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Effects of oral dexmedetomidine on incidence of anxiety and emergence delirium in surgical and non-surgical anesthesia in preschool children

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ABSTRACT

Background: Anxiety and emergence delirium (ED) are common complications of anesthesia in preschool children. Several causes had been attributed to them. Emergence delirium might be related to preoperative anxiety. We aimed to detect the incidence of anxiety and emergence delirium in anesthesia for surgical and non-surgical procedures, also to detect if oral dexmedetomidine as a premedication affects the incidence and severity of them in these procedures.

Methods: The study involved 180 children undergoing anesthesia who were randomly assigned to one of four groups, with each group containing 45 children. The study was clinical, controlled, comparative, and prospective. Groups **A1&A2** had surgical intervention, while groups **B1&B2** had MRI scanning. Groups **A1&B1** were given 20 ml plain apple juice (Placebo) and groups **A2&B2** received oral Dexmedetomidine (4 µg/kg) inserted in 20 ml apple juice 45 minutes prior to anesthesia induction. Anxiety was assessed pre-procedural, emergence delirium and pain at different intervals post-anesthesia.

Results: Incidence of anxiety and emergence delirium showed no difference between surgical and non-surgical procedures. Patients who received oral dexmedetomidine in groups A2 and B2 had significantly lower Parental Separation Anxiety scores than corresponding control groups A1 and B1 ($p = 0.001$). Occurrence of emergence delirium and severe pain were much decreased in groups received dexmedetomidine. PAED and FLACC exhibited significantly reduced scores in groups received dexmedetomidine than groups received Placebo drug ($p < 0.05$) in both surgical and non-surgical procedures. Rescue analgesia was needed more significantly for patients in groups A1 and B1 relative to other groups ($p = 0.002$). The incidence of complications revealed no statistical significance.

Conclusion: Anxiety and emergence delirium were similar in surgical and non-surgical procedures. Premedication of preschool children with oral dexmedetomidine lowered the frequency and intensity of anxiety, emergence delirium and severe pain. Emergence delirium was correlated to pain, especially in surgical procedures.

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1. Introduction

It has been reported that many children who undergo anesthesia and surgery experience fear and anxiety during the preoperative holding area and anesthesia induction. Therefore, children transition to the operating room (OR) can be eased by different methods as sedating them, thereby reducing perioperative discomfort, and improving behavioral outcomes [1].

Emergence delirium (ED) is a condition of non-purposeful restlessness, non-cooperation, and inconsolability occurring after anesthesia. It is defined in pediatric anesthesia as a disruption in the attention or awareness of a child to surroundings with disorientation [2]. This behavior is linked mainly to preoperative anxiety but there are additional causes as age, anesthetic technique, and pain [3]. ED is a diagnosis of exclusion since there are many contributing factors. Children have ED two to three times as frequently as adults do. Recent research revealed ED prevalence from 20% to 80% among pediatric anesthesia cases [4]. It is unknown if surgical and non-surgical anesthesia result in similar incidence of emergence delirium or not.

Recently, α2-adrenoceptor agonist dexmedetomidine drug (DEX) has been utilized in the pediatric population as a sedative and analgesic. Numerous studies have explored the impact of drug as a premedication before different surgeries and procedures [5].

Our study aimed at answering two questions: Does the incidence of anxiety and emergence delirium differ between surgical and non-surgical anesthesia? How oral Dexmedetomidine affects the incidence and

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severity of anxiety and emergence delirium in surgical and non-surgical procedures?

2. Patients and methods

The clinical study was carried out at Ain Shams University Hospitals starting from January 2022. It was double-blind (neither researchers nor participants knew which drug was given to them as a premedication, it was organized by the researcher who is collecting the data), randomized, controlled, and prospective. It received approval from the research ethics committee at the faculty of medicine, Ain Shams University, Cairo, Egypt (FMASU MD 207/2021) and registered with Pan African Clinical Trial Registry, identifier: PACTRPACTR202208892145772. Prior to the study, patients' legal guardians were provided with written informed consent.

2.1. Sample size calculation

We utilized the G power software to determine the sample size, adjusting power at 80%, α-error at 0.05 and effect size difference between study groups at 0.25 (f) (medium effect size) regarding anxiety and delirium scales, sample size of **(45)** children per group needed based on studies (Keles S. & Kocaturk O., 2017) [5] and (Isik et al., 2006) [6] with total 180 children in all groups.

One hundred and eighty patients of both males and females, ranging from 2 to 6 years old, ASA (American society of Anesthesiologists) status I and II were planned for tonsillectomy operation with or without adenectomy or undergoing MRI imaging under general anesthesia. Procedures are expected to be less than 60 minutes in duration. Using 2×2 experimental design, the closed envelope technique was used to assign patients to one of four equal groups, with each group consisting of 45 patients. A computer program was employed for randomization procedure, and the following names were given to the groups:

- **Group A1**: 45 patients were given plain apple juice (20 ml) 45 minutes prior to anesthesia induction in tonsillectomy with or without adenectomy surgeries.
- **Group A2**: 45 patients received 4 µg/kg of Dexmedetomidine (Precedex^{R}) as an oral route in apple juice (20 ml) 45 minutes prior to anesthesia induction in tonsillectomy with or without adenectomy surgeries.
- **Group B1**: 45 patients were given plain apple juice (20 ml) 45 minutes prior to anesthesia induction in MRI imaging procedures.
- **Group B2**: 45 patients received 4 µg/kg of Dexmedetomidine (Precedex^{R}) as an oral route in apple juice (20 ml) 45 minutes before induction of anesthesia in MRI imaging procedures.

2.2. Exclusion criteria

- Parent's refusal.
- Behavioral, mental, or developmental abnormality.
- Patients with coagulation disorders.
- Patients with respiratory problems.
- Hypersensitivity to any of the medications utilized in study.

2.3. Outcomes

Primary: To evaluate the incidence of anxiety and emergence delirium among anesthesia for surgical and non-surgical procedures. Would oral Dexmedetomidine reduce their occurrence?

Secondary: Effect of oral Dexmedetomidine on severity of emergence delirium and pain.

3. Study tools

3.1. Pre-operative settings

- A history, clinical examination, and investigations tailored to the patient's condition were performed for each patient. Age, sex, and weight were recorded.
- Preoperative anxiety was measured using Parental Separation Anxiety Score (PSAS) [7] 45 minutes after receiving apple juice, either mixed with dexmedetomidine or plain juice. Patients were given the juice 45 minutes before starting anesthesia.

Parental Separation Anxiety Score (PSAS) consists of 4 points scale as follows:
1 = easy separation
2 = whimpers but can be reassured easily
3 = cries and cannot be reassured easily, but not attached to parents
4 = cries and attached to parents

A score 1 or 2 indicates satisfactory separation, while a score 3 or 4 indicates unsatisfactory separation.

3.2. Anesthesia technique

All patients were required to fast for a minimum of 6 hours for solids and fluids prior to anesthesia. Standard monitors were used to patients from arrival to operating theater until recovery from anesthesia by; non-invasive automated blood pressure measurement (N I B P), electrocardiogram (ECG), capnography, and pulse oximetry (SpO2).

Anesthesia was induced in all patients with inhalational agent (6% Sevoflurane) using Ayres' T-piece with fresh Oxygen gas 6 L/min.

During deep anesthesia, which can be detected by centralized and constrictive pupils and slowed breathing patterns, intravenous access was applied.

Before endotracheal tube insertion, all patients received intravenous Atracurium (0.5 mg/kg). Anesthesia was maintained by Sevoflurane 2% in an oxygen-air mixture 2:1 and Atracurium 0.1 mg/kg (if needed).

A pressure-controlled ventilation mode was adjusted to maintain 6 ml/kg tidal volume, 35-40 mmHg ETCO2 and 4-5cmH2O PEEP. Intraoperative analgesia was administered by intravenous Fentanyl (1mcg/kg) and Paracetamol (15 mg/kg) to surgical groups. However, non-surgical groups needed no additional analgesia.

Following the procedure, Sevoflurane was stopped. Atracurium residuals were reversed with 0.05 mg/kg IV Neostigmine and 0.02 mg/kg IV atropine. Endotracheal tube was removed immediately after hemodynamic stability verification using standard extubation criteria, including eye opening, purposeful movements, and facial grimacing.

Patients were transferred to the PACU for monitoring until they were fit for discharge. In case of oxygen desaturation, a face mask with a flow rate of 6 L/min was utilized to administer oxygen supplementation to the patient.

3.3. Postoperative settings

Each group were observed for incidence and severity of ED by PAED score, and pain by FLACC score every 5 minutes for 30 minutes.

Pediatric Anesthesia Emergence Delirium (PAED) score: [8]

It is a tool utilized to evaluate patients based on five psychometric criteria as shown in Table 1.

The total score is out of 20, severity of ED increases proportionally with the total score, where a score of 10 or above indicates the presence of ED.

Face, Legs, Activity, Cry, and Consolability (FLACC) score: [9]

It includes five behavioral categories: facial expression, bodily activity, leg movement, cry or verbalization, and consolability. The pain is rated in each category at a scale of 0 to 2, thus the total pain score is calculated by adding the scores for all categories, which ranges from 0 to 10. Each score represents a finding as:

0= Relaxed and comfortable, 1–3= Mild discomfort, 4–6= Moderate pain, 7–10= Severe discomfort/pain

Children with Emergence delirium **(PAED score ≥ 10)** or **(FLACC scale ≥ 7)** received increments of intravenous fentanyl 1 µg/kg. Children with ED had been carefully nursed not to harm themselves. Any complications were recorded as vomiting, bradycardia, or hypotension.

The criteria for discharging children from the PACU included being fully conscious, having stable vital signs, ability to protect their airway, having normal oxygen saturation and regular respiratory rate.

4. Statistical analysis

The Statistical Package for Social Science (SPSS) version 26.0 was utilized to analyze the data. Quantitative data were reported as mean± standard deviation (SD) or Median (IQR) based on the information provided. Qualitative data, on the other hand, were presented in terms of percentage and frequency.

The following tests were utilized:

- Chi-square (X2) test was employed to determine the significance of the difference in proportions between two qualitative parameters.
- One-way analysis of variance (ANOVA) measured the differences between the means of various subgroups within a variable (multiple testing), Post-hoc test is carried out to determine significant differences between subgroups when the ANOVA test is positive.
- The Kruskal–Wallis test is done to compare different subgroups in non-parametric data. Pairwise comparison is done when the test is positive.
- Correlation analysis investigates the relationship between two variables using the Spearman correlation coefficient r. which ranges from −1 to 1. This coefficient indicates the extent to which two variables tend to change in a corresponding manner. Positive correlation indicates a change in

Table 1. PAED score.

		Scoring				
Point	Description of items	Not at all	Just a little	Quite a bit	Very much	Extremely
1	The child makes eye contact with the caregiver	4	3	2	1	0
2	The child's actions are purposeful	4	3	2	1	0
3	The child is aware of his/her surroundings	4	3	2	1	0
4	The child is restless	0	1	2	3	4
5	The child is inconsolable	0	1	2	3	4

variables in same direction, result will approach 1, while negative correlation indicates a change in different directions, result will approach −1.

- A 95% confidence interval was established with a 5% margin of error. P-value <0.05 was considered significant.

5. Results

One hundred eighty (180) children were enrolled in the study, 45 in each group. Seven patients were eliminated from all groups due to long anesthesia time (>1 hour) and were replaced by other patients. They were comparable for their demographic data (Table 2) regarding age (in years), weight (in kilograms Kg) and Sex (male or female).

The main findings of the study revealed that the incidence of anxiety detected by (PSAS score) before anesthesia did not differ statistically between surgical (53.3% in group A1) and non-surgical procedures (48.9% in group B1) (Table 3). There is no statistical significance difference in the incidence of ED measured by (PAED score) after anesthesia between surgical (46.7% in group A1) and non-surgical procedures (42.2% in group B1) (Table 3).

Patients who received oral dexmedetomidine in groups A2 and B2 had significantly lower Parental Separation Anxiety scores than control groups (A1 and B1) ($p = 0.001$) (Table 4). Satisfactory separation from parents' percentage was significantly higher in group A2 and B2 compared to group A1 and B1 respectively ($p = 0.002$) (Table 3).

The incidence of ED was significantly higher in group A1 and B1 (46.7% and 42.2%) compared to A2 and B2 (20% and 15.6%) respectively ($p = 0.002$). (Table 3).

There was statistically significant difference among groups throughout the times ($p < 0.001$) regarding PAED scores. Pairwise comparison was used to localize the site of differences. Group A2 exhibited a significantly decreased PAED score than A1 at all time intervals postoperatively ($p < 0.05$). Likewise, PAED score was significantly lowered in group B2 than B1 at same time intervals ($p < 0.05$). No significant difference was observed in score between groups B2 and A2 postoperatively. Throughout all the post-procedure times, group B1 demonstrated a significantly lowered PAED score than group A1 ($p < 0.05$) (Figure 1).

Figure 2 presents FLACC score for all groups at different time intervals. Severe pain post procedure was assessed after recovery of anesthesia by FLACC score (score ≥7). The incidence was significantly higher in groups A1 (37.8%) and B1 (26.7%) compared to A2 (17.8%) and B2 (13.3%) respectively ($p < 0.05$). Group B2 had the lowest incidence of severe pain in all groups (Figure 2). Using pairwise comparisons, FLACC score was significantly lower in group A2 compared to group A1 during the first

Table 2. Comparison between groups regarding demographic data.

		A1 (N = 45)	A2 (N = 45)	B1 (N = 45)	B2 (N = 45)	F/x2	p-value
Age (years)		3.49 ± 1.2	3.58 ± 1.2	3.98 ± 1.4	3.82 ± 1.3	1.4^{f}	0.24
Weight (Kg)		15.62 ± 2.9	15.93 ± 2.8	15.38 ± 3.0	15.80 ± 3.2	0.29^{f}	0.83
Sex	Male	26 (57.8%)	25 (55.6%)	24 (53.3%)	24 (53.3%)	0.2^{x2}	0.97
	Female	19 (42.2%)	20 (44.4%)	21 (46.74%)	21 (46.74%)		

Data presented as mean ± SD, proportion and percentage, f= one way ANOVA, X2=chi-Square test.

Table 3. Comparison between groups regarding parental separation satisfaction, incidence of emergence delirium and incidence of severe pain.

		A1 (N = 45)	A2 (N = 45)	B1 (N = 45)	B2 (N = 45)	X2	P value
Satisfactory separation by (PSAS) score	Count	21_a	33_b	23_a	34_b	14.5	**0.002**
	% within group	46.7%	73.3%	51.1%	75.6%		
Unsatisfactory separation by (PSAS) score	Count	24_a	12_b	22_a	11_b		
	% within group	53.3%	26.7%	48.9%	24.4%		
Incidence of emergence delirium	Count	21_a	9_b	19_a	7_b	15.3	**0.002**
	% within group	46.7%	20.0%	42.2%	15.6%		
Incidence of severe pain	Count	17_a	8_b	$12_{a,\ b}$	6_b	8.6	**0.03**
	% within group	37.8%	17.8%	26.7%	13.3%		

Data expressed as proportion and percentage, X2=chi-Square test, each subscript letter signifies a subset of group categories with column proportions that do not show a significant difference from one another at the .05 level.

Table 4. Comparison between groups as regards PSAS score.

	A1 (N = 45)			A2 (N = 45)			B1 (N = 45)			B2 (N = 45)			z	p-value
	Range	Median	IQR	Range	Median	IQR	Range	Median	IQR	Range	Median	IQR		
PSAS	1–4	3	2–4	1–4	2	1.75–3	1–4	2	2–4	1–4	2	1.75–2.25	17.2	**0.001**

Data expressed as range, median and IQR, z= Kruskal–Wallis Test.

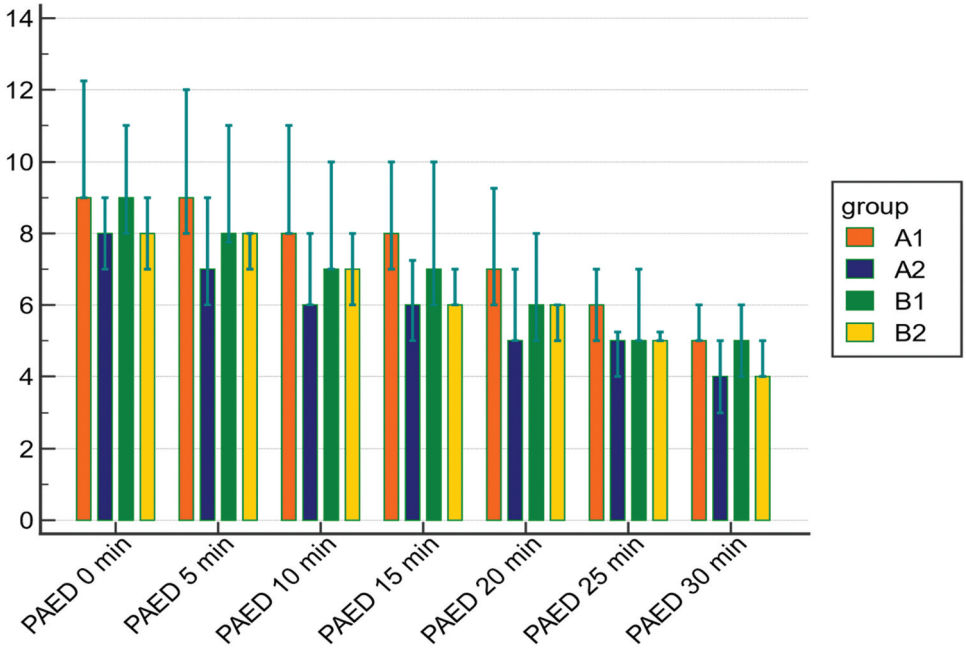

Figure 1. Bar comparison graph between four groups as regard PAED score, median and IQR were used for data expression.

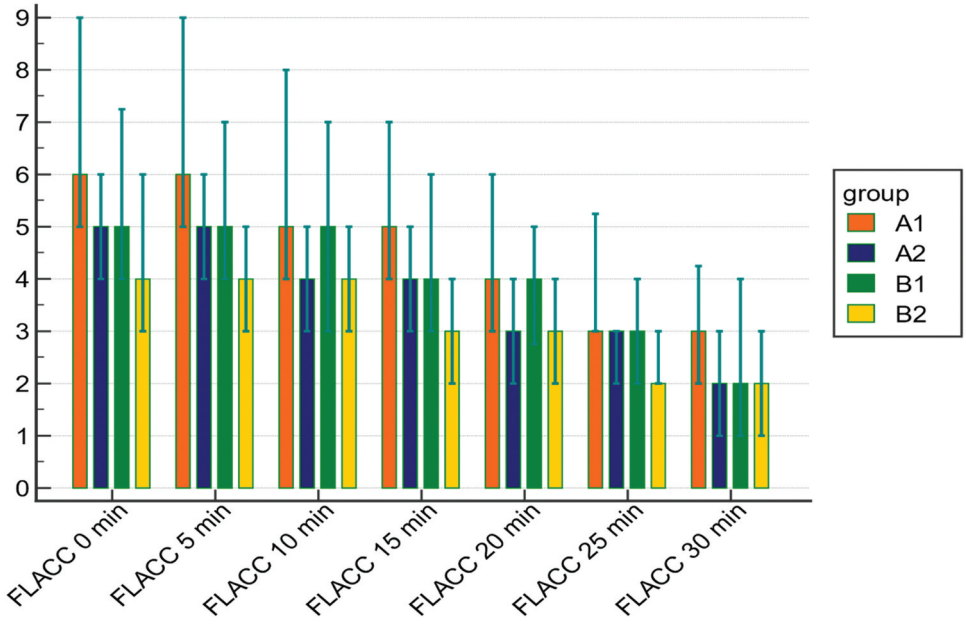

Figure 2. Bar comparison graph between four groups as regard FLACC score, median and IQR were used for data expression.

30 minutes post procedure ($p < 0.05$). Likewise, group B2 exhibited a significantly decreased FLACC score than group B1 and A2 during the same period ($p < 0.05$).

The groups A1 & B1 didn't differ significantly in FLACC score at time intervals of (0 and 5 min), but it was higher in group A1 than B1 at 10,15,20,25 and 30 min ($p < 0.05$).

Spearman rank correlation coefficient (r value) detected correlation between emergence delirium and severity of pain postprocedural. In group A1, there was moderate to strong correlation between PAED and FLACC as r value was (0.859, 0.793, 0.764, 0.784, 0.733, 0.690, 0.564) at time intervals 0,5,10,15,20,25 and 30 min respectively. In group A2, there was moderate correlation between PAED and FLACC as r value (0.722, 0.602, 0.688, 0.589, 0.618, 0.449, 0.527) at time intervals 0,5,10,15,20,25 and 30 min respectively. Correlation for group A1 was stronger than group A2 as shown by corresponding r value.

Rescue analgesia was needed more significantly for patients in groups A1 and B1 than other groups ($p = 0.002$) (Table 5).

In all groups, the incidence of complications showed no statistical significance (Table 5).

Table 5. Comparison between groups regarding the need of rescue analgesia and anesthesia complications (vomiting, bradycardia, and hypotension).

		A1 (*N* = 45)	A2 (*N* = 45)	B1 (*N* = 45)	B2 (*N* = 45)	X2	P-value
Rescue analgesia	Count	21_a	9_b	18_a	7_b	14.5	**0.002**
	% within group	46.7%	20.0%	40.0%	15.6%		
Vomiting	Count	5_a	5_a	4_a	3_a	0.7	0.87
	% within group	11.1%	11.1%	8.9%	6.7%		
Bradycardia	Count	3_a	7_a	2_a	6_a	4.1	0.24
	% within group	6.7%	15.6%	4.4%	13.3%		
Hypotension	Count	2_a	2_a	1_a	3_a	1.04	0.79
	% within group	4.4%	4.4%	2.2%	6.7%		

Data expressed as proportion and percentage, X2=chi-Square test, each subscript letter signifies a subset of group categories with column proportions that do not show a significant difference from one another at the .05 level.

6. Discussion

The current study revealed that the incidence of anxiety and emergence delirium (ED) did not differ between surgical and non-surgical procedures. This would eliminate the significance of pain as a risk factor for ED when controlling it by narcotics. Our study showed that dexmedetomidine reduced anxiety, emergence delirium and pain scores in both surgical and nonsurgical anesthesia in preschool children. Emergence delirium was at least moderately correlated to severe pain (when present) in the surgical groups. Nonsurgical anesthesia for MRI was followed by significant pain scores during the first 30 minutes of recovery and was reduced by dexmedetomidine premedication.

Parental separation and mask induction in children lead to increased anxiety levels, which increases the probability of postoperative delirium, pain, negative behavior, and increased need for analgesics [10]. Administering sedatives or premedication to pediatric patients before entering the operating room or procedural vicinity can minimize anxiety, enable painless anesthesia induction, and improve recovery [11].

We used oral Dexmedetomidine as a convenient and painless option for children, it has bioavailability of 16% compared to 82% in buccal mucosa [12]. However, it might be challenging for children to hold fluid in their mouths for a few minutes. The dose of 3–4 µg/kg of oral dexmedetomidine in children undergoing surgical operations was first suggested by Zub et al. [13] They proposed that dexmedetomidine intravenously prepared may be taken orally with tolerable taste. We used a dose of 4 µg/kg in apple juice as it is nonparticulate with accepted flavor.

Our objective was to find out if there is a difference in incidence of preoperative anxiety and post-procedure emergence delirium in surgical and non-surgical procedures and how dexmedetomidine would affect it.

Dexmedetomidine, Midazolam and Clonidine were given orally as a premedication to reduce anxiety in pediatrics before elective surgery [14]. Lang and his colleagues in their meta-analysis on 34 studies involving 2281 children showed more satisfactory parent's separation and less incidence of ED [15]. In contrast, Bong et al. found no considerable advantage in MRI studies for dexmedetomidine or propofol as a prophylactic treatment, indicating no significant decrease in ED incidence [16].

Our findings showed that anxiety occurs in preschool children at parental separation and mask induction, also ED after anesthesia did not differ between surgical and nonsurgical procedures. On the other hand, dexmedetomidine premedication reduced ED occurrence in drug-prescribed groups than other groups. Taking into consideration the intraoperative narcotic analgesia and controlling other causes of ED that would affect patients in both surgical and non-surgical groups.

Recovery from anesthesia frequently involves pain which raises catecholamine levels, α2-adrenoceptor agonists as Dexmedetomidine may be adventurous due to their analgesic and sympatholytic actions without respiratory depression [17].

The analgesic effect of Dexmedetomidine reduced pain incidence in both Dexmedetomidine groups compared to placebo groups. The pain score showed a difference between placebo groups from **10 minutes** after recovery till discharge from PACU, probably secondary to wearing off fentanyl effect.

When there was pain, it was positively correlated to emergence delirium. This correlation was stronger as pain increases. Somaini and his colleagues found that pain and ED could occur separately and in conjunction with differentiation between them was challenging [18]. In our study pain scores especially during the first 10 minutes of recovery from anesthesia for MRI were high and mostly related to cases who had ED.

Rescue dose of narcotics was needed more in groups who did not receive Dexmedetomidine. Any child who experienced ED was given Fentanyl whether having pain or not as it was used for management of ED [19].

Akin and his colleagues found that the number of children receiving Dexmedetomidine required less

postoperative analgesia compared to Midazolam in adenotonsillectomy patients [20]. Olutoye and colleagues found that a single intraoperative dose of Dexmedetomidine 0.5 µg/kg provided similar postoperative analgesic effects as morphine 50 µg/kg. This suggests that Dexmedetomidine, can be effective in reducing pain after surgery [21].

Finally, complications which were detected in our study occurred in a few cases and managed immediately. Bradycardia was the most one as it occurred in seven children in Group A2 and with six children in group B2 and responded to atropine.

Doing the study only on two types of procedures might be considered as a limiting factor.

7. Conclusion

The current study concluded that the incidence of anxiety and emergence delirium (ED) did not differ between surgical and non-surgical procedures. Premedication with oral dexmedetomidine lowered the severity and frequency of anxiety, emergence delirium and severe pain in preschool children. Emergence delirium was correlated to pain, especially in surgical procedures. When controlling precipitating for this issue, surgical and non-surgical groups did not reveal significant differences.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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