

# Emergence agitation in paediatric patients using sevoflurane and isoflurane anaesthesia: a randomised controlled study

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**Background:** Emergence agitation (EA) is a well-recognised phenomenon often observed in children following general anaesthesia. The aim of this study was to compare the incidence and severity of EA in the paediatric age group under sevoflurane or isoflurane anaesthesia using the PAED Scale (Pediatric Anaesthesia Emergence Delirium Scale) (the primary outcome) and its correlation with preinduction agitation as well as its association with pain using the FLACC (Face Legs Activity Cry Consolability) score (the secondary outcome).

**Method:** In this randomised controlled trial, 60 children aged between 2 and 6 years were enrolled and randomly divided into two groups. All patients were induced with sevoflurane, relaxed with atracurium and the airway secured with an appropriate device. Anaesthesia was maintained with O<sub>2</sub>, N<sub>2</sub>O and sevoflurane or isoflurane. Adequate analgesia was ensured. Post-procedure, they were observed in the post-anaesthesia care unit (PACU) for development of EA. The statistical package SPSS<sup>®</sup> version 17 was used and data were analysed using Student's unpaired t-test and a chi-square test. Statistical significance was accepted at  $p < 0.05$ .

**Results:** The mean PAED scale was 12.9 in the sevoflurane group and 9.4 in the isoflurane group ( $p < 0.001$ ). The incidence of EA was significantly related to preinduction agitation ( $p = 0.00$ ). Higher FLACC scores were observed only within the initial 10 min in the sevoflurane group ( $p = 0.009$ ).

**Conclusions:** An increased incidence of EA was observed with sevoflurane maintenance anaesthesia, particularly during the initial 10–20 min of the postoperative period. EA was strongly associated with preinduction agitation, but it was poorly correlated to pain, i.e. not all patients who developed EA had a high FLACC score.

**Keywords:** sevoflurane anaesthesia, emergence agitation, preinduction anxiety, paed scale, preschool children

## Introduction

Emergence agitation (EA) is a common and well-recognised phenomenon in paediatric patients observed after general anaesthesia. It was first reported by Eckenhoff *et al.* in 1961 as 'post-anaesthetic excitement'. Emergence agitation (EA) is defined as a state of postoperative confusion and disorientation associated with restlessness, involuntary movements and inconsolability. This can be accompanied by various behavioural changes such as thrashing, screaming, prolonged crying and combativeness.<sup>1</sup> It is usually self-limiting and short-lived. It occurs within the first 30 min after anaesthesia, lasts for a few minutes to hours but may take up to 2 days to resolve.<sup>2–4</sup> The incidence of EA ranges from 5% to 15% with some studies reporting an incidence as high as 80%.<sup>4,5</sup>

Although emergence agitation is self-limiting, it can be very frightening and disturbing for the parents. An agitated child may pull out intravenous lines, drains and dressings or injure the caregiver. They are at increased risk of bleeding from the surgical site, increased incidence of postoperative maladaptive behaviours (such as anxiety, aggression, temper tantrum, sleep disturbance, and eating problems) and delay in discharge. All these problems account for an additional need for nursing help and care, and may require additional medications. Over the years, several scales have been developed to evaluate the severity of EA.<sup>6</sup>

The risk factors for EA are preschool age, male patients, preoperative anxiety, lack of premedication, inhalational agents, type of surgery (otorhinolaryngeal procedures, ophthalmologic procedures), awakening in a strange environment, inadequate pain relief, and children with low adaptability.<sup>6</sup> The exact cause of

EA is still unknown but considered as multifactorial. Some possible causes for agitation are hypoxia, hypercarbia, hypoglycaemia, pain, airway obstruction, raised intracranial pressure, drugs, fear/anxiety and the child's temperament.<sup>3,7</sup>

Hence, we decided to compare the incidence and severity of EA in the paediatric age group under maintenance sevoflurane (Group S) or isoflurane (Group I) anaesthesia using the PAED (Pediatric Anaesthesia Emergence Delirium) Scale. We also wanted to study the effect of preinduction anxiety on emergence agitation as well as its association with pain using the FLACC (Face Legs Activity Cry Consolability) score.

## Methods

After ethics committee approval, written and informed consent was obtained from parents/guardians, and 60 children between 2 and 6 years of age, ASA 1–2, posted for sub-umbilical surgeries, were enrolled. A detailed history was taken; complete physical examination was done for all patients.

The sample size was calculated based on the formula, =  $\frac{2(Z\alpha + Z\beta) * \sigma^2}{d^2}$

with 95% confidence level and 80% power; the sample size reached 27 in each group. We enrolled 30 patients in each group to round off. They were randomly allocated into two groups, with 30 patients in each group. Group S received anaesthesia using sevoflurane and Group I received isoflurane for maintenance. Patients with a history of active airway disease, sleep apnoea, febrile convulsions, developmental delay, psychological/neurological disorder or cardiovascular abnormality were excluded.

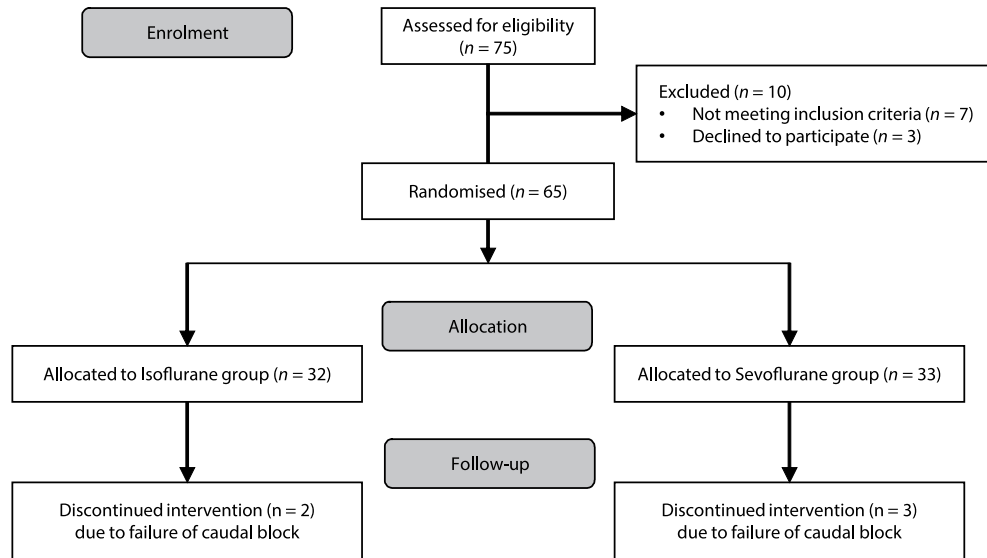


Figure 1: The flow of participants through each stage of study.

All patients were premedicated with trichlophos syrup (100 mg/kg) one hour before surgery. Drugs which are potentially known to inhibit EA such as midazolam were avoided. In the operating room, all children were induced with 8% sevoflurane in oxygen via face mask. After anaesthesia induction, intravenous access was established and fentanyl (2 mcg/kg) was given intravenously. Atracurium 0.5 mg/kg was used for neuromuscular blockade and the airway was secured with an appropriate airway device. Analgesia was provided with caudal block with bupivacaine 0.1% and a paracetamol suppository in appropriate doses was administered before the surgical incision. If there were variations in heart rate and blood pressure of more than 20%, the caudal block was considered to be inadequate and such patients were excluded from the study. For maintenance of anaesthesia, patients were assigned to group S or group I. Minimum alveolar concentration (MAC) of anaesthetic agent was maintained between 1.0 and 1.2.

Intraoperatively, the patient's heart rate, blood pressure, SpO<sub>2</sub>, ETCO<sub>2</sub> and anaesthetic gas concentrations were monitored and documented as per standard care. Ondansetron (0.1 mg/kg) was given as an antiemetic. The last maintenance dose of atracurium was given approximately 15 min prior to the last surgical stimulus and the volatile anaesthetic agent was turned off with the last surgical stimulus. Patients were extubated after reversal of residual neuromuscular blockade with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg), and the resumption of regular breathing, purposeful movements and eye opening. After extubation, patients were transferred to the post-anaesthesia care unit (PACU) and were observed for development of emergence agitation and pain, every 10 min for 30 min, by anaesthesiologists who were blinded as to the treatment group, using the PAED (Pediatric Anaesthesia Emergence Delirium) and the FLACC scales. Fentanyl 1 mcg/kg stat was given intravenously, if any of the following were observed:

(1) PAED scale 16 or more; (2) PAED scale 4–5 and pain score 3–4; or (3) pain score more than 5. Total requirement for rescue analgesics in patients with high pain scale was calculated.

The statistical package SPSS® version 17 (SPSS Inc, Chicago, IL, USA) was used and data analysis was made using Student's

unpaired t-test and a chi-square test. Statistical significance was determined at the level of  $p < 0.05$ .

## Results

A total of 75 children were initially enrolled but 7 were found not to meet inclusion criteria, 3 declined to participate, and 5 were deleted due to apparent failed caudal block leaving 30 children in each treatment arm (Figure 1). The age, weight, physical status, and other demographic data are presented in Tables 1–2; there were no significant differences in any of these demographics between groups. Group S demonstrated greater PAED scores compared with Group I, at 0 ( $p = 0.002$ ), 10 min ( $p < 0.001$ ) and 20 min ( $p = 0.021$ ) but there was no difference at 30 min (Figure 2). The incidence of EA was significantly related to preinduction agitation, ( $p = 0.00$ ) (Table 3). The FLACC pain scores were greater within the initial 10 min in group S ( $p = 0.009$ ); however, there were no statistical differences in pain scores between groups between 10 and 30 min (Table 4). Twelve out of 30 patients (40%) in group S and 4 out of 30 patients (13.3%) in group I developed emergence agitation. Therefore, the overall incidence of EA was significantly greater in group S compared with group I (chi-square = 5.455,  $p = 0.02$ ). Some 14 patients (46.7%) in group S and 7 patients (23.3%) in group I required rescue analgesia post-extubation either due to high PAED scale or FLACC score; this difference was not statistically significant (chi-square = 3.59,  $p = 0.058$ ).

## Discussion

Sevoflurane is the most popular inhalational agent for inducing paediatric patients. However, due in part to rapid awakening after sevoflurane anaesthesia, there is an association with post-anaesthesia emergence agitation (EA).<sup>8</sup> Studies have shown that EA is more common in preschool children, i.e. 2–6 years of age; it can also be seen in adults, especially the elderly.<sup>9</sup> However, the 'at risk' age for EA is considered as 3 years or below.<sup>10</sup> This may in part be due to a number of factors such as emotional lability, the trauma of parental separation, recovery in a strange environment, and others. Some studies suggest that EA is more common with short procedures as patients will be wide awake before the peak effect of analgesics has been achieved; others found a higher incidence of EA with longer duration of anaesthesia.<sup>6</sup> In contrast, our study found no effect of duration of anaesthesia on EA.

Table 1: Demography

(a) Gender					
		Group			Total
		Sevoflurane	Isoflurane		
Sex	F	Count	4	6	10
		%	13.3	20	16.7
	M	Count	26	24	50
		%	86.7	80	83.3
Total	Count	30	30	60	
	%	100	100	100	

Chi-square = 0.48; p = 0.488 n.s.

(b) Age distribution

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		Group			Total
		Sevoflurane	Isoflurane		
Age	2	Count	11	11	22
		%	36.7	36.7	36.7
	3	Count	7	10	17
		%	28.3	33.3	28.3
	4	Count	3	4	7
		%	10	13.3	11.7
5	Count	3	2	5	
	%	10	6.7	8.3	
6	Count	6	3	9	
	%	20	10	15	
Total	Count	30	30	60	
	%	50	50	100	

Chi-square = 1.872; p = 0.759 n.s.

(c) Weight

Group	n	Mean (kg)	SD	Total
Sevoflurane	30	12.267	2.532	p = 0.175
Isoflurane	30	12.133	3.306	p = 0.861

SD = standard deviation.

(d) ASA status

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		Group			Total
		Sevoflurane	Isoflurane		
ASA	1.00	Count	26	26	52
		%	86.7	86.7	86.7
	2.00	Count	4	4	8
		%	13.3	13.3	13.3
Total	Count	30	30	60	
	%	100.0	100.0	100.0	

The association of preoperative anxiety and postoperative behavioural problems is well known.<sup>11</sup> A study of 791 children using modified Yale Preoperative Anxiety Scale (YPAS)<sup>11</sup> demonstrated that for each increase of 10 points on the anxiety score, the risk of EA increases by 10%. Our study also found a strong correlation between patient's preinduction anxiety and the incidence of EA. Children who were agitated before induction were observed to have more risk of EA since they remain agitated during recovery from anaesthesia (Table 3).

Table 2: Intra-op and post-op variables

Factor	Group	n	Mean	SD	t
Duration of surgery (min)	Sevoflurane	30	85.600	51.397	1.056 p = 0.295
	Isoflurane	30	72.500	44.419	
Duration of anaesthesia (min)	Sevoflurane	30	108.233	55.070	0.868 p = 0.369
	Isoflurane	30	96.567	48.839	
Time of regular breathing (min)	Sevoflurane	30	3.550	.747	5.140 p < 0.001
	Isoflurane	30	4.633	.880	
Time of awakening (min)	Sevoflurane	30	5.033	.870	2.854 p = 0.006
	Isoflurane	30	5.800	1.186	
Time of extubation (min)	Sevoflurane	30	6.100	.923	1.513 p = 0.136
	Isoflurane	30	6.517	1.193	
Time to meet	Sevoflurane	30	36.433	23.850	0.792
Discharge criteria (min)	Isoflurane	30	31.767	21.714	p = 0.431
Duration of stay in PACU (min)	Sevoflurane	30	56.633	36.875	1.044 p = 0.301
	Isoflurane	30	46.933	35.070	

Table 3: Sevoflurane induction (agitated/smooth)

Factor	Induction with sevoflurane		Total		
	Agitated	Smooth			
Incidence of EA	Yes	Count	14	2	16
		%	82.4	4.70	26.70
	No	Count	3	41	44
		%	17.60	95.30	73.30
Total	Count	17	43	60	
	%	100.00	100.00	100.00	

Chi-square tests

	Value	df	Asymp. sig. (2-sided)
Pearson's chi-square	37.615	1	0

Table 4: FLACC Score in PACU

Group	n	Mean	SD	t	
FLACC score 0 min	Sevoflurane	30	2.633	1.033	2.692 p = 0.009
	Isoflurane	30	1.933	0.98	
FLACC score 10 min	Sevoflurane	30	2.967	1.474	1.244 p = 0.219
	Isoflurane	30	2.5	1.432	
FLACC score 20 min	Sevoflurane	30	3.067	1.461	1.426 p = 0.159
	Isoflurane	30	2.5	1.614	
FLACC score 30 min	Sevoflurane	30	2.933	1.552	1.250 p = 0.216
	Isoflurane	30	2.433	1.547	

To reduce the incidence of EA, several drugs have been used as an adjuvant to general anaesthesia. These drugs include propofol, midazolam, ketamine, opioids and alpha<sub>2</sub> agonists including clonidine and dexmedetomidine.<sup>12-16</sup> The administration of such drugs for premedication or at the end of surgery significantly reduces the incidence of EA. Fentanyl (2.5 mcg/kg) was effective whereas smaller doses were ineffective.<sup>17</sup> Ketamine when given orally (6 mg/kg) as premedication reduced the incidence of EA,<sup>18</sup> whereas propofol (1 mg/kg) 10 min before the end of surgery

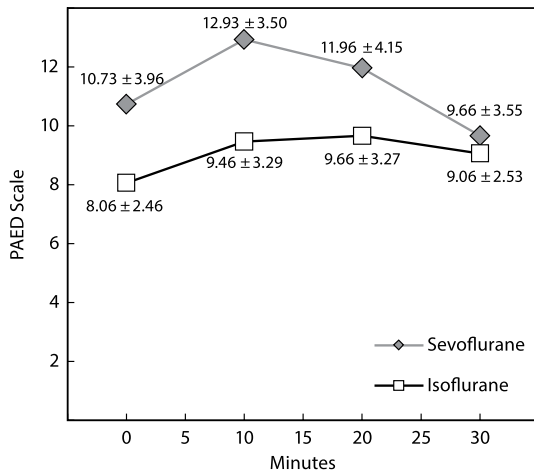


Figure 2: PAED Scale in PACU.

showed similar results but delayed the time of awakening.<sup>19</sup> Caudal analgesia may decrease the duration/severity of EA but does not affect the incidence, when sevoflurane was compared with halothane.<sup>20</sup> In our study, not all patients who developed EA had high FLACC score whereas others had high FLACC scores without manifestation of EA. There was no statistically significant difference in the requirement for pain rescue medications between the groups. Children with EA had on average a longer recovery phase in PACU but this difference was not statistically significant.

### Conclusion

Children who had sevoflurane for maintenance of anaesthesia had a higher incidence of EA for the first 20 min in PACU compared with those maintained on isoflurane, which was not affected by the duration of anaesthesia. A strong association was observed between preinduction anxiety and emergence agitation. Since it is clear the EA is associated with sevoflurane anaesthesia, strategies to reduce EA are strongly recommended when this inhalation agent is utilised.

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Received: 27-11-2015 Accepted: 14-03-2017