Original Article

Comparative Study between Nebulized Dexmedetomidine and Nebulized Midazolam in Reducing Preoperative Anxiety and Emergence Delirium in Children Undergoing Lower Abdominal Surgeries

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ABSTRACT

Background and Aims: An ideal premedication drug should result in a sedated child to allow easy separation of a child from the parents, facilitating smooth induction of anesthesia and a pleasant perioperative experience for both children and parents the present study evaluated the safety and efficacy of nebulized dexmedetomidine in a dose of 3μg/kg and nebulized midazolam in a dose of 0.3mg/kg in reducing preoperative anxiety and emergence delirium in children undergoing lower abdominal surgeries.

Methods: A prospective, randomized, double-blind study was done involving 60 children of age 3–8 years, randomly allocated into two equal groups and pre-medicated with either nebulized dexmedetomidine 3μg/kg (Group D), or midazolam 0.3mg/kg (Group M). The scores of sedation scale, parental separation anxiety scale, mask acceptance scale and emergence agitation scale were compared along with hemodynamic parameters, total narcotics consumption, recovery time and postoperative nausea and vomiting.

Results: Dexmedetomidine provided statistically significant Parental Separation and emergence delirium than midazolam with *P* value 0.003 and 0.001 respectively. Moreover both provide satisfactory mask acceptance with no statistically significant difference regarding adverse effects as hypotension, bradycardia and postoperative nausea and vomiting.

Conclusion: Children premedicated with nebulized demedetomidine in the dose of 3μg/kg experienced more satisfactory peroperative sedation and emergence delirium, better mask acceptance, shorter recovery time and lower perioperative narcotics use than children premedicated with nebulized midazolam with no significant increase in the incidence of bradycardia or hypotension.

Key Words: Children, dexmedetomidine, emergence agitation, midazolam, premedication, separation anxiety.

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BACKGROUND

Hospitalization and surgery can provoke significant stress and anxiety in children. The induction of anesthesia may be the most distressing procedure a child experiences during the entire perioperative period[1].

The preoperative period can be a traumatic time for young children undergoing surgery. Preoperative anxiety stimulates the sympathetic, parasympathetic, and endocrine systems, leading to an increase in heart rate (HR), blood pressure, and cardiac excitability[2].

Many preschool children experience significant anxiety during the preoperative period. This may cause distress to the child which, in turn, may have a negative impact on their postoperative recovery and cause long-term impairment in cognition. Thus, an optimal drug for premedication in young children is crucial[3].

An ideal premedication drug should result in a sedated child to allow easy separation of a child from the parents, facilitating smooth induction of anesthesia and a pleasant perioperative experience for both children and parents. Although many studies have reported the effects of benzodiazepines, α-2 agonists, opioids, and ketamine as premedication drugs via various routes, there is no widely accepted drug or route of choice[4].

Most of these drugs produce variable sedation, with a risk of respiratory depression. Studies have reported higher bioavailability and fewer adverse events with the nebulized route than with oral or intranasal administration[5].

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Midazolam has long been the most commonly used drug for premedication in children. It has been shown to alleviate anxiety and provide adequate sedation. However, midazolam has untoward side effects with increased risk of respiratory depression, amnesia, and paradoxical reactions[6].

Dexmedetomidine is an α-adrenoceptor agonist with dose-dependent α2-adrenoceptor selectivity. Its primary site of action in the central nervous system is the locus coeruleus, where it induces electroence-phalographic activity similar to that of natural sleep, with easy arousal by external stimulation[7].

A successful pediatric day-case service is one which minimizes postoperative morbidity, has low in-patient admission rates and demonstrates high parental and child satisfaction. Good quality anesthesia is essential in achieving these goals with experienced clinicians working in child-friendly facilities. Traditional premedication are unsuitable, as they tend to produce excessive postoperative sedatio[7].

The aim of this study was to compare and evaluate the efficacy of nebulized dexmedetomidine in a dose of 3µg/kg and nebulized midazolam in a dose of 0.3mg/kg in reducing preoperative anxiety and emergence delirium in children undergoing lower abdominal surgeries.

PATIENTS AND METHODS

Double blinded randomized study that was performed at Ain Shams university hospitals. After departmental ethical committee approval and an informed consent had been taken from the guardians of the pediatric patients, 60 healthy pediatric patients aged between 3 to 8 years of age boys and girls, (ASA) physical status I and II undergoing elective lower abdominal surgeries under general anesthesia in Ain Shams university hospitals. Patients were blindly randomized using their medical record number into two equal groups and subjected to a comparative study.

Group D received 3 micrograms/kilograms of body weight dexmedetomidine by nebulized route; group M received 0.3 milligrams/kilograms of body weight Midazolam by nebulized route. The study was completed in six months.

Inclusion Criteria

Children aged 3-8 years, ASA I&II, undergoing lower abdominal surgeries (hernia repair, orchiopexy and circumcision).

Exclusion Criteria

Children with chest infection, respiratory disease, cardiac disease. Children with mental or physical disabilities, treatment with sedatives and anticonvulsants. Parental refusal. Allergy to study drugs. Children with any abnormal vital signs especially hypotension and/or bradycardia. children have an illness with significant nasal congestion. Operations lasting more than 60 minutes, unanticipated increased blood loss, difficult intubation and multiple manipulations of the airway and finally difficult cannulation were excluded from the study.

Sixty patients were randomized to receive premedication by inhalation, nebulized dexmedetomidine 3µg/kg (Group D, 30 patients), or nebulized midazolam 0.3mg/kg (Group M, 30 patients).

Randomization

Was based on a computer-generated randomization table, with group allocation concealed in sealed opaque envelopes. An independent investigator not involved in the study opened the envelopes 1h before induction of anesthesia and prepared the study drug solutions in identical syringes with matching random codes. Study drugs was diluted in 3ml of 0.9% saline and was given as nebulizer with a continuous flow of 100% oxygen at 6L/min for 10 to 15min. The attending anesthesiologist, physician, data collection personnel, and the patient guardians were blinded to the patient group assignment.

The drug was administered by an independent anesthesiologist who was not involved in the observation and the observer was blinded to the type of drug given and baseline vital parameters were recorded.

The children were observed for acceptance of premedication, sedation and anxiety according to Ramsey sedation scale at 10, 20 and 30 minutes after administration of premedication.

Level of anxiety of the child at the time of separation from parents (30 minutes after premedication) was assessed by Parental separation scale (PSAS).

Level of anxiety of the child at the time of applying facemask was observed and assessed by Mask acceptance score (MAS).

Children had routine monitoring including electrocardiography, pulse oximetry, non-invasive blood pressure and temperature. Vital signs were recorded every 5 minutes intra-operatively.

Induction of anesthesia was achieved with sevoflurane up to 6% in 100% oxygen till the loss of eye lash reflex using appropriate size face mask. Appropriate sized laryngeal mask was inserted and anesthesia was maintained with sevoflurane 2-3%, the child was turned to left lateral position Caudal anesthesia was given by 1ml/kg 0.2% Bupivacaine, fentanyl 1µg/kg was given

every 30 minutes for intra-operative analgesia if HR or MAP increased more than 20% of baseline. The child was breathing spontaneously or may be assisted if apnea or hypoventilation occurred to achieve end tidal CO_2 <45mmHg.

Peri-operative incidence of vomiting, nystagmus, emergence delirium or any other side effects and post anesthetic recovery time were noted.

Post-procedure, all the children were continuously monitored in the recovery room until discharged to the ward. The children were discharged from ward after they become fully awake, able to sit by themselves, and haemodynamically stable.

Data Collected

1. The level of anxiety of the child during separation from parents according to 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[8].
2. The level of sedation when the child was first seen in the operating room 30 minutes after sedation using Ramsey sedation scale[9] where: 1: Anxious and agitated, restless, or both; 2: Cooperative, oriented, and calm; 3: Responsive to commands only; 4: Exhibiting brisk response to light glabellar tap or loud auditory stimulus. 5: Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus; 6: Unresponsive. The child was considered agitated when Ramsey sedation score= 1
3. Tolerance of mask induction by 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].
4. Hemodynamic changes if more than 20% change in mean arterial pressure (MAP) or Heart Rate (HR).
5. Incidence of emergence delirium, wake up behaviour was assessed according to Watcha scale where Score is observed values as follows: 0= asleep, 1= calm, 2= crying but can be consoled, 3= crying but cannot be consoled, 4= agitating and thrashing around[8].
6. Incidence of post-operative nausea and vomiting.
7. Recovery time, time between laryngeal mask removal and discharge from recovery room.
8. Total fentanyl use.

The end point of the study when the child was discharged from recovery room.

Sample Size Calculation

Using PASS 15 program for sample size calculation, setting power at 90% and alpha error at 0.05. It was estimated that sample size of a minimum 10 children per group will be needed to detect the difference between two groups regarding sedation score after 30 minutes assuming that median sedation score in M group= 3.5(1-4) and in D group= 2 (2-3)[11].

Statistical package and Analysis

Data presented as mean and standard deviation (±SD) for quantitative prometric data. Suitable analysis done according to the type of data obtained. For example Fisher's exact test was used It is typically used as an alternative to the Chi-Square Test of Independence when one or more of the cell counts is less than 5.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following: *P*-value <0.05: Significant (S).

RESULTS

The main findings of the current study revealed that dexmedetomidine provides statistically significant Parental Separation and emergence delirium than midazolam with *P* value 0.003 and 0.001 respectively.

Sixty 60 children were enrolled in the study after excluding eleven patients not meeting inclusion criteria or declined to participate , thirty patients were allocated in each of dexmeditomidine group and midazolam group (Figure 1).

Patients enrolled in the study were comparable for their demographic data and no statistical significant difference between the studied groups regarding age, sex, weight, ASA physical status and type of surgery (Table 1).

Patients who received nebulized dexmeditomidine had more satisfactory reduction of preoperative anxiety than patients who received nebulized midazolam as Parental separation anxiety scores were lower in dexmedetomidine group than that in midazolam group with high significance (*P*= 0.003) (Table 2 and Figure 2).

Nebulized dexmeditomidine provided lower incidence of Emergence Delirium compared with nebulized midazolam as showed in (Figure 3) Watcha scale was lower in Dexmedetomidine group than in Midazolam group with high significance (*P*= 0.001) (Table 3).

Patients who received nebulized dexmedetomidine experienced better level of sedation when the child was first seen in the operating room according to Ramsey sedation scale which was significantly higher in dexmedetomidine group than in midazolam group (P= 0.012) (Table 4).

Mask acceptance (MAS) score was lower in Dexmedetomidine group than in Midazolam group with high significance (P= 0.008) (Table 5).

Both groups were comparable regarding the incidence of adverse effects such as bradycardia, hypotension and vomiting.

Incidence of bradycardia (lower heart rate more than 20% from baseline) was non-significantly more frequent in dexmedetomidine group than midazolam group (16.7% and 3.3% respectively) (Table 6).

Hypotension (>20% decrease in MAP) occurred in 4 patients (13.3%) in dexmedetomidine group compared to nil patient in midazolam group, however this was not statistically significant using Fisher's Exact test (P= 0.112) (Table 7).

Regarding Vomiting, occurrence was non-significantly less frequent in dexmedetomidine group than Midazolam group (Table 8).

Recovery time was shorter in dexmedetomidine group than midazolam group with high significance (Table 9).

Total fentanyl consumption was lower in Dexmedetomidine group than in Midazolam group with high significance (Table 10).

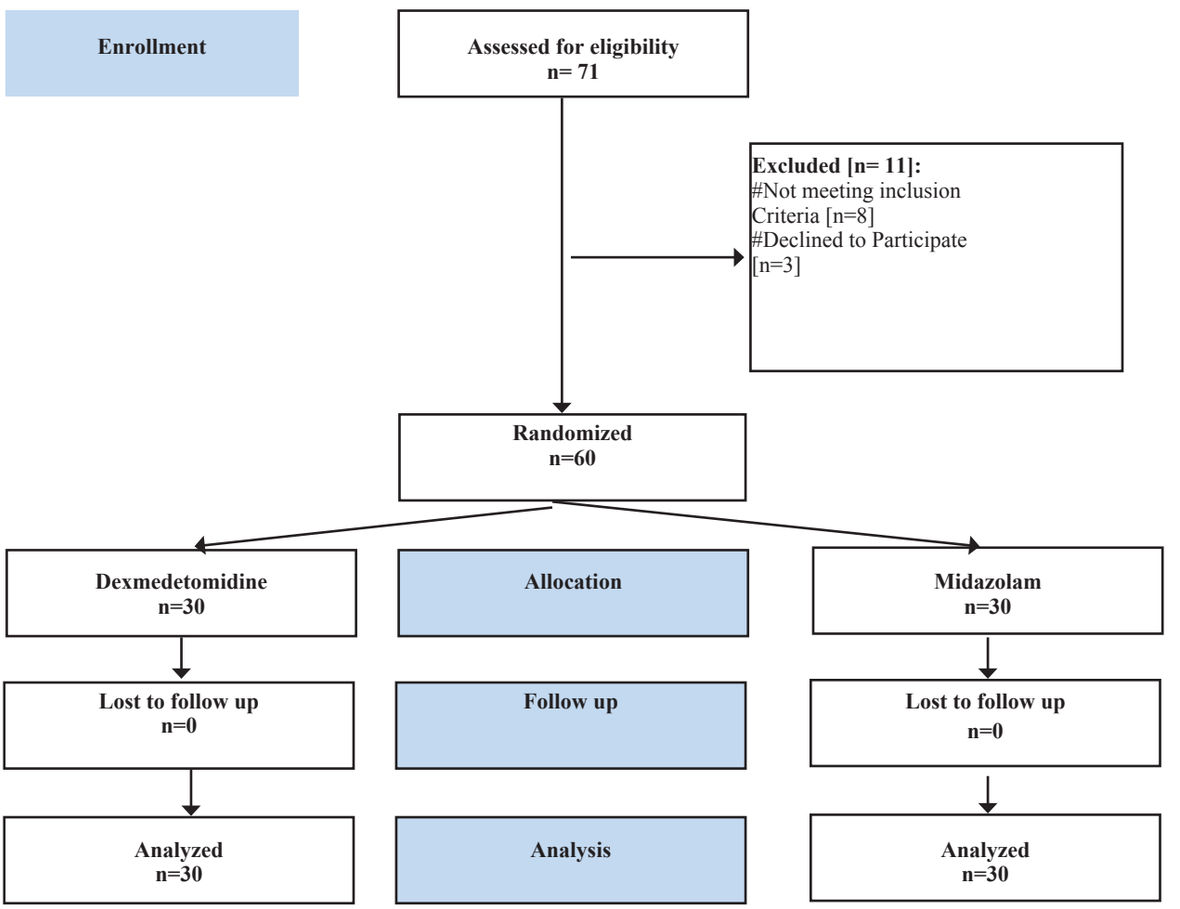

Fig. 1: Flow chart of the studied cases.

Table 1: Baseline characteristics among the studied groups:

Vatiables		Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value
Age	Mean±SD	5.6±1.8	5.0±1.8	^0.256
(years)	Range	3.0–8.0	3.0–8.0	
Sex	Male	28(93.3%)	28(93.3%)	#1
	Female	2(6.7%)	2(6.7%)	
Weight	Mean±SD	18.9±4.0	17.8±3.7	^0.274
(kg)	Range	12.0–26.0	11.0–25.0	
ASA	I	30(100.0%)	30(100.0%)	NA
Type of Surgery	Urethroplasty	12(40.0%)	8(26.7%)	§0.765
	Cystoscopy	5(16.7%)	5(16.7%)	
	Orchiopexy	3(10.0%)	5(16.7%)	
	Inguinal hernia	4(13.3%)	4(13.3%)	
	Circumcision	2(6.7%)	5(16.7%)	
	Rectal/anal prolapse	4(13.3%)	3(10.0%)	

Data presented as n (%) unless mentioned otherwise; ASA: American Society of Anesthesiologists; NA: Not applicable; ^: Independent *t*-test; #: Chi square test; §: Fisher's Exact test.

Table 2: Parental separation scale (PSAS) among the study groups:

Measures	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Mean±SE 95% CI
Mean±SD	2.1±0.8	2.8±0.9	^	-0.7±0.2
Range	1.0–4.0	1.0–4.0	0.003*	-1.1–0.3

^: Independent *t*-test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; SE: Standard error; CI: Confidence interval.

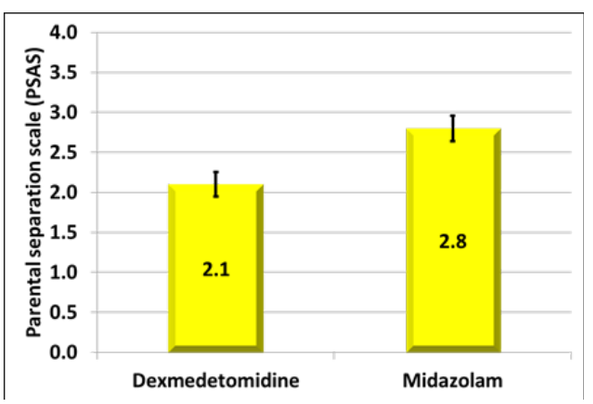

Fig. 2: Parental separation scale (PSAS) among the studied groups.

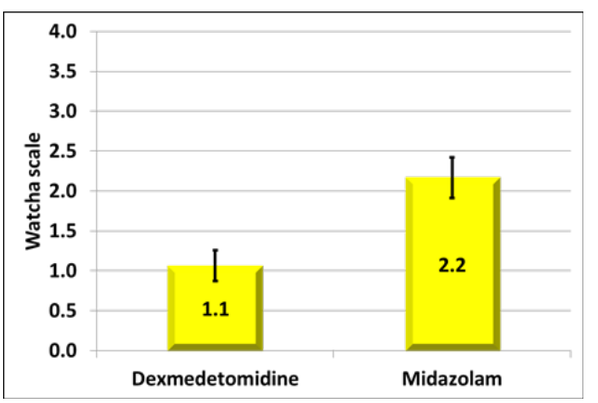

Fig. 3: Watcha scale among the studied groups.

Table 3: Watcha scale among the study groups:

Measures	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Mean±SE 95% CI
Mean±SD	1.1±1.0	2.2±1.4	^	-1.1±0.3
Range	0.0–3.0	0.0–6.0	0.001*	-1.7–-0.5

^: Independent *t*-test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; SE: Stndard error; CI: Confidence interval.

Table 4: Ramsay sedation scale among the study groups:

Measures	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Mean±SE 95% CI
Mean±SD	2.4±0.8	1.8±0.8	^	0.5±0.2
Range	1.0–4.0	1.0–3.0	0.012*	0.1–0.9

^: Independent *t*-test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; SE: Standard error; CI: Confidence interval.

Table 5 : Mask Acceptance Score (MAS) among the study groups:

Measures	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Mean±SE 95% CI
Mean±SD	1.5±0.7	2.0±0.8	^	-0.5±0.2
Range	1.0–3.0	1.0–3.0	0.008*	-0.9–-0.1

^: Independent *t*-test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; SE: Standard error; CI: Confidence interval.

Table 6: Bradycardia among the study groups:

Finding	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Relative risk 95% CI
Present	5(16.7%)	1(3.3%)	§0.195	5.0(0.6−40.3)
Absent	25(83.3%)	29(96.7%)		

§: Fisher's Exact test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; CI: Confidence interval.

Table 7: Hypotension among the study groups:

Finding	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Relative risk 95% CI
Present	4(13.3%)	0(0.0%)	§0.112	Not applicable
Absent	26(86.7%)	30(100.0%)		

§: Fisher's Exact test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; CI: Confidence interval.

Table 8 : Vomiting among the study groups:

Finding	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Relative risk 95% CI
Present	0(0.0%)	2(6.7%)	§0.492	Not applicable
Absent	30(100.0%)	28(93.3%)		

§: Fisher's Exact test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; CI: Confidence interval.

Table 9 : Recovery time (minutes) among the study groups:

Measures	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Mean±SE 95% CI
Mean±SD	15.9±1.9	19.9±3.1	^	-4.1±0.7
Range	13.0–20.0	15.0–25.0	<0.001*	-5.4–-2.7

^: Independent *t*-test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; SE: Stndard error; CI: Confidence interval.

Table 10: Total fentanyl consumption (mcg/kg) among the study groups:

Measures	Dexmedetomidine (Total= 30)	Midazolam (Total= 30)	*p*-value	Relative effect Mean±SE 95% CI
Mean±SD	0.4±0.6	0.9±0.7	^	-0.5±0.2
Range	0.0–2.0	0.0–2.0	0.004*	-0.9–-0.2

^: Independent *t*-test; Relative effect: Effect in Dexmedetomidine group relative to that in Midazolam group; SE: Stndard error; CI: Confidence interval.

DISCUSSION

The main finding of this study is that perioperative anxiety using PSAS (Parental Separation Anxiety Scale) and emergence delirium using Watcha Score were significantly lower in children premedicated by inhaled nebulized dexmedetomidine in the dose of 3μg/kg than nebulized midazolam in the dose of 0.3mg/kg. Premedication with nebulized dexmedetomidine provides higher level of sedation according to Ramsay sedation score, better mask acceptance during induction of anesthesia, shorter recovery time and lower perioperative narcotics use than premedication by nebulized midazolam. Moreover, there was no significant increase in the incidence of hemodynamic changes such as bradycardia or hypotension and adverse effects particularly incidence of nausea and vomiting.

Premedication drugs can be administered by many routes, including oral, intramuscular, intravenous, intranasal, rectal, transdermal, and nebulized routes. We choose to nebulize drugs for better absorption than nasal, buccal, and respiratory mucosa, with better patient acceptance[12]. The nebulized pulmonary route (NPR) is a non-invasive method that allows a rapid onset of drug action and good bioavailability because of a large available area of mucosal absorption. Nebulized route is better accepted and tolerated by pediatric patients than gargles or

even the oral route. Unlike the oral route, the taste is not a factor and there is no risk of aspiration[13].

Dexmedetomidine, a drug of non-barbiturate class is a potent and highly selective alpha 2- adrenergic agonist with sedative, analgesic and anxiolytic effects as well as prevent emergence agitation following general anesthesia. Dexmedetomidine produces dose dependent sedation, anxiolysis and analgesia (involving spinal and supraspinal levels) without respiratory depression[14].

Midazolam is an imidazobenzodiazepine. It is used as a premedicant, a sedative and as an induction anesthetic drug. It possesses unique physical and chemical properties that distinguish it from other benzodiazepines regarding its pharmacokinetics and pharmaco-dynamics characteristics[15]. The sedative effects are linked to the α1 subunit, the most common of the GABAA subunits and present all through the brain, specifically on hippocampal and cortical interneurons. This subunit does not cause variation in sleep EEG[16].

Previous data on drug pharmacokinetics through nebulized route are limited although previous clinical studies was done using the dose of 2μg/kg for dexmedetomidine and 0.2mg/kg for midazolam[16-18]. Anupriya and Kurhekar[19] analyzed different age groups of children and found that 2–3μg/kg inhaled nebulized dexmedetomidine was safe and effective for sedation and that 3μg/kg increased the frequency of satisfactory parental separation among younger children. Further, 3μg/ kg−1 gives better mask acceptance in both younger and older children. We decided to use the dose of 3μg/kg for dexmedetomidine and 0.3mg/kg for midazolam to test the clinical effectiveness and adverse effects which was found to provide effectiveness for reducing preoperative anxiety and emergence delirium with no significant increase in adverse effects specifically bradycardia and hypotension compared to midazolam group.

Preoperative anxiety may obstruct anesthesia induction, extend its duration, and significantly affect early postoperative recovery[20]. Taking into consideration the high prevalence and the associated adverse outcomes of preoperative anxiety, treatment is indicated[21]. Procedural sedation is an emerging cornerstone in pediatrics seeking for controlling pain, decreasing fear and emotional response when immobility is required or during painful procedures. The ideal sedative drug should have a prompt onset of action, be easy to administer, with a short elimination half time, offering efficacious pain relief with or without minimal side effects[22].

Feng *et al*.,[23] conducted a meta-analysis that included 12 Randomized control trials that compared the pharmacological effect of dexmedetomidine versus midazolam in children undergoing anesthesia with sevoflurane. In accordance with our results they suggested that dexmedetomidine provided more satisfactory sedation, parental separation, and total use of analgesia than midazolam.

The incidence of Emergence Delirium in children is unclear, but is likely low in modern pediatric anesthesia practice. Older studies reported estimates between 10 and 80 percent in young children. However, the incidence of ED varies with the anesthetic agent used, age of the child, the procedure or surgery and in particular, with the criteria used to diagnose ED. Current practice routinely includes preemptive administration of analgesics, often sedatives (dexmedetomidine) and other adjunct agents to ensure a smooth emergence from anesthesia, which has reduced the clinical incidence of ED in the PACU. In one single institution observational study, the incidence of ED was <2 percent[23].

In accordance to our results Awad AA. *et al*.,[17], concluded that Nebulization with dexmedetomidine produced more satisfactory sedation, easy parental separation and face mask acceptance nebulization than those who received nebulized midazolam. But unlike our study they used dexmedetomidine in a dose of 2mic/kg and midazolam 0.2mg/kg , did not compare the incidence of side effects or effect on hemodynamics and also incidence of Emergence delirium was not compared.

Abdel-Ghaffar *et al*.,[24] Compared nebulised dexmedetomidine, ketamine, and midazolam and concluded that children premedicated with nebulized dexmedetomidine had more satisfactory sedation, shorter recovery time, and less postoperative agitation than those who received nebulized ketamine or midazolam. As well as our study same Parent Separation Anxiety Scale was used which hinders same results, Regarding Emergence delirium they used three points scale compared with Watcha scale used in our study, however both concluded that incidence of ED was lower in demedetomidine than other groups.

Shereef *et al*.,[16] compared nebulized demedetomidine, midazolam and ketamine regarding Recovery that was assessed using the three-point emergence agitation scale as follows: 1—Calm, 2—Restless but calms in response to verbal instructions, 3—Combative and disoriented. In our study Emergence delirium was determined using Watcha score which may have a higher overall sensitivity and specificity than other scales according to Bajwa *et al*.,[25] However same results were obtained that emergence delirium was significantly lower using dexmedetomidine than midazolam.

Plambech and Afshari[26] stated that the most common adverse effects of dexmeditomidine with slight effect on respiration. In our study effect on respiration was not assessed further studies are needed for the assessment of the effect on respiration after nebulized premedication we found that children who received nebulised dexmedetomidine showed lower heart rate and mean arterial blood pressure values in the preoperative period.

Although dexmedetomidine was used in the dose of 3μg/kg these hemodynamic changes were not clinically significant and did not require any intervention as well as in children received nebulized midazolam. Unlike Medhat and Abd Elnaby[27] in which significant bradycardia was seen in dexmeditomidine group.

Using Intranasal route Patel *et al*.,[28] found that dexmeditomidine is superior to midazolam regarding sedation and parent separation scores, but significant lower heart rates than baseline occurred in demeditomidine which was non-significant in our study using the nebulized route.

There are a few limitations to our study. First the scoring system used for the determination of parental separation and mask acceptance was not validated[5]. Second, after using the nebulized route of premedication the serum concentrations of dexmedetomidine and midazolam were not measured. Third the time of onset of sedation was not compared. At last the results of our study were not tested for children younger than 3 years old.

We concluded that, children premedicated by nebulized demedetomidine in the dose of 3μg/kg experienced more satisfactory peroperative sedation and emergence delirium, better mask acceptance, shorter recovery time and lower perioperative narcotics use than children premedicated by nebulized midazolam with no significant increase in the incidence of bradycardia or hypotension or nausea and vomiting.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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