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Dexmedetomidine versus Ketamine for the Prevention of Emergence Agitation in Pediatric: A Prospective, Randomized, and Controlled Clinical Trial

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Abstract

Background: This study compares the effect of dexmedetomidine versus Ketamine for the prevention of emergence agitation in children undergoing general anaesthesia. **Method:** 75 Children are randomly allocated into three groups. Group C: Were assigned to receive normal saline. Group K: Were assigned to receive Ketamine 0.25 mg/kg. Group D: assigned to receive 0.25 ug /kg of dexmedetomidine, before the end of surgery. **Results:** There was no statistically significant difference in demographic data and intraoperative parameters between the three groups. But as regards to time to discharge, there was a significant difference between group C, group K and group D (group C = 39.96 ± 2.84, group K = 37.28 ± 3.80, group D = 35.08 ± 3.36 and P value = 0.0002). FLACC scale was low after extubation, before leaving the operating room and on arrival to PACU (small FLACC scale in group K, D than group C). PAED scoreless in Group K and Group D than Group C (postoperative, at 10 minutes, 20 min, 30 min). **Conclusion:** Ketamine and dexmedetomidine reduced the incidence and severity of emergence delirium effectively when compared to normal saline, and the effects of dexmedetomidine being much superior to Ketamine.

Keywords

Emergence Agitation, Ketamine, Dexmedetomidine

1. Introduction

Emergence agitation in children is a common problem in pediatric patients which includes manifestations such as crying, excitation, agitation, delirium, and

behavioural disturbances during early emergence from general anaesthesia and continues through the initial recovery period [1].

The true incidence of emergence agitation is unclear. Still, it can occur in as many as 30 to 50 percents of children who have general anaesthesia, and it is essential to diagnose emergence agitation, pain must control entirely [2].

Sevoflurane commonly used as an inhalational anaesthetic for pediatric patients. Sevoflurane induction can be achieved quickly and safely by inhalation using a mask, sevoflurane does not cause substantial hemodynamic changes, and return to the preoperative level of consciousness following anesthesia is rapid. However, sevoflurane can result in emergence agitation. The incidence of emergence agitation after sevoflurane anaesthesia estimated at 80%. Emergence agitation occurs most frequently in preschool children during the early stage of emergence from anaesthesia [3] [4].

This emergence of agitation must manage by providing smooth emergence to pediatric patients. Under other circumstances, uncooperative, an irritable, inconsolable, and crying child with excessive motor activity may cause many complications for the parents, nursing and maybe children also harm themselves [5].

Although EA is commonly self-limited and happens within the first 30 min of stay in a postanesthesia care unit (PACU) and also can lead to disconnection of monitoring devices or intravenous catheters, physical damage, falling, increase in the risk of bleeding, and self-extubation [6] [7].

There are many factors to decrease the incidence of emergence agitation, such as Parental presence at emergence, physical restraints, or pharmacologic interventions [8]. But pharmacologic interventions remain to be the better method. Different studies proved that medications such as ketamine propofol, fentanyl, ketofol, dexmedetomidine, clonidine, and midazolam had used to reduce the incidence of emergence agitation [9] [10].

This study compares the effect of dexmedetomidine versus Ketamine for the prevention of emergence agitation in children undergoing general anaesthesia.

2. Patients and Method

After approval of the institutional ethics committee and written informed consent by the parents of children, children aged ranged between 6 and 10 years belonging to ASA grade I and II scheduled for elective tonsillectomy, adenoidectomy or both. These patients randomly allocated for this prospective, randomized, controlled, study which conducted in Benha university hospitals from August 2019 to March 2020.

Exclusion criteria included children with developmental problems, inborn errors of metabolism, cerebral palsy, down syndrome, a history of epileptic fits, body weight less than 10 kg or greater than 30 kg (children below the age of 6 years with body weight more than 30 kg are obese with a risk of airway obstruction); patients with previous history of agitation after sevoflurane anesthesia and patients with respiratory distress of any cause; also, children with known allergy to any of the

medications used. Patients are randomly assigned via computer-generated random to three groups.

- Group C: Were assigned to receive normal saline (as a placebo) in a single syringe, the total volume made up to 10 ml. was given 10 min before the end of surgery.
- Group K: Were assigned to receive Ketamine 0.25 mg/kg in a single syringe, the total volume made up to 10 ml. was given 10 min before the end of surgery.
- Group D: Were assigned to receive 0.25 ug /kg of dexmedetomidine, the total volume made up to 10 ml to ensure blinding, was given 10 min before the end of surgery.

All the children must fast 6 h for solid & 3 h for clear fluid. All the children were premedicated with oral midazolam 0.25 mg/kg 25 min before surgery. General anaesthesia induction was done by the gradual rise of sevoflurane concentration to reach a maximum of 6 Vol. % in 100% oxygen (6 L/min) through a facemask. After the loss of eyelash reflex, started to insert of an intravenous (IV) catheter and the airway was secured with an oral end tracheal tube after an adequate depth of anaesthesia reached with fentanyl 1 μg/kg and cisatracurium 0.1 mg/kg. Oxygen saturation (SpO_2), electrocardiogram, heart rate (HR), mean arterial pressure, end-tidal CO_2 concentration ($EtCO_2$), and end-tidal sevoflurane concentration were monitored continuously. Sevoflurane concentration maintained at 2 - 4 Vol, All the patients, were ventilated to keep an end-tidal CO_2 of 30 - 35 mmHg. Data collection and monitoring were done by another a junior resident who was unknowing of the study drugs and allocation. Then at the end of the surgery, sevoflurane was discontinued, the reversal of neuromuscular block done by neostigmine bromide 20 μg/kg plus atropine sulfate 20 μg/kg, and when the patients met the criteria of extubation, the end tracheal tube was removed in lateral decubitus. The interval time from the end of surgery to tracheal extubation defined as the time of extubation and the time of first response to command or eye-opening on command after extubation defined as emergence time that also recorded. The duration of surgery defined as the time between the insertion and removal of the mouth gag and also recorded it and the time from sevoflurane mask induction until the extubation time recorded as the duration of anaesthesia. After extubation, children were shifted to the post-anaesthetic care unit (PACU) and monitored for the following parameters until they moved to the ward.

- Hemodynamic parameters: Heart rate (HR), Noninvasive blood pressure (NIBP), and Oxygen saturation (SpO_2), at the same six-time points (after extubation, then on leaving the OR, on arrival to PACU, at 10, 20, and also at 30 min after arrival in PACU).

Pain assessment was done by using Face, Legs, Activity, Cry, and Consolability (FLACC) scale at the same six-time points (after extubation, then on leaving the OR, and also on arrival to PACU, at 10, 20, and even at 30 min after arrival

in PACU). Nalbuphine as a rescue analgesic at a dose of 0.1 mg/kg is given if FLACC scores ≥ 5 (Table 1) [11].

The severity of emergence delirium evaluated using the pediatric anaesthesia emergence delirium scale (PAED) (Table 2) with scores ranging from 0 to 20. PAED scale was monitored immediately after emergence and at 10 min intervals after that until discharge from PACU (Table 2) [12] [13].

Patients transferred to the ward after being fully conscious with stable vital signs, calm, PAED score < 10. FLACC score < 5 and the absence of bleeding, pain, nausea or vomiting.

Statistical Analysis

Analysis of data is done by using SPSS Version 16. Quantitative data were presented as mean ± Standard deviation and analyzed by using the one way ANOVA test. Qualitative data were presented as numbers and percentages and analyzed by using the Chi-square test and Fisher exact test. We used repeated measure ANOVA test yo analyzed the Quantitative data of repeated measures in the same group, and the significant rules detected by post-hoc analysis. P-Value < 0.05 was considered statistically significant, and P-Value < 0.01 was considered statistically highly significant.

The sample size was determined to assume that the likelihood of sevoflurane

Table 1. FLACC score.

Category	Score		
	0	1	2
Face	No particular expression or smile	Occasional grimace	Frequent to constant frown
Legs	Normal Position	Uneasy, restless	Kicking or leg drawn up
Activity	Lying quietly moves quickly.	Squirming, shifting Back	Arched rigid
Cry	No crying	Moans or whimpers	Crying steadily Screams
Consolability	Content, relaxed	Reassured by occasional touching, hugging	Difficult to console

Each scale was added and expressed as total points. [11]

Table 2. PAED score Pediatric Anesthesia Emergence Delirium (PAED) scales.

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

One-calm, two-not calm but could be easily consoled, three-moderately agitated or restless and not quickly quiet, four-combative, excited and thrashing around. PAED: Pediatric emergency delirium scale [12].

agitation was 30% or more. We needed to find a significant difference ($P < 0.05$) ($\alpha = 0.05$, one-tailed) with a power of 90% (error = 0.1) to detect a difference of 25%. Twenty-one patients per group would have been sufficient. Still, we expected some exclusions from the protocol (which did not happen) and increased this number to 25 (which allowed finding the same significant difference with a power of 90%).

3. Result

The total number of patients registered during the study period was 75 in three groups 25 in each group**.** All the patients who enrolled in the study completed the study. The three groups were comparable for demographic characters as represented in Table 3, and as regards to the duration of surgery, duration of anaesthesia, emergence of time and time of discharge in Table 4. Heart rate between the three groups is shown in Table 5 and mean arterial pressure (Table 6). Oxygen saturation between the three groups is presented in Table 7 and FLACC scale is presented in Table 8. PAED score was showed in Table 9.

There were no significant differences between the three groups as regard age, weight, sex (male or female), ASA grade (I or II) and type of surgery (Table 3).

There were no significant differences between the three groups as regards to

Table 3. Demographic data in groups (mean ± SD).

		Group C N = 25	Group K N = 25	Group D N = 25	*p*-value
Age (yrs.)		5.64 ± 1.46	5.58 ± 1.91	6 ± 2.10	0.37
Weight (kg)		19.94 ± 4.24	19.85 ± 5.36	19.89 ± 6.04	0.99
Sex	M	17 (68%)	15 (60%)	18 (72%)	0.65
	F	8 (32%)	10 (40%)	7 (28%)	
ASA	I	20 (80%)	18 (72%)	19 (76%)	0.80
	II	5 (20%)	7 (28%)	6 (24%)	
Type of surgery	Tonsillectomy	10 (40%)	11 (44%)	9 (36%)	
	Adenoid	5 (20%)	5 (20%)	6 (24%)	0.98
	adenotonsillectomy	10 (40%)	9 (36%)	10 (40%)	

Data presented as mean ± SD. Gender presented as numbers.

Table 4. Intraoperative parameters (mean ± SD)

	Group C N = 25	Group K N = 25	Group D N = 25	*p*-value
Duration of anaesthesia	28.12 ± 4.26	28.64 ± 3.59	28.84 ± 3.32	0.78
Duration of surgery	19.64 ± 3.03	19.12 ± 3.35	19.16 ± 2.96	0.80
Emergence of time	12.8 ± 1.65	12.4 ± 1.25	12.04 ± 0.88	0.12
Time to discharge	39.96 ± 2.84	37.28 ± 3.80	35.08 ± 3.36	0.0002*

Values are expressed when Mean ± SD or Number (%). *P < 0.05, statistically significant. C: control, K: ketamine, D: Dexmedetomidine.

Table 5. Show heart rate between the three groups (mean ± SD).

HR (beat/min.)	Group C N = 25	Group K N = 25	GROUP D N = 25	*p*-value
After extubation	113.24 ± 4.85	117.36 ± 6.54	113.16 ± 9.09	0.06
Before leaving OR	98.28 ± 4.86	103.52 ± 4.43	98.92 ± 5.52	0.005*
On arrival to PACU	96.88 ± 5.67	100.4 ± 6.57	95.96 ± 6.47	0.03*
10 min. postoperative	93.8 ± 3.89	93.24 ± 4.21	93.84 ± 4.59	0.8
20 min. postoperative	93.16 ± 3.7	93.48 ± 4.80	93.04 ± 4.07	0.9
30 min. postoperative	92.12 ± 3.05	92.56 ± 3.67	92.64 ± 4.57	0.8

Values are expressed when Mean ± SD or Number (%) *P < 0.05, statistically significant. C: control, K: ketamine, D: Dexmedetomidine. Bpm: Beats per minute.

Table 6. Show Mean Arterial Pressure between the three groups. (mean ± SD).

MAP (mmHg)	Group C	Group K	GROUP D	*p*-value
After extubation	55.2 ± 4.44	55.04 ± 5.99	52.88 ± 11.88	0.52
Before leaving OR	54.84 ± 4.25	54.64 ± 3.8	54.4 ± 4.07	0.93
On arrival to PACU	53.08 ± 4.29	53.04 ± 5.37	52.68 ± 4.72	0.95
10 min.	52.44 ± 3.79	52.2 ± 4.24	54.12 ± 3.29	0.95
20 min.	50.48 ± 3.38	49.36 ± 4.05	49.48 ± 4.36	0.54
30 min.	46.76 ± 3.39	46.12 ± 3.96	46.08 ± 3.88	0.77

Values are expressed when Mean ± SD or Number (%). *P < 0.05, statistically significant. C: control, K: ketamine, D: Dexmedetomidine.

Table 7. Show oxygen saturation between the three groups. (mean ± SD)

SPO_2 (%)	Group C	Group K	GROUP D	*p*-value
After extubation	99.6 ± 0.57	99.68 ± 0.55	99.48 ± 0.87	0.58
Before leaving OR	99.72 ± 0.59	99.72 ± 0.67	99.44 ± 0.82	0.25
On arrival to PACU	99.64 ± 0.56	99.4 ± 0.86	99.16 ± 1.02	0.13
10 min.	99.64 ± 0.63	99.48 ± 0.96	99.72 ± 0,67	0.53
20 min.	99.6 ± 0.76	99.72 ± 0.73	99.4 ± 0.76	0.31
30 min.	99.52 ± 0.82	99.8 ± 0.5	99.28 ± 0.97	0.07

Values are expressed when Mean ± SD or Number (%) *P < 0.05, statistically significant. C: control, K: ketamine, D: Dexmedetomidine.

Table 8. FLACC scale between three groups. (mean ± SD)

FLACC scale	Group C	Group K	GROUP D	*p*-value
After extubation	7.04 ± 1.76	5.76 ± 1.76	5.76 ± 1.45	0.009*
Before leaving OR	6.44 ± 1.44	4.84 ± 1.37	4.6 ± 1.15	0.006*
On arrival to PACU	6.04 ± 1.17	4.04 ± 0.84	3.96 ± 1.17	0.003*
10 min.	3.68 ± 0.85	3.2 ± 1.58	3.24 ± 0.87	0.26
20 min.	2.64 ± 1.03	2.44 ± 1.35	2.52 ± 0.82	0.81
30 min.	1.8 ± 1.32	1.8 ± 0.95	1.88 ± 1.01	0.95

Values are expressed when Mean ± SD or Number (%) *P < 0.05, statistically significant. C: control, K: ketamine, D: Dexmedetomidine.

Table 9. PAED score between three groups. (mean ± SD).

PAED score	Group C	Group K	GROUP D	*p*-value
On arrival to PACU	13.4 ± 1.82	13.68 ± 1.86	13.16 ± 2.11	0.63
10 min.	11.96 ± 1.67	10.08 ± 1.46	9.32 ± 1.10	o.003*
20 min.	8.32 ± 1.14	5.48 ± .0.09	5.08 ± 1.03	0.001*
30 min.	4.64 ± 1.07	2.04 ± 0.97	1.2 ± 0.918	0.001*

Values are expressed when Mean ± SD or Number (%) *P < 0.05, statistically significant. C: control, K: ketamine, D: Dexmedetomidine.

the duration of surgery, duration of anaesthesia and emergence of time (Table 4). But as regards to time to discharge significant between-group C and group K and group D. Time of discharge in group K and group D were significantly less than group C, and time of discharge was lower in group D than group K (Table 4).

Also there were no significant differences between the three groups as regards to Heart rate after extubation, postoperative at 10, 20, 30 minutes but before leaving OR (OPERATING ROOM) and on arrival to PACU, there is rise of heart rate in the group K (Table 5).

There were no significant differences between the three groups as regards to mean arterial pressure between the three groups (Table 6). Also there were no significant differences between the three groups as regard to oxygen saturation between the three groups (Table 7).

There were significant differences between the three groups as regards to FLACC scale after extubation, before leaving the operating room (OR) and on arrival to PACU (low FLACC scale in group K, D than group C). But postoperative at 10, 20, 30 minutes, there were no significant differences between the three groups (Table 8). Also there were significant differences between the three groups as regards to PAED score, on arrival to PACU but postoperative, at 10 minutes, 20 min, 30 min, there are significant differences between, Group C with Group K and GROUP D. PAED score was small in Group K and GROUP D than Group C. Also PAED score in Group D smaller than Group K (Table 9).

4. Discussion

Emergence agitation defined as the number of children with disturbance of postoperative behaviour during emergence from sevoflurane anesthesia that measured by agitation scores mentioned in our study. Predisposing factors for emergence agitation include rapid emergence, pre-operative pain and anxiety, an intrinsic characteristic of the anaesthetic, preschool children, baseline mood of the child, and the type of surgery. Emergence agitation is the most common irritant complication during the time of extubation and in early recovery period [14].

Our study demonstrates that Ketamine and dexmedetomidine reduced the incidence and severity of emergence delirium effectively when compared to nor-

mal saline, (as placebo) and the effects of dexmedetomidine being much superior to Ketamine.

Patel *et al.* compared the effect of dexmedetomidine infusion versus IV fentanyl. This study concluded that infusion of dexmedetomidine leading to significantly reduced for requirements of the postoperative opioid and also decrease of incidence of emergence agitation in children undergoing tonsillectomies and adenoidectomies [15].

Also in the study of Jain *et al.* have shown that dexmedetomidine reduced the rate of emergence agitation ranging between 4.8% and 17% with no hemodynamic effects after IV administration in doses between 0.3 and 1 ug/kg after induction of anesthesia [16]. It proved that $\alpha 2$ agonists decrease emergence agitation by their analgesic effect as well as by reducing the anaesthetic requirements [17].

In another study conducted by Tawfik M, *et al.*, showed that double-blind, randomized study on 90 children between 4 and 8 years of age and of American Society of Anesthesiologists I undergoing adenotonsillectomy under sevoflurane-based anaesthesia enrolled in the study. Children randomly allocated to one of the two equal groups: group (N) received nalbuphine 0.1 mg/kg, and group (M) received midazolam 0.03 mg/kg. The study drugs were administered 5 min before the end of surgery. In the postanesthesia care unit, the incidence of EA assessed with Aonos four-point scale. The severity of EA was assessed with the pediatric anaesthesia emergence delirium scale upon admission (T0), after 5 min (T5), 10 min (T10), 15 min (T15), and 30 min (T30. The incidence and severity of EA were lower in the group (N) as compared with a group (M) at T0, T5, and T10 16 [18].

And also study done by. Nan Zhao *et al.* showed that the incidence of EA in PACU (Aono's scale ≥ 3: 21.43% vs 57.14%; Pediatric Anesthesia Emergence Delirium [PAED] scale ≥ 10: 21.43% vs 54.76%; both $P < 0.01$), the percentage of patients with severe EA (PAED score ≥ 15; 7.69 % vs 40.48%; $P < 0.01$), and peak pain score (2.60 ± 2.07 vs 4.10 ± 2.49; $P = 0.004$) were significantly lower in the Group N compared to the Group S. Emergence time was significantly longer in the Group N, but there was no difference in time to discharge from the PACU [19].

Another study had reported to decrease the rate of emergence agitation and decrease the frequency of postoperative analgesic requirement which is done by Prasad; *et al.* also found that Dexmedetomidine (0.3 ugs/kg) and ketofol (0.25 mg/kg and 1 mg/kg) caused a significant reduction in the incidence and severity of emergence agitation when compared to control group. Ketofol was as effective as dexmedetomidine in the prevention of emergence agitation when administered before the end of the surgery. Still, children delivered dexmedetomidine was calm and satisfied discharge criteria earlier than ketofol group [20].

Another study was done by Abd El-Hamid, *et al.* This study showed that a dose of 1 ug/kg intranasal dexmedetomidine that given after the induction of anaesthesia leading to decrease of post-sevoflurane incidence and severity of emergence agitation in children undergone tonsillectomy and adenoidectomy

with no adverse effects and smooth postoperative course [21].

5. Conclusion

Ketamine and dexmedetomidine reduced the incidence and severity of emergence delirium effectively when compared to normal saline, and the effects of dexmedetomidine being much superior to Ketamine.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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