Clinical Investigation

Comparative evaluation of incidence of emergence agitation and post-operative recovery profile in paediatric patients after isoflurane, sevoflurane and desflurane anaesthesia

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ABSTRACT

Background: Emergence agitation (EA), although well documented in the clinical literature, still has uncertainties and confusion abound on this subject because of the absence of a clear definition and lack of reliable and valid assessment tools. **Aim:** To compare the incidence and severity of EA and recovery characteristics in paediatric patients under isoflurane, sevoflurane or desflurane anaesthesia and evaluate the effect of age and duration of anaesthesia on the incidence of EA. **Settings and Design:** Randomized prospective double-blinded study. **Methods:** Seventy-five American Society of Anaesthesiologists I and II patients, aged between 4 months and 7 years, were included in the study. Patients were induced with sevoflurane and oxygen. Anaesthesia was maintained with O_2 + N_2O and isoflurane, sevoflurane or desflurane according to randomization. Caudal block and paracetamol suppository was administered before the surgical incision. In the Post-Anesthesia Care Unit (PACU), degree of agitation was assessed using the Paediatric Anaesthesia Emergence Delirium Scale. Aldrette score, Face, Legs, Activity, Cry, Consolability score and any adverse events were noted. **Statistical Analysis:** Chi-square/Fischer exact test was applied for categorical variables; for continuous variables, the analysis of variance/non-parametric Kruskall–Wallis test was applied. Two-sample t-test/non-parametric Wisconsin Mann–Whitney test was applied between the two groups. Statistical significance was determined at $P<0.05$. **Results:** Incidence and intensity of EA were comparable in all three groups. Age and duration of anaesthesia do not appear to have any bearing on the incidence of EA. Rapid emergence with sevoflurane and desflurane did not translate into early discharge from PACU. **Conclusions:** EA is a multifactorial syndrome. More well-conducted studies using validated scales and standardized protocols should be carried out to better understand this phenomenon.

Key words: Emergence agitation, desflurane, isoflurane, paediatrics, sevoflurane

INTRODUCTION

Emergence agitation (EA) has been defined as a dissociated state of consciousness in which the child is inconsolable, irritable, uncooperative, typically thrashing, crying, moaning or incoherent.[1,2] Wells attributed EA to paranoid ideation with disorientation to time, misinterpretation of stimuli and differing central nervous system effect of sevoflurane as putative mechanisms for this behaviour.[3]

EA is associated with adverse events such as increased bleeding from surgical site, damage to surgical repair, pulling out a surgical drain or an intravenous access and increased pain at the operative site. This phenomenon may also result in physical harm to

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the child or caregiver and may require additional treatment. This behaviour is disruptive to the Post-Anaesthesia Care Unit (PACU), often requiring constant nursing supervision, which strains nursing manpower resources and increases chances of parental dissatisfaction about quality of child's recovery.[4,5] As patients with EA are difficult to control, discharge from the recovery area may be delayed; thus, negating any beneficial effect that rapid emergence may have on length of stay in the recovery area.[6]

Despite an ample amount of published literature on this subject, little is known about its actual incidence, pathophysiology, causal factors and appropriate remedy for the phenomenon. Factors that have been presumed to be associated with the high incidence of EA include pre-school age, no previous surgery, poor adaptability, ophthalmological, otorhinolaryngology procedures, newer inhalational anaesthetics, adjuvant medications, short time to awakening, environmental factors such as noise, unfamiliarity and pre-operative anxiety and temperament of the child. EA may well be considered a result of interplay of anaesthetic factors, surgical factors, age, patient characteristics, family and environmental attributes.[7,8]

Sixteen rating scales and two visual analogue scales have been used to measure EA in children. These scales are deficient in two main respects: Scale content and psychometric evaluation and included behaviours that are not specific to EA. Furthermore, there is lack of consensus on what level of behavioural disturbance and for what period constitutes EA. Consequently, interpretation of the current literature is confounded with significant limitations, contradictions and inconclusive outcomes, and explains the wide margin of reported prevalence in the literature that ranges from 10% to 80%.[8-11] To overcome these drawbacks, Sikkich *et al.* developed a reliable and valid Paediatric Anaesthesia Emergence Delirium (PAED) scale [Table 1] to measure EA in children with the objective of minimizing errors in the clinical assessment of agitation in children.[4]

We in our study aim to compare the incidence and severity of EA in the paediatric age group undergoing surgery under isoflurane, sevoflurane or desflurane anaesthesia using the PAED scale, to evaluate the effect of age and duration of anaesthesia on the incidence and severity of EA and to compare and evaluate the recovery characteristics in these groups.

METHODS

The study was conducted after approval from the hospital medical ethics committee. Seventy-five paediatric patients belonging to American Society of Anaesthesiologists physical status I–II, of either sex, between 4 months and 7 years of age, scheduled for elective subumbilical surgery under general anaesthesia, were included after obtaining written informed consent from the parents/guardians. Children with a history of active airway disease, sleep apnoea, developmental delay, psychological, neurological disorder, cardiovascular abnormality or requirement of post-operative ventilation were excluded from the study.

The study was conducted in a randomized controlled prospective double-blinded manner. The patients were divided into three groups of 25 each. Anaesthesia was induced with sevoflurane in 100% O_2 and maintained with O_2 + N_2O and sevoflurane, isoflurane, desflurane in group S, group I and group D, respectively.

No premedication was administered. Parental presence was allowed during induction of anaesthesia. Intra-operatively, the patients' pulse, blood pressure, arterial oxygen saturation, temperature, end tidal carbon dioxide and anaesthetic gas concentrations were monitored. Anaesthesia was induced with 8% sevoflurane in 100% O_2 via facemask. After anaesthesia induction, intravenous access was established and inj. fentanyl 2 μg/kg and inj. atracurium 500 μg/kg was administered to secure the airway. Inj. dexamethasone 0.5 mg/kg (up to a maximum of 8 mg) was administered as prophylactic antiemetic. Dexamethasone was chosen as ondansetron is known to prevent EA. Anaesthesia was maintained with 1.0 to 1.2 MAC concentration of anaesthetic agent according to randomization. Caudal block with

Table 1: Paediatric anaesthesia delirium scale

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

Minimum score is 0 and maximum score is 20. The degree of emergence delirium increases directly with the total score

bupivacaine 0.2% and paracetamol suppository 30 mg/kg was administered before the surgical incision. Those children whose heart rate/blood pressure rose by 20% were considered to have ineffective caudal block and were excluded from the study. Volatile anaesthetic agent was turned off with the last surgical stimulus. Post extubation, the children were transferred to the PACU.

In the PACU, degree of agitation using PAED scale and post-operative recovery characteristics using Aldrette score were recorded. Pain was assessed using the FLACC scale. For patients in whom simple comfort measures (presence of parent, physically holding the child, oral fluids) did not ameliorate the symptoms and patients with PAED scale variable of 4 or 5 with an intensity 3 or 4 or those who experienced pain exceeding a pain score of 5 received intravenous pethidine 0.5 mg/kg with a repeat dose of 0.5 mg/kg after 20 min if the agitation did not subside. Emesis was treated with intravenous metoclopramide 0.15 mg/kg. PAED score of 16 or greater was used to define EA. Incidence of adverse events [bradycardia, desaturation (SpO_2 <95%), vomiting, shivering, coughing, breath holding, laryngospasm] were also recorded.

We calculated 24 patients who were required to find a significant difference ($P<0.05$) ($\alpha=0.05$) with a power of 80% (β error=0.2) to detect a difference of 25% in the incidence of EA. Chi-square/Fischer exact test was applied for categorical variables. For continuous variables, ANOVA/non-parametric Kruskall-Wallis test was applied. Two-sample *t*-test/non-parametric Wisconsin Mann Whitney test was applied between the two groups. Statistical significance was determined at the level of $P<0.05$. Data was analyzed using SPSS statistical software version 12.0. All the data are expressed as mean+SD wherever applicable.

RESULTS

All three groups were comparable to each other with respect to demographic profile [Table 2], duration of surgery, duration of anaesthesia and time to establishment of regular breathing pattern [Table 3]. Mean time to awakening, defined as time from discontinuation of anaesthesia to time of initial arousal (eye opening, child showing purposeful movements), was significantly shorter with sevoflurane and desflurane compared with those with isoflurane anaesthesia (*P* value=0.001). Mean time to extubation, defined as time to extubation after discontinuation of anaesthesia, was significantly lesser in the sevoflurane and desflurane groups compared with the isoflurane group (*P* value=0.001). Time to awakening and extubation time were comparable between the sevoflurane and desflurane groups [Table 3].

Table 2: Demographic profile

	Group S	Group D	Group I	*P* value
Mean age (years)	3.45±1.95	3.68±1.84	3.5±1.74	0.849
Age distribution (<4 years/>4 years)	15:10	14:11	15:10	0.946
Weight (kg)	14.60±5.31	14.64±3.85	14.76±5.32	0.842
Male:Female	23:2	21:4	20:5	0.429
ASA I:ASA II	22:3	21:4	20:5	0.743

ASA: American Society of Anaesthesiologists

In our study, patients under desflurane anaesthesia met the discharge criteria faster (defined as time to reach Aldrette score ≥9) compared with patients under sevoflurane and isoflurane anaesthesia (*P* value=0.025). No difference was observed in time to home readiness in patients under sevoflurane and isoflurane anaesthesia. The duration of stay in PACU was comparable in the three groups (*P* value=0.207) [Table 3].

In our study, we observed no statistically significant difference in incidence of EA among sevoflurane, desflurane and isoflurane (*P* value=0.168). However, we did observe a higher incidence of EA with sevoflurane (40%) compared with desflurane (28%) and isoflurane (16%). There was no statistically significant difference in the intensity of EA among the three groups at any point of time, although sevoflurane tended to have higher PAED scores [Figure 1]. We observed no correlation between incidence of EA and duration of anaesthesia or age in any of the three groups [Table 3].

In our study, patients in the sevoflurane group tended to have higher pain scores compared with those in the isoflurane and desflurane groups. No significant difference in the pain scores was noted between the isoflurane and desflurane groups. We did not find a statistically significant difference in the requirement of rescue medications among the three groups (*P* value=0.186), although 11 (44%) of the patients under sevoflurane anaesthesia required analgesics compared with nine (36%) with desflurane and five (20%) with isoflurane [Table 3]. There was no incidence of intra-operative/post-operative adverse events in any of our patients.

DISCUSSION

We observed faster times to awakening and extubation

Table 3: Intra- and post-operative variables

	Group S	Group D	Group I	*P* value
Surgical time (min)	67.12±29.22	72.24±30.51	73.88±47.32	0.704
Anaesthesia duration (min)	80.08±34.40	87.12±38.18	88.04±51.04	0.854
Distribution of anaesthetic duration (<1 h to >1 h)	12:13	11:14	12:13	0.87
Time to regular breathing (min)	2.60±1.00	2.56±1.15	4.00±3.73	0.434
Time to awakening (min)	4.12±1.81	4.36±2.28	7.16±3.38	0.001
Time to extubation (min)	5.32±2.21	5.12±2.00	8.96±4.40	0.001
Time to meet discharge criteria (min)	24.40±9.60	18.60±7.14	24.00±8.78	0.025
Duration of stay in PACU (min)	43.40±12.13	36.84±8.93	39.04±8.65	0.207
Incidence of EA	10	7	4	0.168
Rescue analgesic requirement (patients)	11	9	4	0.186

PACU: Post-anesthesia care unit; EA: Emergence agitation

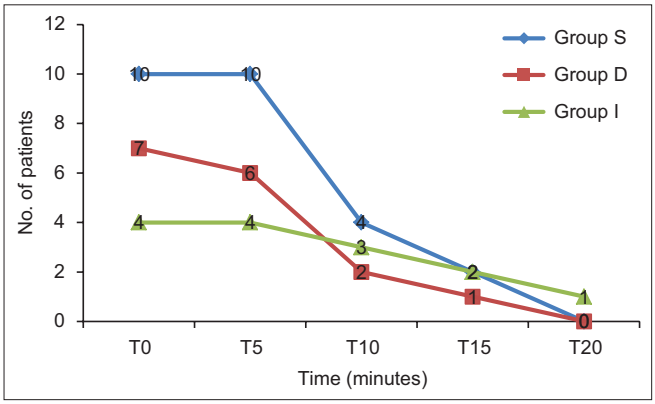

Figure 1: Incidence of EA over time

with sevoflurane and desflurane compared with isoflurane. This is expected as sevoflurane and desflurane are both less soluble compared with isoflurane and will be washed out more rapidly.[12-15] Bailey observed that after anaesthetic exposure of intermediate duration, the 80% decrement time for anaesthestic concentration of sevoflurane and desflurane is approximately 5 min; it is only in longer duration surgeries that decrement times for sevoflurane increases significantly, while it remains less than 10 min for desflurane.[16] Decrement times for isoflurane increases significantly after 60 min of exposure.[15,17]

Desflurane allowed for early recovery from anaesthesia. No difference in time to home readiness was observed between sevoflurane and isoflurane. Other investigators observed faster recovery after sevoflurane compared with isoflurane.[14,15,18] Our measurements might have been confounded by the fact that higher number of patients in the sevoflurane group required rescue analgesics in the post-operative period.

Rapid awakening did not translate to early discharge from PACU. Discharge may be affected by many other factors such as waiting for doctor's visit before discharge, type and duration of surgery, degree of physiological trespass, hospital practices depth of anaesthesia maintained and adjuvant used during anaesthesia. These factors can sometimes be more important than the choice of anaesthetics used.[10,11,19-21]

To our knowledge, no study has used PAED scale to compare incidence of EA among isoflurane, sevoflurane and desflurane. We did not find a significant difference in the incidence of EA among the three agents. In the literature, the results of incidence of EA among various anaesthetic agents are quite contradictory.[19-28] Wide variability in anaesthetic techniques, surgeries, definition and scales used to quantify EA, pre-operative medications, pain relief and methodology of data interpretation precludes comparison between clinical trials and affects reliability and validity of measurements. The difference in time intervals in which EA was measured also affects the results.[29]

Wellborn[10] observed a higher incidence of EA with desflurane compared with sevoflurane, while others reported no difference between the two agents.[30,31] Many authors have observed a higher incidence of EA with sevoflurane compared with isoflurane.[7,32] In contrast, Meyer observed no difference in the incidence of EA between sevoflurane and isoflurane,[19] while Valley observed a higher incidence with isoflurane compared with sevoflurane.[20] Other authors have observed a higher incidence with desflurane compared with isoflurane,[2,9,12] while we in our study found the incidence of EA to be comparable between the two agents.

We found EA to be a short-lived phenomena, peaking early in the post-operative period. EA generally occurs within the first 30 min after anaesthesia and is generally self-limiting, with a mean duration of 5–15 min[7,32,27] [Figure 1]. However, agitation and regressive behaviour lasting up to 2 days have also been described.[2,32]

Studies examining the effect of duration of anaesthesia on incidence of EA have yielded contradictory results.[3,11,23,33] Higher incidence has been observed in short-duration surgeries[21,24,34] and long-duration surgeries,[33,35] while some noted no effect of duration on incidence of EA.[7] EA has been attributed to shorter duration surgeries that allowed for rapid washout of anaesthetics from the body, causing rapid emergence before analgesics had time to act and reach their peak effect. We observed no correlation between EA and duration of anaesthesia. The incidence was comparable between surgeries lasting less than 1 h to those lasting longer. Inadequate analgesia appears to be an unlikely cause of EA in our study as pain was adequately taken care of with pre-emptive multimodal analgesia.

EA has been commonly observed in pre-school children. This may be attributed to the psychological immaturity coupled with the rapid awakening in a strange environment. Small children are easily confused and frightened by unexpected and unpredictable experiences. Martini attributed it to brain immaturity with a consequent decline in norepinephrine, acetylcholine, dopamine and gamma amino butyric acid (GABA) in the genesis of this phenomenon.[36] $GABA_A$ receptor could be excitatory rather than inhibitory in the early post-natal period.

We found no difference in the incidence of EA between children below 4 years and those above 4 years. The literature on the subject of association of age with EA is quite contradictory. Some authors found no association of age with EA.[24], while even in those studies where a positive correlation was observed, the range of "at risk age" varied considerably.[1,28,37]

The higher pain scores with consequent higher requirement of analgesics with sevoflurane may be due to more number of patients exhibiting features of EA, necessitating need for analgesics to calm them down. We did find a positive correlation between EA and higher pain scores; however, not all patients with higher FLACC scores had features suggestive of EA, similarly not all patients with EA had FLACC scores greater than 4 [Table 4]. Post-operative pain unlikely appears to be the cause of EA in our study as pain was adequately taken care of with pre-emptive rectal paracetamol and caudal block. Pain has been the most confounding variable that poses a diagnostic dilemma when assessing a child's behaviour upon emergence because of the overlapping clinical picture with EA, especially in pre-verbal children who cannot vocalize.[2]

Table 4: Correlation between EA and FLACC scores >4

Groups	FLACC score	PAED score <16	PAED score ≥16	*P* value
Group S	≤4	8	1	0.034
	>4	7	9	
Group D	≤4	14	2	0.034
	>4	4	5	
Group I	≤4	17	0	0.006
	>4	4	4	

EA: Emergence agitation; FLACC: Face, legs, activity, cry, consolability

Measurement tools to assess pain in pre-school children are observational scales and also to incorporate agitation as a part of their assessment; unfortunately, none of the pain scales have been tested to differentiate EA from pain. Studies have demonstrated a three- to four-fold decline in EA with pre-emptive analgesia, suggesting that pain may be its major source.[22,24,38] However, EA has also been recorded in patients undergoing non-painful interventions.[5,6] Pain during emergence may be the cause of EA in some patients, but may not be the sole etiology.

To conclude, incidence and intensity of EA did not reach statistical significance in any of the three groups. However, sevoflurane appears to have the highest propensity to cause EA among the three volatile anaesthetic agents, while incidence was least with isoflurane. Age and duration of anaesthesia do not appear to have any bearing on the incidence of EA. Although sevoflurane and desflurane lead to more rapid emergence from anaesthesia and shorter times to extubation when compared with isoflurane, it did not translate into early discharge from PACU. Discharge times were similar among the three groups. A higher number of patients in the sevoflurane group were agitated in the recovery period and required rescue medications compared with desflurane and isoflurane.

EA appears to be a multifactorial syndrome. More studies using appropriate definitions, validated scales and standardized protocols should be carried out to better understand this phenomenon in terms of its incidence and identify risk factors in the perioperative period, allowing us to selectively treat patients at risk.

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