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Research Article

The effect of different drugs on sevoflurane emergence agitation in pediatric patients undergoing hypospadias repair surgery

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KEYWORDS

Sevoflurane;
Agitation;
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Ketamine

Abstract *Background:* Various methods are used to decrease the incidence of emergence agitation (EA) in children following general anaesthesia with sevoflurane.
Objective: The present study aims to compare the effect of intravenous injection of small dose of propofol, fentanyl or ketamine at the end of surgery, just before the discontinuation of sevoflurane on the incidence and severity of sevoflurane emergence agitation in children undergoing hypospadias repair operations.
Patients and methods: Eighty patients undergoing elective hypospadias repair under sevoflurane general anaesthesia with caudal block were randomly divided into four groups (20 patients each); group P received intravenous 1 mg/kg propofol, group K received intravenous 0.25 mg/kg ketamine, group F received intravenous 1 μg/kg fentanyl, and group S received intravenous saline as control group. All those injections were given just before the discontinuation of sevoflurane. The emergence agitation was evaluated by emergence agitation scale from awakening every 5 min for 30 min. Complications like laryngospasm, desaturation, cough, and vomiting were recorded. Awakening time and PACU duration were also recorded.
Results: The incidence of emergence agitation was significantly lower in groups P and F ($p < 0.05$). The time for awakening was significantly prolonged in groups P, K and F ($p < 0.05$), while PACU duration was significantly prolonged in group F ($p < 0.05$). No significant complications occurred except a significantly higher incidence of vomiting in group F.
Conclusion: The use of propofol or fentanyl just before the discontinuation of sevoflurane reduces the incidence of emergence agitation in children, on the other hand fentanyl was accompanied with a significantly longer PACU duration and higher incidence of vomiting.

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1. Introduction

Emergence agitation (EA) or delirium is a frequent problem among pediatrics during recovery from general anaesthesia specially with sevoflurane. It is a mental disturbance in the form of excitation, hallucination, involuntary physical activity with crying or even thrashing about in bed which can lead to self injury and cause stress to both caregivers and parents although it does not increase morbidity [1].

The incidence of EA is up to 80% and more frequently observed in the preschool age [2].

Sevoflurane now is the inhalational anaesthetic agent of choice for pediatrics, as it is nonpungent, with minimal airway irritation characters, and its cardiac adverse effects are minimal like cardiac depression and dysrhythmias [3].

On the other hand, sevoflurane has low blood/gas solubility, and causes rapid induction and recovery which were documented in several studies to increase the incidence of EA when used for anaesthesia in children [4].

The pathogenesis of postoperative EA is still undefined [5], but sevoflurane has intrinsic effects that may share in emergence agitation like its different electroencephalogram pattern from halothane [6,7], and its degradation to inorganic fluoride ions and compound A which may have a role in the occurrence of EA [8].

Even if propofol-based anaesthesia is used from the start to achieve smoother recovery, maintenance with sevoflurane is still preferred by many anaesthetists [9]. So many strategies have been used to decrease the severity and incidence of EA of sevoflurane like premedication with sedative agents, changing the technique of maintenance, or administration of certain agents at the end of anaesthesia which were thought to be the most effective and applicable strategies in clinical practice [10].

Several studies were done before on our studied drugs regarding their effect on emergence agitation, and they found that administration of small dose of ketamine or propofol just before the end of sevoflurane anaesthesia would decrease emergence agitation incidence without delaying patient awakening or discharge from post anaesthesia care unit (PACU) [11,12]. Also other studies were done on fentanyl found that involving fentanyl in the anaesthetic technique would decrease agitation of sevoflurane independent of any effect of pain [13].

This study was performed to compare the administration of small dose of either propofol, ketamine, or fentanyl before discontinuation of sevoflurane anaesthesia in decreasing the incidence of EA without serious side effects.

2. Patients and methods

After approval of the local medical ethics committee and obtaining written informed consent from parents, this comparative prospective study was conducted in Zagazig University hospital on 80 healthy male children aged from 1 to 3 years, ASA I-II physical status scheduled for ambulatory hypospadias repair under general sevoflurane anaesthesia. Children with psychological/emotional disorder, cognitive problem, developmental delay, parents refusal, or children under certain medications like sedatives, anticonvulsants were excluded.

Children were randomly assigned by means of random numbers generated by computer to one of the four groups (twenty patients each), referred to as the propofol (P) group, the ketamine (K) group the fentanyl (F) group, and the saline (S) group. These medications were administered by the resident according to the group to which the patient was randomized.

All patients were requested during the preanaesthetic visit to be fasting for 6–8 h with permission of clear fluids up to 4 h before operation.

No premedication was used. After application of pulse oximetry, anaesthesia was induced inhalationaly by mask with 8% sevoflurane in 100% O2 and then sevoflurane concentration was decreased to 2–2.5% after child loss of consciousness and all thorough the operation for maintenance of anaesthesia. Then peripheral intravenous cannula was inserted and 0.01 mg/kg atropine injected intravenously. Monitors were applied like electrocardiography, noninvasive blood pressure monitor then capnography connected to laryngeal mask (LMA) which was inserted after adequate jaw relaxation and oral airway tolerance, its size was chosen according to the body weight of the child as written by the manufacturer. All monitors' data were recorded every 5 min, then caudal block was performed with 1 ml/kg Bupivacaine 0.25% (20 ml max). If LMA insertion failed for three trials the child was intubated and excluded from the study to avoid effects of muscle relaxants on some parameters measured in the study like awakening time and postanaesthesia care unit (PACU) duration.

Spontaneous ventilation was maintained but was assisted to achieve end tidal CO2 (PETCO2) levels between 35 and 40 mmHg.

10 ml/kg of Lactated Ringer's solution was infused over 20 min after intravenous line insertion followed by standard fluid maintenance therapy according to the child's weight.

Adequate caudal block was assessed by skin incision, if heart rate did not increase by more than 20% of the basal heart rate within 60 s, it was considered adequate, if not the child was excluded from the study.

Just before the end of the surgery and the discontinuation of sevoflurane, patients of the fentanyl (F) group were given 1 μg/kg fentanyl IV, patients of ketamine (K) group were given 0.25 mg/kg ketamine IV, patients of propofol (P) group were given 1 mg/kg propofol IV all medications completed to 10 ml by saline, and those of saline (S) group were given equal volume of saline IV. All solutions were given over 1 min.

At the end of surgery, LMA was removed semi inflated to sweep secretions with it under anaesthesia and then sevoflurane was discontinued immediately. Face mask with jaw thrust and 100% oxygen was used with careful suction while the patient was still deeply anaesthetized and carefully observed for any upper airway obstruction, laryngospasm or breathholding. Oral airway was used in some patients but removed once reflexes started to be regained. Then when patent airway and spontaneous respiration without assistance were confirmed patients were transferred to the PACU where their parents or one of them were present. Moreover there was one resident anaesthesiologist who was blinded about the study observed the patients for 30 min for any complications like laryngospasm, desaturation, cough, vomiting which was treated by i.v. 150 μg/kg dexamethasone if occurred, and agitation which was assessed using the 5-step Emergence Agitation Scale (EAS) to be recorded every 5 min from awakening and for 30 min.

Emergence Agitation Scale (EAS)

1 = obtruded with no response to stimulation.

2 = asleep (not initiating reaction with the observer) but responsive to movement or stimulation.

3 = awake and responsive.

4 = crying.

5 = thrashing behaviour that requires restraint.

If score was $\geqslant 4$ for more than 5 min the child was considered agitated and was treated with i.v. 1 mg/kg propofol as rescue medication.

Then the patient was discharged to the ward after fulfilment of discharge criteria which are full awakeness, stable vital signs, oxygen saturation more than 95% on room air with patent airway without support.

Moreover, the awakening time which is the time between administration of the study agent to emergence (time to transfer to PACU) and the PACU duration which is the time between admission and discharge from the PACU were also recorded.

2.1. Statistical analysis

Data were checked, entered and analysed by using (SPSS version 19). Data were expressed as mean ± SD for quantitative variables. Number and percentage for categorical variables Chi-squared (X2) or fisher exact test, ANOVA (F test) were used when appropriate and LSD (when ANOVA was significant) for comparison in between groups. $P < 0.05$ was considered statistically significant.

3. Results

The present study involved 80 male children aged 1–3 years, and there were no significant difference among the four groups as regard to demographic data (age, weight) and the procedure duration (Table 1).

Regarding the awakening time which is the time between administration of the study agent to emergence, it was comparable between groups (K&F), (K&P) and (P&F) but all groups awakening times were significantly longer than group S ($P < 0.001$) (Table 2).

But regarding the PACU duration which is the time between admission and discharge from the PACU, it was significantly longer in group F than group S ($P < 0.05$). Otherwise all groups showed nonsignificant differences among them as regard the same parameter (Table 2).

There were significantly more agitated children in group S at 5, 10, 15, and 30 min ($p < 0.05$). More patients from group K developed agitation when compared with group P and group F at 10, 15, and 30 min ($p < 0.05$), but the difference was not statistically significant between group P and group F (Table 3). We omitted the readings of 20 and 25 min as we found readings at 20 min were not different from 15 min readings and 25 min readings were not different from 30 min readings.

The four groups showed nonsignificant differences among them as regard the incidence of complications in theatre after LMA removal like laryngospasm, desaturation and cough, but there was significant appearance of vomiting in group F in PACU ($P < 0.05$). Vomiting also occurred in other groups but it was statistically nonsignificant (Table 4).

4. Discussion

Emergence agitation (EA) had been studied by many investigators as it is a common phenomenon in children after sevoflurane or desflurane based anaesthesia [14].

As sevoflurane now is the inhaled anaesthetic agent of choice especially for children, several attempts have been made to reduce the incidence of sevoflurane emergence agitation. Although it is self-limiting it can cause self-injury to the child and stress to the child's family [15].

Pain can produce behavior similar to that of anaesthetic-induced EA, so this study used a caudal block with general anaesthesia in all groups to control pain and either to minimize emergence agitation after sevoflurane anaesthesia in agreement with Aouad et al. [16] or to exclude the contribution of pain as a cause for EA in agreement with Aono et al. [17].

In this study, three different pharmacological agents were administered just before the end of the surgery and the discontinuation of sevoflurane in a trial to decide which of them is better in decreasing the EA of sevoflurane anaesthesia without serious side effects in their comparison with control group.

The three agents were propofol, ketamine and fentanyl.

While choosing the medications of the study, investigators concerned about the possible complications not only the benefits of each medication, as injection of these agents at the end of anaesthesia may lead to airway obstruction and desaturation, so close monitoring was achieved for each patient for adequate time before transferring the patient to PACU.

The study recorded that there were significant increase in the incidence of vomiting in the fentanyl group while other complications like laryngospasm, cough, and desaturation were nonsignificant.

Table 1 Demographic data and procedure duration.

	Age (mo)	Weight (kg)	Procedure duration (min)
Group S ($n = 20$)	24.6 ± 10.2	14.7 ± 2.1	60.9 ± 8.9
Group P ($n = 20$)	26.8 ± 9.5	13.1 ± 2.5	55.2 ± 8.9
Group K ($n = 20$)	26.9 ± 9.1	14.2 ± 2.1	54.9 ± 10.1
Group F ($n = 20$)	25.5 ± 10.6	13.2 ± 3.0	58.7 ± 10.2
P value	0.86	0.11	0.14

Data represented by mean ± SD and numbers.
No significant differences among the 3 groups.
Group S = Saline.
Group P = Propofol.
Group K = Ketamine.
Group F = Fentanyl.

Table 2 Time for awakening and PACU stay duration among the four groups.

	Time for awakening (min)	PACU duration (min)
Group S (n = 20)	15.8 ± 3.1	35.2 ± 7.1
Group P (n = 20)	23.9 ± 4.2*	39.1 ± 8.0
Group K (n = 20)	25.4 ± 4.1*	40.0 ± 10.2
Group F (n = 20)	28.2 ± 5.0*	43.9 ± 6.3*
P value	< 0.001	0.009

Data represented by mean ± SD.
Group S = Saline.
Group P = Propofol.
Group K = Ketamine.
Group F = Fentanyl.
* Significant compared with group S (P < 0.05).

Table 3 Incidence of agitation among the four groups after PACU admission.

	After 5 min		After 10 min		After 15 min		After 30 min	
	NO	(%)	NO	(%)	NO	(%)	NO	(%)
Group S (n = 20)	4*	(20.0)	5*	(25.0)	7*	(35.0)	8*	(40.0)
Group P (n = 20)	0	(0.0)	0	(0.0)	1	(5.0)	1	(5.0)
Group K (n = 20)	0	(0.0)	3**	(15.0)	5**	(25.0)	4**	(20.0)
Group F (n = 20)	0	(0.0)	0	(0.0)	1	(5.0)	2	(10.0)
P value	0.005		0.018		0.02		0.024	

Data represented as number and percentage.
Group S = Saline.
Group P = Propofol.
Group K = Ketamine.
Group F = Fentanyl.
* Significant compared with all groups P(< 0.05).
** Significant compared with group P and group F P(< 0.05).

Table 4 Incidence of complications.

	Laryngospasm		Desaturation		Cough		Vomiting	
	NO	%	NO	%	NO	%	NO	%
Group S (n = 20)	1	(5.0)	0	(0.0)	1	(5.0)	0	(0.0)
Group P (n = 20)	1	(5.0)	1	(5.0)	0	(0.0)	1	(5.0)
Group K (n = 20)	1	(5.0)	1	(5.0)	2	(10.0)	3	(15.0)
Group F (n = 20)	0	(0.0)	1	(5.0)	0	(0.0)	6*	(30.0)
P value	0.79		0.79		0.28		0.02	

Data represented as number and percentage.
Group S = Saline.
Group P = Propofol.
Group K = Ketamine.
Group F = Fentanyl.
* Significant compared with all groups (P < 0.05).

Regarding to the time for awakening, it was significantly prolonged in all groups (P, K, F) versus control group but showed nonsignificant differences among the other three groups. These results are similar to those reported by Aouad et al. [12] as regard propofol, and Kim et al. [18] as regard propofol and fentanyl but against what Abelhalim et al. [19] found as regard ketamine may be due to giving ketamine 10 min before the end of anaesthesia but in this study ketamine given just before the end of anaesthesia.

On the other hand, the study found that the PACU stay was longest in the fentanyl group, but there were nonsignificant differences among the other groups. Unfortunately this is against what Cravero et al. [13] proved in their study regarding fentanyl, on patients receiving sevoflurane anaesthesia without surgery may be due to giving fentanyl 10 min before the end of anaesthesia but in this study fentanyl given just before the end of anaesthesia. But regarding ketamine and propofol this study results are in agreement with Dalens et al. [11] and Aouad et al. [12] respectively.

The study proved that administration of IV 1 mg/kg of propofol, or 1 μg/kg fentanyl just before the discontinuation of sevoflurane showed significant decrease in the number of

agitated patients than the other groups. That is similar to what Kim et al. found in their study [18].

Also Dalens et al. found [11], that IV ketamine just before the closure of sevoflurane vaporizer decreased the incidence of agitation than the saline group and that what has been proved in this study.

But the results regarding incidence of EA after injection of fentanyl and propofol were nonsignificantly different from each other.

Limitations of the present study are the investigation of one type of surgery although the incidence of EA is different with different types of surgeries so the studied agents may be modified with other surgeries, as emergence agitation is found to be more with otorhinolaryngological or ophthalmological procedures [20]. Also the present study used the EAS however the Pediatric Anaesthesia Emergence Delirium (PAED) score utilized in some of the recent studies [12,21] is the most comprehensive and validated score currently available to assess emergence agitation as it incorporates psychomotor items that differentiate delirium from postoperative pain.

Moreover, the lack of follow up after discharge specially for nausea and vomiting, All of the above may have affected our study results interpretations. So additional structured multicenter studies in more suitable environment with larger numbers of patients are required. Moreover we recommend further studies to be done on the same medications but when given at earlier time to avoid delay in awakening which happened in all groups other than the control group.

Current study supports the use of 1 mg/kg propofol or 1 μg/kg fentanyl intravenously just before the discontinuation of sevoflurane to reduce the incidence of emergence agitation in children, and propofol was found to be superior to fentanyl due to its lower incidence of inducing vomiting.

Conflict of interest

We have no conflict of interest to declare.

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