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A Comparative Evaluation of Intranasal Dexmedetomidine and Intranasal Midazolam for Premedication in Children

Authors
Anita Pareek[1], Vandana Gupta[2], Kiwi Mantan[3], Aditya Sharma[4]
[1]Senior Professor, [2]Resident, [3]Associate Professor, [4]Medical Student
Department of Anaesthesia, Sardar Patel Medical College & AGH, Bikaner, Rajasthan
*Correspondence Author
Vandana Gupta
Resident, Department of Anaesthesia, Sardar Patel Medical College & AGH, Bikaner, Rajasthan, India
Email: *drvandanagupta17@gmail.com*

Abstract

Introduction: *Children undergoing surgical procedures can experience significant anxiety and distress during perioperative period. Sedation in preoperative room remains one of the widely used methods. Intranasal route is preferred, as it is noninvasive and more convenient.*

Aim: *To compare the efficacy of intranasal dexmedetomidine and Intranasal midazolam for paediatric premedication.*

Method: *In this prospective, randomised controlled trial 100 patients of 2 to 9 years of age of either sex belonging to ASA class 1 and 2 Undergoing various elective surgery were divided into two groups. Group-1 received 0.2 mg / kg intranasal midazolam, group-2 received 1mcg/kg Intranasal dexmedetomidine 45-60 minutes prior to induction. Onset of sedation, degree of sedation, parent separation anxiety scale, acceptance of mask, venipuncture score were assessed.*

Results: *The mean onset of sedation were higher in Group 2(19.34±4.16 Vs 15.46±5.09) which was statistically significant (P=.001). Mean sedation score were lower in group 2(2.6±0.61 Vs 2.98±0.59) which was statistically Significant (P=0.003). The Mean acceptance of mask score were lower In group 2(1.2±0.49 Vs1.54±0.73) which was statistically significant (P =0.008).The mean venipuncture score were lower in group 2(2.06±0.31 Vs 2.18±0.39) which was Statistically Insignificant (P=0.09).The mean parental separation anxiety scale were lower in group 2 (1.38±0.57 Vs 1.66±0.74) which was statistically significant (P <0.03).*

Conclusion: *Intranasal dexmedetomidine results in higher sedation level, better parental separation and better acceptance of mask than intranasal midazolam but has slower onset of action than midazolam. Both the drugs having similar response to cannulation.*

Introduction

Children undergoing surgical procedures can experience significant anxiety and distress during perioperative period which may be due to separation from parents, or fear of injections or the operating theatre. This lead to stress, tachycardia, agitation or excess crying, which make the management of such patients difficult during induction of anaesthesia. Preoperative anxiety can have negative physiological and psychological effects on a child[1].

Various interventions used to allay the anxiety of a child during the perioperative period are sedative premedications, parental presence during induction and preoperative preparation programs. Sedation remains one of the widely used method[2].

Effective premedication may facilitate a smooth induction of general anaesthesia with minimal haemodynamic alterations, minimize emotional trauma in children undergoing surgery, reduce preoperative anxiety, facilitate separation from parents and acceptance of mask induction[3].

A noninvasive approach is preferred for anaesthetic premedication because children often exhibit an exaggerated psychological response to the needle. oral, rectal routes are not reasonable methods for titrating drugs and have considerable delay in onset. The advantage of intranasal route are lace of pain, ease of use, avoidance of injection and rapid absorption of the drug directly into the systemic circulation from an area rich in blood supply without the disadvantage of passing through portal circulation[4].

Benzodiazepines are the most commonly used group of drugs for premedication[5].

Midazolam has a number of beneficial effects when used as premedication in children such as good sedation, fast onset, and limited duration of action, anxiolysis and reduction of postoperative vomiting. A recent evidence-based clinical update has shown that intranasal midazolam 0.2 mg/kg is effective in reducing both separation and induction anxiety in children, with minimal effect on recovery time. However, the acceptability of intranasal midazolam by paediatric patients may vary. Other undesirable effects including restlessness, paradoxical reaction, and negative postoperative behavioral changes have made it a less than ideal premedication[6].

Alpha-2 adrenergic agonists produce sedation, facilitate parental separation, and improve conditions for induction of general anaesthesia while preserving airway reflexes[7]

Dexmedetomidine is a newer alpha 2-agonist with a more selective action on the alpha 2-adrenoceptor and a shorter half-life. Dexmedetomidine has a faster onset of action with analgesics, sedative properties, and it is devoid of respiratory depressive action. It is also tasteless, odourless and painless. Its bioavailability is 81.8% (72.6–92.1%) when administered via the nasal mucosa[8].

Hence, in this study, we compared the efficacy of intranasal dexmedetomidine (1 μg/kg) and intranasal midazolam (0.2 mg/kg) as premedicants in pediatric age group[9].

Material & Methods

After approval by the Institute Ethical Committee & written informed consent from patient's parents or caretaker, the study was conducted as hospital based prospective randomized double blind observational study in 100 ASA Grade I & II patients, Age 02 to 9 yrs, undergoing various elective surgeries under general anaesthesia, performed in the year 2017-2018.

Exclusion

Patients aged < 02 years and > 9 years, history of clinically significant cardiovascular, pulmonary, renal, neurologic disease, history of coexisting disease, allergic to anaesthetic drugs, psychotropic medication use and mental retardation, any nasal disorder that may interfere with nasal administration of drugs, patient's parents or caretaker's refusal were excluded from study.

On the day prior to surgery a thorough clinical examination of the patient was performed including general physical examination and systemic examination. All patients were explained about the anaesthesia technique and written informed consent was taken from parents. Patient was kept NBM for 8 hours (for solid foods),6 hours (for formula & fortified breast milk), 4 hours (for breast milk), 2 hours (for clear liquids) prior to surgery. Routine investigations were done. HB%, BT, CT, urine analysis, chest x-ray, blood urea, serum creatinine & fasting sugar. Patients were randomly allocated in two groups to receive-

Group 1: Intranasal midazolam (0.2mg/kg)

Group 2: Intranasal Dexmedetomidine (1micro gram/kg)

100 children aged 02 –9 years were selected for this study in accordance with American Society of Anesthesiologists (ASA) physical status I & II scheduled for various elective surgeries divided into two groups: intranasal midazolam group (group 1) (n = 50) 0.2 mg/kg and intranasal Dexmedetomidine group (group 2) (n = 50) (1 micro gram/kg). Medications were administered 45 to 60 min prior to induction, in the pre-anesthesia area, with the parent(s) attendance. Calculated dose of drug was diluted to a total volume of 1 ml was administered 0.5 ml in each nostril using a 2-mL syringe with the child in the recumbent position. Before induction in operation theatre, each patient was observed for onset of sedation, degree of sedation, parental separation anxiety, response to venipuncture & acceptance of mask. Inhalation induction was initiated by face mask with a mixture of sevoflurane 8% with O2 100%. When adequate depth of anesthesia reached appropriate LMA was placed and the patient was left to breath spontaneously. The anesthetic level was delivered in a concentration that maintained a stable heart rate, blood pressure and respiratory rate (baseline ± 20%). Standard monitoring was done by using ECG, noninvasive blood pressure, respiratory rate, pulse oximetry and capnography. After the end of surgery anesthetic gases were discontinued to 0% and replaced with O2 100% ⩾4 L/min. LMA was removed when the patient awaked. In postoperative monitoring, each patient was monitored for vital signs (NIBP, PR, SPO2 & RR), restlessness, PONV, emergence reactions. Each patient was followed and observed in post anaesthesia care unit for monitoring of vital signs and any adverse effects.

Five point sedation scale

1) Asleep
2) Drowsy
3) Calm
4) Alert
5) Agitated

Acceptance of mask

1) Accepts readily
2) Accepts with persuation
3) Refuses

Venipuncture score

1) Asleep
2) Calm-no withdrawal for IV cannulation
3) Withdrawal for painful stimuli
4) Crying, uncooperative, not able to start IV line

Parent separation anxiety scale

1) Asleep, cooperative, unafraid
2) Slight fear or crying, quite with reassurance
3) Moderate fear, crying not quite with reassurance
4) Crying need for restraint

Statistical Analysis

- Collected data were entered into excel sheet & analysed with help of SPSS software version 21.
- Results were interpreted in terms of mean, standard deviation and p value.
- Student's unpaired t-test for Quantitative data.
- P<0.05 was considered statistically significant.

Results

Statistical analysis shows no significant difference in average taken for age, weight and gender among two groups.

Out of 50 patients all 50 patients were in ASA grade I in both groups.

Maximum 60% patients in group-1 and 78% patients in group-2 were of urogenital surgery followed by 10% in each group were of eye surgery.

Mean time of onset of sedation in group-1 was 15.46±5.09 minuteand in group-2 was 19.34±4.16 minute. The difference between both groupsis statistically significant.

Mean sedation scale in group-1 was 2.98±0.59 and in group-2 was 2.6±0.61. The difference between both groupsis statistically significant.

The Mean mask acceptance score were higher in group 1 (1.54Vs1.2) as compare to group 2 which is statistically significant ($P < 0.05$).

The Mean venipuncture score were higher in group 1 (2.08Vs2.06) as compare to group 2 which is statistically insignificant ($P > 0.05$).

The Mean parental separation anxiety scale were higher in group 1 (1.66Vs 1.38) as compare to group-2 which is statistically significant ($P < 0.05$).

The differences of vital parameters (Pre-operative, intra operative and post-operative) in both groups were found statistically insignificant.

Table No. 1 Statistical Analysis of Demographic Data

S.No.	Characteristics	Group 1		Group 2		P-value
		Mean	SD	Mean	SD	
1	AGE	5.22	2.41	5.17	2.50	0.929
2	WEIGHT	17.05	5.22	16.24	4.98	0.471

Group	Male	Female	Total	p-value
Group 1	45	5	50	0.712
Group 2	47	3	50	

Table No. 2 Onset of sedation

Group	Mean time of onset of sedation(Min.)	SD	p-value
Group 1	15.46	5.09	0.001
Group 2	19.34	4.16	

Table No. 3 Sedation scale

Group	Mean sedation scale	SD	p-value
Group 1	2.98	0.59	0.003
Group 2	2.6	0.61	

Table No. 4 Acceptance of mask

Group	Mean mask acceptance score	SD	p-value
Group 1	1.54	0.73	0.008
Group 2	1.2	0.49	

Table No. 5 Venipuncture score

Group	Mean venipuncture score	SD	p-value
Group 1	2.18	0.39	0.09
Group 2	2.06	0.31	

Table No. 6 Parental separation anxiety scale

Group	Mean parental separation anxiety scale	SD	p-value
Group 1	1.66	0.74	0.03
Group 2	1.38	0.57	

Fig. 1 Onset of sedation

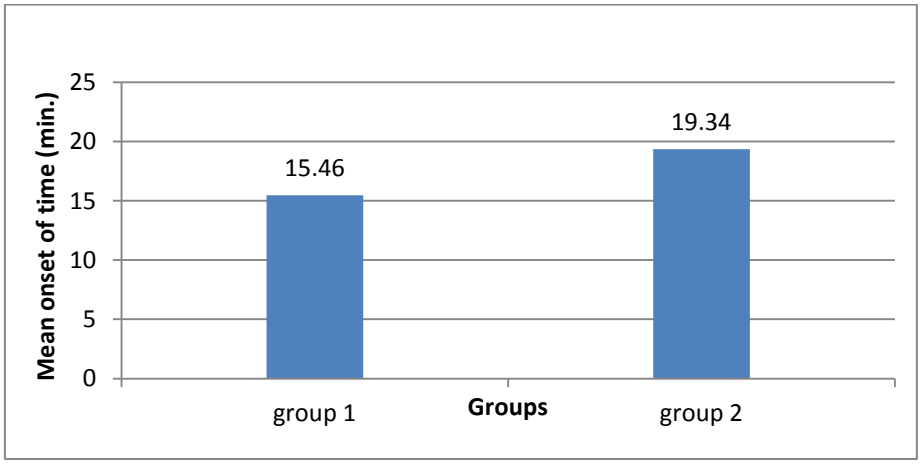


Fig. 2 Sedation scale

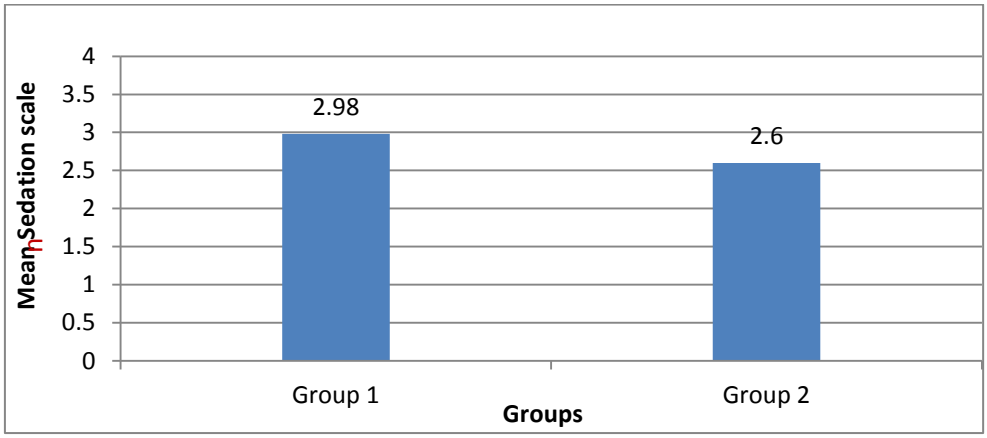


Fig. 3 Acceptance of mask

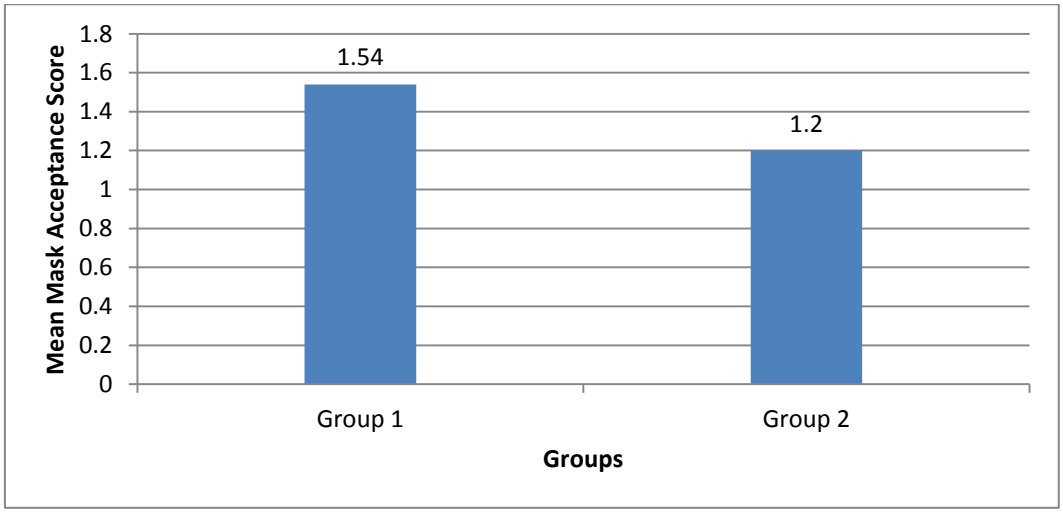


Fig. 4 Venipuncture score

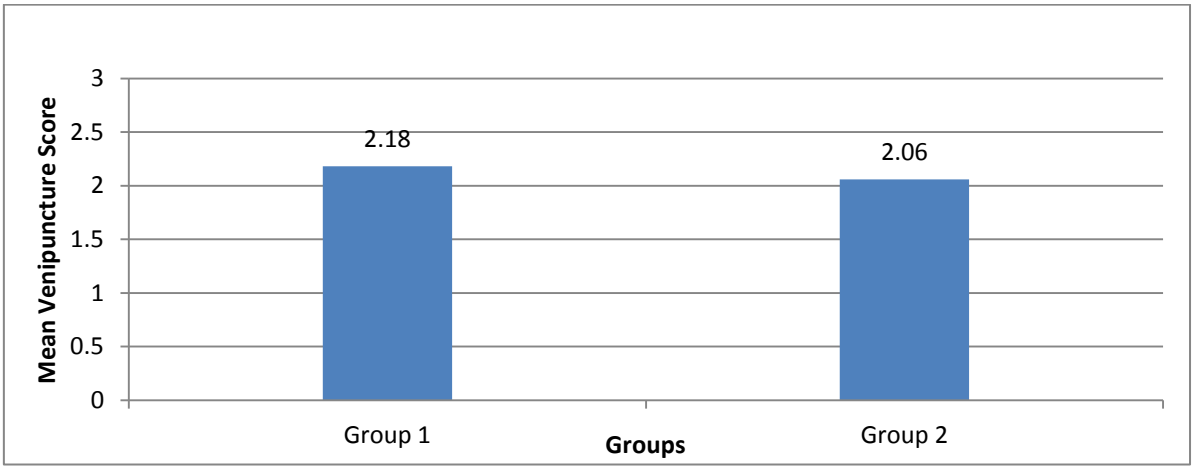
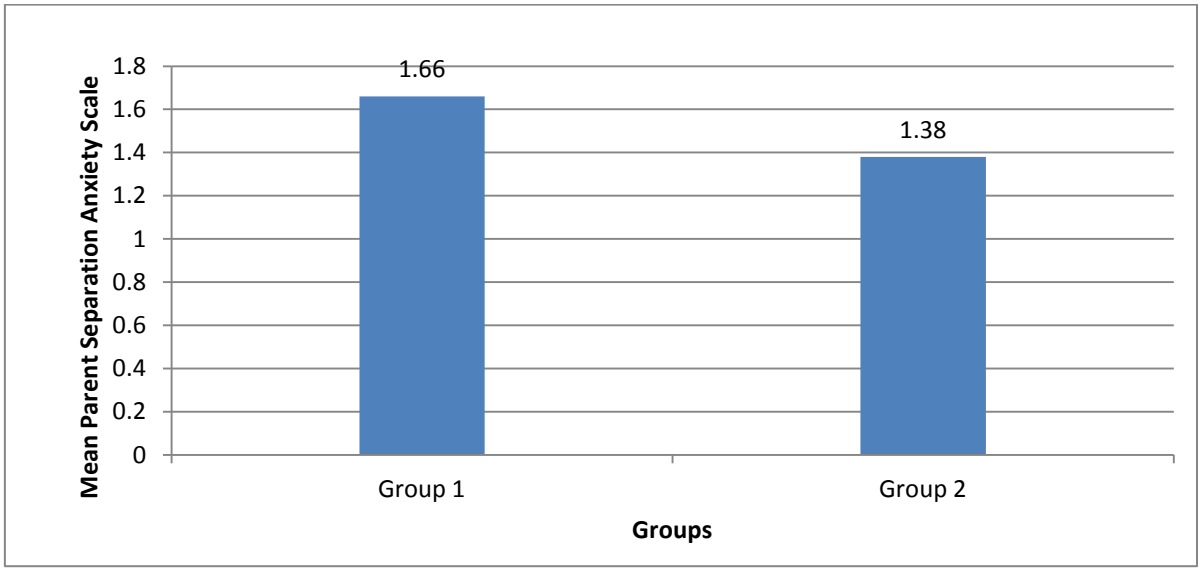


Fig. 5 Parental separation anxiety scale



Discussion

The aims of premedication in pediatric population is to alleviate the stress and fear of surgery as well as to ease parent – child separation and promote a smooth induction of anaesthesia thereby reducing the occurrence of postoperative behavioural disturbances associated with bad preoperative experience.

To avoid emotional trauma associated with parent – child separation and facemask application during induction, it was planned to premedicate the children, appearing for elective surgery, with the most commonly utilized premedicants Midazolam and Dexmedetomidine via intranasal route.

The first clinical investigation of intranasal Midazolam in children was reported by Niall CT Wilton and colleagues[11]. Advantages of nasal administration of Midazolam include rapid absorption without passing through portal circulation, and high systemic availability. It provides effective premedication when given 30 minutes before separation from parents.

In our study we selected 0.2 mg/kg dose of intranasal Midazolam as preliminary studies conducted by Niall CT Wilton, et al.[11] using 2 doses of intranasal Midazolam, 0.2 mg/kg and 0.3 mg/ kg, found that significant changes in sedation occurred early in low dose Midazolam as compared to high dose.

Similar results were obtained in a study conducted by Pradipta Bhakta, et al. (2007)[12], and Davis PJ, et al. (1995)[10], who compared 0.2 mg/ kg versus 0.3 mg/ kg of Midazolam intranasally. They concluded that 0.2 mg/ kg was an effective dose and no added advantage was found with 0.3 mg/kg. With the above evidences we have opted for a lower dose of 0.2 mg/kg intranasally for our study.

Recently, alpha-2 receptor agonists such as Dexmedetomidine have also been found to be useful for premedication in children. The site of action of Dexmedetomidine is in locus coeruleus where it causes EEG activity similar to normal sleep. This results in anxiolytic effect, sedation and analgesia without excessive drowsiness. The intranasal route was used in our study as it is non-invasive, unlike intravenous and intramuscular routes, and Produces a more rapid onset of action than the oral route.

In our study, intranasal Midazolam (0.2 mg/kg) was compared with intranasal dexmedetomidine (1 microgram/ kg) for premedication in pediatric surgery. Children of age 2- 9 years were chosen for the study, as this is the most vulnerable group for the stress response. 100 children awaiting elective surgery who did not meet the exclusion criteria were randomly assigned into two groups of 50 each group 1 and group 2. Group 1 received 0.2 mg/ kg of intranasal Midazolam and group 2

received 1 microgram/ kg of Dexmedetomidine in the preoperative holding area.

We studied the following parameters like Demographic profile, preoperative sedation scale using five point sedation scale, acceptance of mask, venipuncture score, parent separation anxiety scale, haemodynamic parameters and complications if any.

Socio-demographic variable

Statistical analysis shows no significant difference in average taken for age, weight and gender among two groups.

Type of surgery

In our study maximum 60% patients in group-1 and 78% patients in group-2 were of urogenital surgery followed by 10% in each group were of eye sugary.

Onset of sedation

In our study mean time of onset of sedation in group-1 was 15.46±5.09 min.and in group-2 was 19.34±4.16 min. The difference between both groups is statistically significant.

Sedation scale

Mean sedation scale were lower in group 2 (2.6±0.61 Vs 2.98±0.59) which was statistically significant (P=0.003) which indicates that dexmedetomidine produces better sedation than midazolam.

Sobhan Aich et al. (2015)[14] observed that the level of satisfactory sedation in dexmedetomidine group was achieved with in 20 min. whereas in midazolam group it was achieved at 30 min and children who were premedicated with intranasal Dexmedetomidine (1μg/kg) were more significantly sedated as compared to Midazolam (0.2mg/kg).

Ayushi gupta et al. (2017)[15] observed that the time of onset of sedation is 8.7 ± 3.7 min (5–15 min) in Group M compared with 14.3 ± 3 min (10–20 min) in Group D. The difference in onset time was statistically significant with early onset in midazolam. They also observed that intranasal dexmedetomidine group yields a higher sedation level at the time of induction of anaesthesia.

Above mentioned previous studies correlate with our study.

Acceptance of mask

The Mean mask acceptance score were lower in group 2(1.2±0.49 Vs1.54±0.73) which was statistically significant (P =0.008).

Parent separation anxiety scale

The mean parental separation anxiety scale were lower in group 2 (1.38±0.57 Vs 1.66±0.74) which was statistically significant (P =0.03).

Malineni N et al. (2017)[9] observed that intranasal dexmedetomidine 1 μg/kg results in better parent separation and better mask acceptance at the time of induction when compared to intranasal midazolam 0.2 mg/kg.

Pasin L et al. (2015)[13] observed that dexmedetomidine provides higher incidence of satisfactory sedation at separation from parents as compared with midazolam.

Singla D et al. (2015)[1] observed that premedication with intranasal dexmedetomidine 1 mcg/kg resulted in lower anxiety levels & better parent separation & mask acceptance as compared with intranasal midazolam 0.2 mg/kg.

Our study correlate with above studies.

Venipuncture score

The mean venipuncture score were lower in group 2 (2.06±0.31 Vs 2.18±0.39) which was statistically insignificant (P=0.09).

Sobhan Aich et al. (2015)[14] observed that the behaviour at venipuncture in both the intranasal Dexmedetomidine and intranasal Midazolam group was comparable that correlate with our study.

Vital parameters

The differences of vital parameters (Pre-operative, intra operative and post-operative) in both groups were found statistically insignificant.

Sobhan Aich et al. (2015)[14] also found that the basal hemodynamic parameters i.e. heart rate, systolic blood pressure, respiratory rate and oxygen saturation of the two groups were comparable.

Our study correlate with above study.

Complications

None of the children in both groups had untoward complications, such as bradycardia, hypotension, hypertension, and respiratory depression, after premedication. Similar findings regarding side effects were noted in other studies.

Limitations of the Study

Our study was designed to compare the efficacy of two drugs for premedication in children. So a sample size just adequate for this purpose was calculated and studied. Therefore, further studies with higher sample size are required to establish the usefulness of intranasal dexmedetomidine as perioperative anxiolytic in children.

We have administered the drug with the help of a needle less syringe; it is possible to use atomiser for this purpose. Midazolam atomiser is available but it is not available for Dexmedetomidine. If we would have used only Midazolam atomiser the process of blinding would have been adversely affected in our study.

Conclusion

Thus from our study and observations, we conclude that Intranasal Dexmedetomidine results in higher sedation level, better parental separation and better acceptance of mask than intranasal midazolam but has slower onset of action than midazolam. Both the drugs have similar response to cannulation.

We conclude that intranasal dexmedetomidine is superior to intranasal midazolam for premedication in paediatric patients.

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