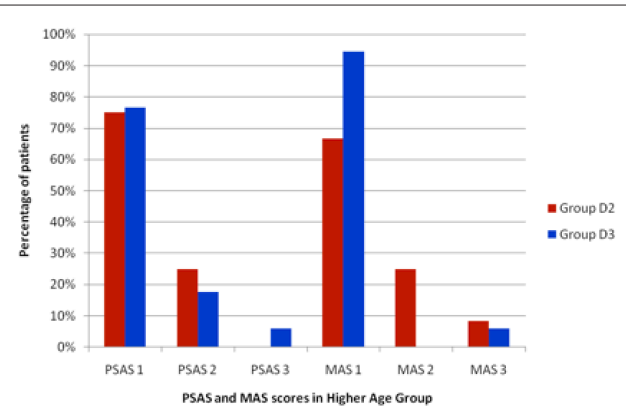

Figure 3. Parental separation and mask acceptance scores in the higher age group

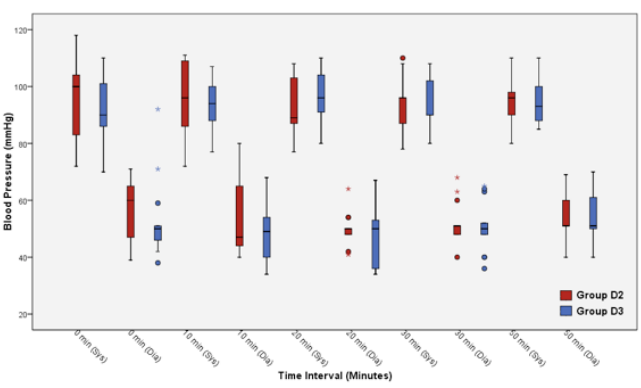

Figure 4. Intraoperative systolic and diastolic BP

Since significantly younger children were observed in the D3 group, both the groups were further divided into the lower age group (1-3 years) and the higher age group (4-8 years). Both the age groups were compared between the D2 and D3 groups again using Mann-Whitney U and chi-square tests. In the lower age group, there were five patients in the D2 group and 13 patients in the D3 group (Table 2). Out of five patients in the D2 group, 80% of the patients had a PSAS of 3 that was significantly more than the D3 group. No patient in the D3 group had a score of 3 (Figure 2). In the lower age group, 100% of the patients in the D2 group had an MAS of 3, whereas only 38.3% in the D3 group had a score of 3. This difference was statistically significant with a p-value of 0.019 (Table 2). In the higher age group, PSAS scores were comparable between the D2 and D3 groups. MAS of 1 was achieved in 94% of the patients in the D3 group (Figure 3), which was significantly better than the D2 group (p=0.036). Occurrence of hypotension and bradycardia was similar in both the groups (Table 1). No patient in either group had desaturation. Decrease in NIBP was similar between the groups (Figure 4). More variability in diastolic BP was noted in both the groups at 30 min. Duration of analgesia in the lower age group was 720 min in the D2 group and 632 min in the D3 group that was comparable with a p-value of 0.390. Duration of analgesia in the higher age group was 615 min in the D2 group and 780 min in the D3 group. This difference was almost nearing statistical significance (p=0.079).

Discussion

In the present study, we compared the effects of two different doses of nebulised dexmedetomidine on parental separation anxiety and on caudal adjuvant effect. Our study shows that parental separation anxiety was significantly less with 3 μg kg^{-1} of dexmedetomidine in lower age group children. Mask acceptance was better in the D3 group than in the D2 group in the lower age group. Parental separation scores were comparable between both the groups in higher age group children. Mask acceptance scores were better in the D3 higher age group. Haemodynamic profile, EA and duration of analgesia were comparable between the groups. Duration of analgesia between the D2 and D3 groups was comparable after age stratification.

Nebulised dexmedetomidine is well absorbed systemically via nasal and buccal routes, and the pharmacological effects are similar after IV administration (4, 12). Previously, only two studies have studied the effects of nebulised dexmedetomidine in a dosage of 2 μg kg^{-1}.

Zanaty and El Metainy (5) compared 2 μg kg^{-1} of nebulised dexmedetomidine with nebulised ketamine and combination of dexmedetomidine with nebulised ketamine. They found

that 60% of the patients in the dexmedetomidine group achieved PSAS one, which is similar to our study findings. MAS one was seen in 15% of the patients in their study. In our study, MAS one was seen in approximately 55% of the patients in both the D2 and D3 groups. Zanaty and EI Metainy (5) have included children from age 3 to 6 years. In the present study, children age <3 years had poor PSAS in the D2 group as compared to the D3 group. Parental separation anxiety is more in children age between 1 and 3 years and is difficult to treat. Qiao et al. (13) studied the effect of 2.5 μg kg^{-1} intranasal dexmedetomidine in children age between 2 and 6 years. They found satisfactory separation from parents in 80% of the patients. In our study, 100% of the patients in the D3 group had satisfactory separation from parents in the younger age group. Children younger than 2 years have larger volume of distribution. Hence, to reach a certain plasma concentration, younger children need larger initial doses of dexmedetomidine than older children (14, 15). Pavithra et al. (16) compared intranasal dexmedetomidine in a dose of 1 μg kg^{-1} and 2 μg kg^{-1} in the 6-12 years old group. They concluded that MASs and sedation scores were better with 2 μg kg^{-1} dose, but PSAS was similar with both the doses. In our study, children age between 3 and 8 years showed similar PSAS in both the groups. However, MAS was better in the D3 group in both the age groups. Tug et al. (17) compared 3 μg kg^{-1} and 4 μg kg^{-1} intranasal dexmedetomidine in children age between 1 and 10 years. They concluded that 67% of children were easily separated from the parents in the 4 μg kg^{-1} group, which was significantly higher than the 3 μg kg^{-1} group. They have assessed parental separation scores after 45 min, whereas in our study, we assessed after 30 min. Pavithra et al. (16) have concluded that after 30 min, both doses of dexmedetomidine produce similar sedation and parenteral separation scores, but after 45 min of drug administration, the higher dose group is significantly better. Lami and Pereira (18) studied 2-3 μg kg^{-1} of dexmedetomidine by transmucosal route and found that 65% of the patients are adequately sedated.

Abdel-Ghaffar et al. (6) found that a PSAS of 1 is achieved in 75% of the patients, and that an MAS of 1 was seen in 55% of the patients with 2 μg kg^{-1} of nebulised dexmedetomidine. Their results are similar to our results. EA scores were less in the study done by Abdel-Gaffer et al. as compared to our study. In our study, we had children age <3 years in whom the incidence of EA is more with sevoflurane (19). Abdel-Ghaffar et al. (6) monitored FLACC scores only for 1 h postoperatively and found that scores were zero. We monitored FLACC scores till requirement of rescue analgesic and found that the duration of analgesia was 10 h in the D2 group and 11 h in the D3 group. Kamal et al. (20) studied the effect of 1 mL kg^{-1} of 0.25% ropivacaine with 2 μg kg^{-1} of dexmedetomidine given in caudal epidural space and found that the duration of analgesia is 750 min. Al-Zaben et al. (21) found that 1 μg kg^{-1} of IV dexmedetomidine prolongs the effect of caudal analgesia up to 9 h. Our results show that 2 μg kg^{-1} of nebulised dexmedetomidine gives analgesia up to 10 h, and that 3 μg kg^{-1} prolongs the duration of analgesia up to 11 h. Olutoye et al. (22) found that the duration of analgesia is significantly more with 1 μg kg^{-1} of IV dexmedetomidine than with 0.75 μg kg^{-1} of IV dexmedetomidine in paediatric patients undergoing tonsillectomy. No previous study has compared the effect of nebulised dexmedetomidine on the duration of analgesia.

Previous studies have used dexmedetomidine in a dose of 1-4 μg kg^{-1} by IV or IM route and concluded that there were no incidences of hypotension or bradycardia, and that decrease in vitals was within 20% of normal with no adverse events (7, 8). Zanaty and EI Metainy (5) found no incidence of bradycardia or hypotension with 2 μg kg^{-1} of nebulised dexmedetomidine. In our study, only one patient in the D3 group developed bradycardia that responded to atropine. All our patients received glycopyrrolate before induction irrespective of HR.

Previous study has proven that the mean time to achieve adequate sedation after transmucosal route is 28 min (18). We assessed PSAS after 30 min of administration of the drug but did not monitor onset time and peak concentration time after nebulisation. This was the limitation of our study. Another limitation of our study was randomisation failure leading to more number of younger children in one group. Owing to this, age-stratified statistical analysis was needed. Previous studies have included children of all age groups ranging from 1 to 10 years in a single study. Parental separation anxiety is different in different age groups, and our study results have shown that the effect of different doses varies with age groups. Hence, further studies are needed for different doses of nebulised dexmedetomidine in the younger age group.

Conclusion

We conclude that nebulised dexmedetomidine in a dose of 3 μg kg^{-1} provides better parental separation in younger children. Further, 3 μg kg^{-1} gives better mask acceptance in both younger and older children. Both the doses can achieve satisfactory parenteral separation in older children and are equally effective in prolonging the duration of caudal analgesia.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Shri Sathya Sai Medical College & Research Institute (IEC No: 2017/342).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – J.A., P.K.; Design – J.A., P.K., Supervision – P.K.; Resources – J.A., P.K.; Materials – J.A., P.K.; Data Collection and/or Processing – J.A., P.K.; Analysis and/or Interpretation – J.A., P.K., Literature Search – J.A., P.K.; Writing Manuscript – J.A., P.K.; Critical Review – J.A., P.K.; Other – J.A., P.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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