Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

Emergence delirium in children: a randomized trial to compare total intravenous anesthesia with propofol and remifentanil to inhalational sevoflurane anesthesia

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Keywords
emergence delirium; total intravenous anesthesia; intravenous agents; sevoflurane; pain; child

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Section Editor: Jerrold Lerman

Accepted 3 November 2012

doi:10.1111/pan.12090

Summary

Background: Emergence delirium (ED) refers to a variety of behavioral disturbances commonly seen in children following emergence from anesthesia. Vapor-based anesthesia with sevoflurane, the most common pediatric anesthetic technique, is associated with the highest incidence of ED. Propofol has been shown to reduce ED, but these studies have been methodologically limited.

Objective: To conduct a randomized-controlled trial comparing the incidence of ED in children following sevoflurane (SEVO) anesthesia and propofol–remifentanil total intravenous anesthesia (TIVA).

Methods: One hundred and twelve children, ASA I-II, aged ≥ 2 and ≤ 6 years, undergoing strabismus repair, were assigned to receive TIVA (intravenous induction and maintenance of anesthesia with propofol and remifentanil) or SEVO (inhalational induction and maintenance of anesthesia with sevoflurane). Parent–child induction behavior was scored using the Perioperative Adult Child Behavior Interaction Scale (PACBIS). Postoperatively, ED was assessed by a masked investigator using the Pediatric Anesthesia Emergence Delirium (PAED) Scale and pain using the Face, Legs, Activity, Cry, Consolability (FLACC) Scale every 5 min.

Results: Data are reported for 94 subjects. Incidence of ED was higher with SEVO (38.3% vs 14.9%, $P = 0.018$). There was no difference in the median PACBIS score. A higher FLACC score was seen with SEVO (median 3 vs 1, $P = 0.033$). Subjects experiencing ED had higher FLACC scores vs those unaffected by ED (median 7 vs 1, $P < 0.0001$).

Conclusion: There was a lower incidence of ED after TIVA. Both intravenous and inhalational inductions were similarly well-tolerated. The use of TIVA was associated with reduced postoperative pain as measured using FLACC scores.

Introduction

Emergence delirium (ED) refers to the wide variety of behavioral disturbances seen in children following emergence from anesthesia, including restlessness, excitation, inconsolable crying, delusions, struggling, and moaning. Such behaviors can predispose children to lasting memory impairment and maladaptive behavior development (1). The incidence of ED in pediatric anesthetics, based on use of inhaled agents, may be as high as 40% and is highest in children aged 2–6 years (2).

All inhalational anesthetic agents commonly used in the developed world are associated with ED. Sevoflurane, the agent most commonly used for induction and

maintenance of anesthesia in the preschool pediatric population, is associated with the highest incidence of ED (2). The ability of many different agents to prevent or mitigate ED with sevoflurane anesthesia, including opioids (3,4), benzodiazepines (5), ketamine (6), α_2-agonists (7,8), and propofol boluses (9), have been investigated. The results from these studies show variable success, and the use of multiple ED observer assessment tools of varying validity and reliability makes comparison between studies difficult.

Total intravenous anesthesia (TIVA) using propofol and remifentanil appears to have a smooth recovery profile (10). Our primary hypothesis was that the incidence of ED would be less in children undergoing anesthesia with TIVA when compared to sevoflurane (SEVO) anesthesia. This hypothesis was tested by comparing the incidence of ED following SEVO anesthesia with propofol-remifentanil anesthesia (TIVA) using a well-validated ED outcome tool.

Methods

Following approval by institutional and university research and ethics boards, a double-blinded study was conducted at a single site tertiary care pediatric hospital. In accordance with the Declaration of Helsinki and the Health Canada Research Guidelines, a research assistant recruited 112 children with an ASA physical status class I or II, aged ≥ 2 and ≤ 6 years, undergoing elective strabismus surgery under general anesthesia. Patients with developmental delay, neurological injury, psychiatric diagnosis, abnormal lipid or carbohydrate metabolism, <3rd or >97th percentile weight for age, anxiety in the preoperative period requiring sedative premedication, previous anesthetic complications, contraindication to either anesthetic regime, or contraindication to Laryngeal Mask Airway use were excluded. Randomization sequence was created by a research assistant not involved in the study, in blocks of 94, using computer-generated random numbers, with group allocation concealed in sequentially numbered opaque envelopes. After informed written parental/guardian consent, subjects were randomized to receive induction and maintenance of anesthesia with either SEVO or TIVA. Subjects were eliminated from data analysis if there were any protocol deviations and an additional substitute subject was recruited. Preoperatively, each enrolled subject had local anesthetic (EMLA) cream applied to the intravenous (IV) access site on the dorsum of the hand. All subjects received a standard preoperative oral analgesic premedication of acetaminophen 20 $mg{\cdot}kg^{-1}$ and ibuprofen 10 $mg{\cdot}kg^{-1}$. A parent was present in the operating room (OR) for each induction.

TIVA induction and maintenance

After placement of an IV cannula, anesthesia was induced with a bolus of lidocaine 1 $mg{\cdot}kg^{-1}$ followed by propofol 5 $mg{\cdot}kg^{-1}$ and remifentanil 2.5 $\mu g{\cdot}kg^{-1}$. Anesthesia was maintained using an infusion of a fixed concentration solution of propofol 10 $mg{\cdot}ml^{-1}$ and remifentanil 5 $\mu g{\cdot}ml^{-1}$ and was titrated as per the staff anesthesiologist.

SEVO induction and maintenance

Anesthesia was induced with a mixture of 70% N_2O in 30% O_2 by mask for 60 s followed by incremental increases in inspired sevoflurane (1–7%). IV access was obtained and a bolus of lidocaine 1 $mg{\cdot}kg^{-1}$ was administered. Anesthesia was maintained by titration of sevoflurane with 40% O_2 in air as per the staff anesthesiologist.

Intraoperative anesthetic management

Following induction of anesthesia, all subjects received IV doses of glycopyrrolate 5 $\mu g{\cdot}kg^{-1}$, fentanyl 1 $\mu g{\cdot}kg^{-1}$ and ondansetron 0.1 $mg{\cdot}kg^{-1}$, and a Laryngeal Mask Airway was inserted. Supplementary doses of fentanyl 0.5 $\mu g{\cdot}kg^{-1}$ were administered each 30 min after the initial dose until the end of surgery, or at the discretion of the attending anesthesiologist. In addition to standard monitoring, the subjects' Entropy (GE Healthcare, Helsinki, Finland) values were recorded.

Behavior during anesthetic induction

The Perioperative Adult Child Behavior Interaction Scale (PACBIS) (Table S1) was used by an investigator to evaluate preinduction behavior of each subject and parent in the OR during the first 60 s of the anesthetic induction. This scale has been recently compared and validated favorably against a variety of behavioral assessment instruments (11) and addresses positive and negative parental behaviors in addition to child coping and distress behaviors. After appropriate training and familiarization with the tool, two investigators independently scored the first 20 inductions using the PACBIS to ensure agreement.

Postanesthesia behavior assessment and time points

The principle outcome variable of ED was evaluated with the Pediatric Anesthesia Emergence Delirium (PAED) Scale (12) (Table S2). This scale has been appropriately validated and used in multiple recent

studies of ED (9,13–15). Concurrently, postoperative pain intensity was assessed by means of the Face, Legs, Activity, Cry, Consolability (FLACC) Scale (16) (Table S3). After appropriate training and familiarization with the PAED and FLACC scales, two investigators independently scored the PAED, and an investigator and the postanesthesia care unit (PACU) bedside nurse independently scored the FLACC for the first 10 subjects to establish agreement.

Observational scoring began immediately following removal of the Laryngeal Mask Airway, which was at the discretion of the PACU nurse after the patient was observed to be alert enough to make purposeful movements. Subjects were observed by an investigator, who remained blinded to the anesthetic technique, for a total of 35 consecutive minutes following Laryngeal Mask Airway removal. The highest PAED and FLACC scores from the previous 5 min was recorded every 5 min during the 35 min observation period. A PAED score of ≥ 10 was defined as an ED event occuring. The PACU bedside nurse, who also remained blinded to the anesthetic technique, independently reported a FLACC score ≥ 4 and/or a FLACC score $\geq$ 7 in a structured postobservational interview, during which the PACU nurse was also asked to evaluate quality of the recovery profile (Table S4). The subject was discharged from the PACU when they met the institutional guidelines of level of consciousness and comfort. Times to Laryngeal Mask Airway removal and PACU discharge (min) were also recorded.

PACU rescue criteria and treatments

A standard IV rescue of ketamine 250 $\mu g \cdot kg^{-1}$ was administered when the PACU bedside nurse deemed the subject to be experiencing pain requiring analgesic rescue and/or for subjects experiencing ED and judged to be at risk of self-harm by the PACU nursing staff in conjunction with a physician investigator. Ketamine was chosen based on evidence of efficacy for both states (6,17). Any perioperative anesthetic complications, including laryngospasm, bronchospasm, bradycardia and arterial oxygen desaturation (defined as a pulse oximeter reading (SpO_2) of less than 90%), (min) were also recorded.

Study power and data management

Based on previous data, we calculated that recruitment of 95 subjects per arm powered the study to detect a 50% reduction in ED incidence (from 35% to 17%) at an alpha of 0.05 and beta of 0.8 (6,9,13,18,19). An interim analysis was planned after the recruitment and successful completion of 95 subjects to detect any dramatic benefits of either treatment. As the analysis was done following 50% of the recruitment, a P value of <0.025 was taken as demonstrating a dramatic benefit. This method is in keeping with CONSORT recommended expert reviews of interim analyses (20). Statistical analysis was performed using MedCalc® (MedCalc Software, Mariakerke, Belgium). Continuous parametric data and nonparametric ordinal data were analyzed with t-tests and Mann–Whitney U tests, respectively. The primary hypothesis was examined using Fisher's exact test. To quantify the severity and duration of the ED events, a graph of PAED score vs time was constructed for ED positive subjects in each group. The area under the curve (AUC) of TIVA and SEVO groups were compared using a Mann–Whitney U test. Examination of the subject data was performed by in-group analyses and not intention-to-treat, as only one subject did not receive the anesthetic technique to which they were randomized. Qualitative observations are summarized in narrative form and are not analyzed.

Results

One hundred and ninety-four patients were approached for consent between June 2009 and August 2011, of which 112 enrolled in the study. One subject was excluded before commencement of the study protocol due to failure to obtain IV access and 17 were excluded from further analysis. Data from 94 subjects are presented (Figure 1).

Demographic data and perioperative characteristics

The two groups were similar with respect to demographics and surgery type (Table 1). Regarding perioperative characteristics, in comparison with the TIVA group, the SEVO group had a lower mean state entropy value (51 ± 11 vs 41 ± 9, $P < 0.0001$). There were no differences between the groups with regard to the PACBIS score, duration of anesthesia, or total intraoperative fentanyl (Table 1).

Observational scoring: emergence delirium

The incidence of ED (maximum PAED $\geq$ 10) was higher in the SEVO group (38.3%) compared to the TIVA group (14.9%) (Fisher's exact test, $P = 0.018$) (Figure 2); thus, criteria were met for stopping study recruitment at the halfway point with a total of 94 subjects analyzed ($P < 0.025$). The number needed to treat (NNT) with TIVA to prevent one episode of ED is 4.3. A higher maximum PAED score was seen in the SEVO group (median, 8; interquartile range (IQR), 5–12) com-

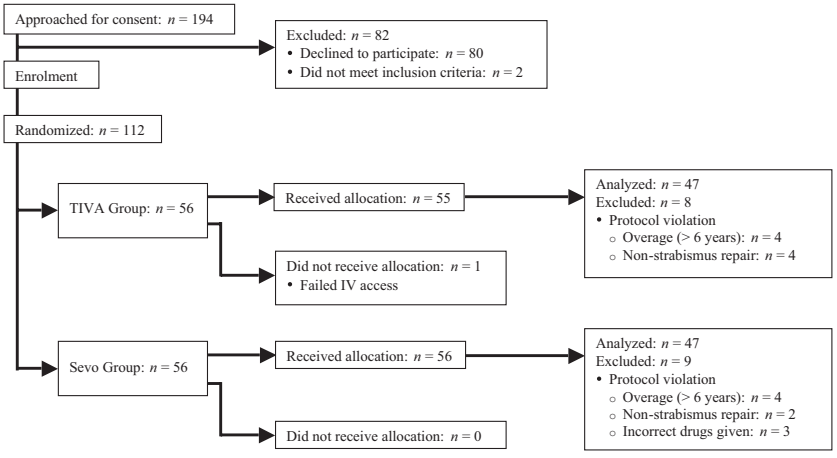

Figure 1 CONSORT flow diagram of patient recruitment and randomization.

Table 1 Patient demographics and perioperative characteristics

	TIVA	SEVO	*P* value
No. of patients	47	47	
Patient demographics			
Age[a] (years)	3.8 ± 1.3	4.2 ± 1.3	NS
Weight[a] (kg)	16.1 ± 3.2	17.7 ± 3.4	0.021
Sex (F:M)	30: 17	23: 24	NS
ASA PS (I:II)	39: 8	41: 6	NS
Strabismus repair (unilateral:bilateral)	8: 39	8: 39	NS
Perioperative characteristics			
PACBIS[b]	1 (0–2)	1 (1–3)	NS
State Entropy[a]	51 ± 11	41 ± 9	<0.0001
Duration of anesthesia[a] (min)	45 ± 14	44 ± 10	NS
	1.4 ± 0.5	1.5 ± 0.3	NS
Total intraoperative fentanyl[a] ($\mu g \cdot kg^{-1}$)			

TIVA, total intravenous anesthesia; SEVO, sevoflurane; F:M, female/male; ASA, American Society of Anesthesiologists; PS, physical status; PACBIS, Perioperative Adult Child Behavior Interaction Scale; NS, not statistically significant.
[a]Mean ± SD.
[b]Median (interquartile range).

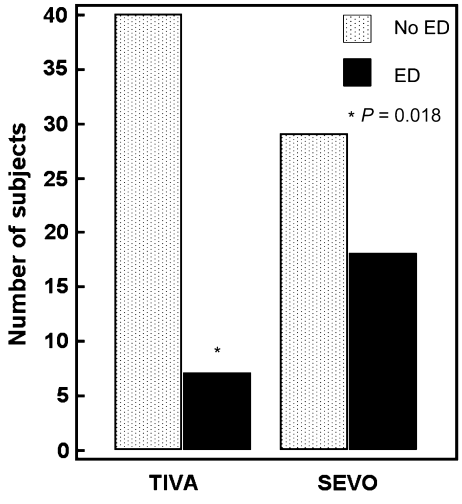

Figure 2 Incidence of emergence delirium (Maximum PAED ≥ 10) between SEVO and TIVA groups. PAED, Pediatric Anesthesia Emergence Delirium; SEVO, sevoflurane; TIVA, total intravenous anesthesia.

pared to the TIVA group (median, 6; IQR, 3–8) (Mann–Whitney *U* test, $P = 0.006$) (Figure 3). A comparison of AUC for severity of PAED score over time in ED positive subjects showed no difference between SEVO and TIVA (Mann–Whitney *U* test, $P = 0.52$). In the affected subjects, ED occurred at a mean recovery time between 5 and 10 min.

Observational scoring: pain

A higher maximum FLACC score (Mann–Whitney *U* test, $P = 0.033$) was observed in the SEVO group (median, 3; IQR, 1–6) compared to the TIVA group (median, 1; IQR, 0–4) (Figure 4). Subjects experiencing ED had a higher maximum FLACC score (median, 7; IQR, 4–8) compared to subjects unaffected by ED (median, 1; IQR, 0–3) (Mann–Whitney *U* test, $P < 0.0001$).

Rescue medications and other postoperative characteristics

Postoperative ketamine rescue was administered to six children (one TIVA, five SEVO, Fisher's exact test, $P = 0.111$). The primary reason for rescue, as identified by the investigator, was pain in three subjects (50%) and ED in three subjects (50%). Only one subject experienced postoperative vomiting. The TIVA group had a prolonged time to Laryngeal Mask Airway removal and longer duration of PACU stay compared to the SEVO

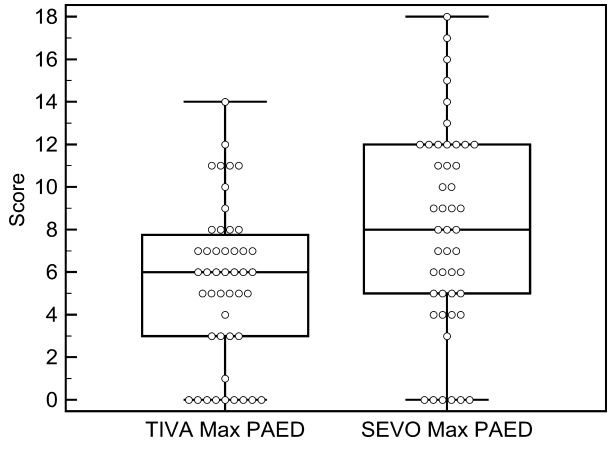

Figure 3 Distribution of Maximum PAED scores between SEVO and TIVA groups. PAED, Pediatric Anesthesia Emergence Delirium; SEVO, sevoflurane; TIVA, total intravenous anesthesia.

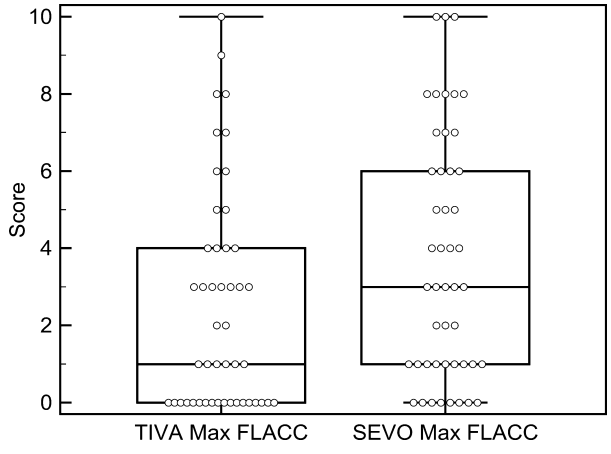

Figure 4 Distribution of Maximum FLACC scores between SEVO and TIVA groups. FLACC, Faces, Legs, Activity, Cry, and Consolability; SEVO, sevoflurane; TIVA, total intravenous anesthesia.

group ($P = 0.044$ and $P = 0.0004$, respectively) (Table 2).

Qualitative data

There was a poor relationship between PACU nurse questionnaire data and PAED score with regard to diagnosis of ED, with PACU bedside nurses reporting a total of three incidences of ED, whereas 25 subjects had a PAED score ≥ 10.

Discussion

The principle finding of this randomized-controlled trial was a lower incidence of ED after TIVA compared to SEVO in children between 2 and 6 years of age after strabismus surgery. Based on these results, we terminated our trial at the halfway point. Using the PAED score as the principle outcome measure, the NNT to avoid ED with TIVA treatment is 4.3. Both groups were comparable in terms of the behavior of parents and subjects at induction (PACBIS scores). Additional differences noted between the study arms included a higher maximum pain (FLACC) score in the SEVO group and prolonged times to Laryngeal Mask Airway removal and PACU discharge in the TIVA group.

Previous investigation of propofol to reduce ED has shown that propofol-only anesthesia maintenance infusions (21–24) have unpredictable effects on the incidence of ED. The most recent studies published demonstrated no significant effect (21,24) while others have reported both an increased (23) and decreased (22) incidence of ED in comparison with volatile anesthesia maintenance. These studies, however, are potentially flawed due to multiple confounding factors, including the use of inhalational inductions in all subjects (21,23,24), uncontrolled midazolam anxiolysis (24) and the use of poorly validated ED assessment tools (22). In contrast, single postoperative propofol boluses (9,13) given at the end of inhalational anesthesia have been reported to be efficacious at reducing ED when compared with sevoflurane alone; these, however, are affected with similar methodological problems to the prior propofol infusion studies. We chose to use propofol-remifentanil TIVA instead of propofol alone as it is our experience that this combination is more frequently used in clinical practice. In addition, the increased doses of propofol necessary when used as a sole agent in children

Table 2 Recovery outcomes

	TIVA	SEVO	*P* value
Time from end of anesthesia to Laryngeal Mask Airway removal[a] (min)	25 ± 11	21 ± 10	0.044
Maximum FLACC Score[b]	1 (0–4)	3 (1–6)	0.034
PAED $\geq$ 10[c]	7 (14.9)	18 (38.3)	0.018
Received postoperative ketamine rescue[c]	1 (2.1)	5 (10.6)	NS
Time from end of anesthesia to PACU discharge[a] (min)	68 ± 28	50 ± 16	0.0004

TIVA, total intravenous anesthesia; SEVO, sevoflurane; FLACC, Faces Legs Activity Cry and Consolability Pain Scale; PAED, Pediatric Anesthesia Emergence Delirium Scale; PACU, Post Anesthesia Care Unit; NS, not statistically significant.
[a]Mean ± SD.
[b]Median (interquartile range).
[c]*n* (%).

result in markedly prolonged time to emergence from anesthesia.

The assessment of ED in previous studies has been accomplished using a range of scales, the most frequently used of which is the PAED scale (25). There are frequent criticisms of this scale, including the inherent subjectivity in scoring each behavior item and suboptimal inter-observer reliability (26). The development of ED scales are fundamentally hindered by choice of a validation method. Given that there is no objective way to diagnose ED, all observational ED assessment tools are compared with the opinion of an experienced clinician (25) or clinicians (12). Additionally, the behavior categories of the PAED score overlap with those of pain scales (16). The results of our study demonstrate a significant correlation between FLACC and PAED scores. Recently, an attempt has been made to improve ED diagnosis by basing scoring on the definition of delirium in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (26). In this study, as in the majority of previous ED studies, a DSM-IV delirium tool was not used concurrently but may be an appropriate direction for future studies.

The type of anesthetic technique administered to each group appeared to have a significant effect on the incidence of postoperative pain as measured by the FLACC score. A higher FLACC score was measured in the SEVO group when compared to the TIVA group (median, 3 vs 1; IQR, 1–6 vs 0–4; $P = 0.034$). This finding is not novel; Pieters *et al.* (24) previously found that propofol anesthesia reduced the need for rescue analgesia as determined by the Children's Hospital of Eastern Ontario Scale (CHEOPS) in the postoperative period. The reason for the apparent analgesic effect of propofol TIVA and its effect on ED may be similar. Consolability and activity/restlessness are scored on both the FLACC and PAED scales. It may be the case that by facilitating a smoother emergence, TIVA also reduces measured pain scores through improving these behaviors. It is our contention that the smoother emergence we demonstrated in the TIVA group is more likely due to reduced ED. We have made every effort to ensure that pain experienced in each group is similar: both groups had no significant difference between fentanyl doses received, the incidence of bilateral vs unilateral surgery, or incidence of receiving topical analgesia. Alternately, propofol may exert a genuine analgesic effect. The possibility that remifentanil is still exerting an analgesic effect in the TIVA group seems unlikely, as the scoring did not commence until an average of 25 min following discontinuation of remifentanil infusion. The pharmacodynamic offset of remifentanil is of the order of 5–6 min (27).

Preoperative scoring using the revised PACBIS (11) demonstrated that both IV and inhalational inductions were tolerated similarly well in these unsedated children. The revised PACBIS was used because it is an uncomplicated, real-time, unambiguous instrument to assess and quantify the behavioral status of, and interactions evident in, the child–parent unit during the potentially distressing perioperative period. This scale has been validated extensively against a range of scales examining child and parental anxiety, behavior and coping in the perioperative period. Interestingly, a relationship between preoperative PACBIS scores and ED was not found, a finding that agrees with recent work on this scale (11). Sedative premedication was avoided in the study population due to the unpredictable effect on ED that has been previously observed (5,28). A higher State Entropy score was recorded in the TIVA group, the significance of which is unclear. It has been demonstrated that levels of compressed electroencephalogram data are not associated with incidence of ED (29). The low incidence of in-hospital postoperative nausea and vomiting (PONV) measured in our population (1%) with the use of single-agent anti-emetic prophylaxis with ondansetron is reassuring. The longer times to Laryngeal Mask Airway removal and PACU discharge seen in our study are similar to previous studies of propofol infusions (21). The improved postoperative experience delivered to subjects in the TIVA group, at the expense of a brief increased time in the PACU is, in our opinion, a price worth paying. Given the literature demonstrating the long-term psychological effects of ED episodes, the positive effect of TIVA on these outcomes should be encouraged.

The postoperative masking of anesthesia technique may not have been complete, as the bedside PACU nurse reported the odor of expired sevoflurane in some subjects. This may have biased nursing observations surrounding pain outcomes and their qualitative assessments, although investigators scoring the PAED were situated at the foot end of the subjects, did not detect any odor, and every effort was made to ensure their blinding. The lack of agreement between the PACU bedside nurses and the PAED score as to which subjects were experiencing ED was an unexpected finding. This again speaks to the need for a more reliable, sensitive, and specific outcome tool.

This investigation has shown that induction and maintenance of anesthesia with propofol–remifentanil TIVA decreased the incidence of ED when compared to sevoflurane in this patient population. Coincident with this was a reduction in postoperative pain as measured with a standard pediatric postoperative pain score.

Acknowledgments

This work was supported by a BC Children's Hospital Telethon Award. The authors are indebted to many BC Children's Hospital staff members, particularly Elizabeth Lamb, nurses in the PACU and the SDCU, ophthalmologists, anesthesiologists, and research staff, including Kate Hunc, Erin Cooke, Jonathan Stinson, Nicholas West, Eugene Choo and Elizabeth Du. This research was carried out without funding.

Conflict of interest

No conflicts of interest declared.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1 Perioperative Adult Child Behavior Interaction Scale (PACBIS).

Table S2 The Pediatric Anesthesia Emergence Delirium (PAED) Scale.

Table S3 The Faces, Legs, Activity, Cry, and Consolability (FLACC) Pain Scale.

Table S4 Post Anesthesia Care Unit (PACU) Nursing Interview.

References

1 Kain ZN, Caldwell-Andrews AA, Maranets I *et al*. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. *Anesth Analg* 2004; **99**: 1648–1654.
2 Vlajkovic GP, Sindjelic RP. Emergence delirium in children: many questions, few answers. *Anesth Analg* 2007; **104**: 84–91.
3 Demirbilek S, Togal T, Cicek M *et al*. Effects of fentanyl on the incidence of emergence agitation in children receiving desflurane or sevoflurane anaesthesia. *Eur J Anaesthesiol* 2004; **21**: 538–542.
4 Picard V, Dumont L, Pellegrini M. Quality of recovery in children: sevoflurane versus propofol. *Acta Anaesthesiol Scand* 2000; **44**: 307–310.
5 Breschan C, Platzer M, Jost R *et al*. Midazolam does not reduce emergence delirium after sevoflurane anesthesia in children. *Pediatr Anesth* 2007; **17**: 347–352.
6 Abu-Shahwan I, Chowdary K. Ketamine is effective in decreasing the incidence of emergence agitation in children undergoing dental repair under sevoflurane general anesthesia. *Pediatr Anesth* 2007; **17**: 846–850.
7 Kulka PJ, Bressem M, Tryba M. Clonidine prevents sevoflurane-induced agitation in children. *Anesth Analg* 2001; **93**: 335–338.
8 Shukry M, Clyde MC, Kalarickal PL *et al*. Does dexmedetomidine prevent emergence delirium in children after sevoflurane-based general anesthesia? *Pediatr Anesth* 2005; **15**: 1098–1104.
9 Abu-Shahwan I. Effect of propofol on emergence behavior in children after sevoflurane general anesthesia. *Pediatr Anesth* 2008; **18**: 55–59.
10 Eyres R. Update on TIVA. *Pediatr Anesth* 2004; **14**: 374–379.
11 Sadhasivam S, Cohen LL, Hosu L *et al*. Real-time assessment of perioperative behaviors in children and parents: development and validation of the perioperative adult child behavioral interaction scale. *Anesth Analg* 2010; **110**: 1109–1115.
12 Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology* 2004; **100**: 1138–1145.
13 Aouad MT, Yazbeck-Karam VG, Nasr VG *et al*. A single dose of propofol at the end of surgery for the prevention of emergence agitation in children undergoing strabismus surgery during sevoflurane anesthesia. *Anesthesiology* 2007; **107**: 733–738.
14 Meyer RR, Münster P, Werner C *et al*. Isoflurane is associated with a similar incidence of emergence agitation/delirium as sevoflurane in young children–a randomized controlled study. *Pediatr Anesth* 2007; **17**: 56–60.
15 Kol IO, Egilmez H, Kaygusuz K *et al*. Open-label, prospective, randomized comparison of propofol and sevoflurane for laryngeal mask anesthesia for magnetic resonance imaging in pediatric patients. *Clin Ther* 2008; **30**: 175–181.
16 Merkel SI, Voepel-Lewis T, Shayevitz JR *et al*. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs* 1997; **23**: 293–297.
17 Roelofse JA. The evolution of ketamine applications in children. *Pediatr Anesth* 2010; **20**: 240–245.
18 Cohen IT, Finkel JC, Hannallah RS *et al*. Rapid emergence does not explain agitation following sevoflurane anaesthesia in infants and children: a comparison with propofol. *Paediatr Anaesth* 2003; **13**: 63–67.
19 Cole JW, Murray DJ, McAllister JD *et al*. Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. *Paediatr Anaesth* 2002; **12**: 442–447.
20 Schulz KF, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. *Lancet* 2005; **365**: 1657–1661.
21 König MW, Varughese AM, Brennen KA *et al*. Quality of recovery from two types of general anesthesia for ambulatory dental surgery in children: a double-blind, randomized trial. *Pediatr Anesth* 2009; **19**: 748–755.
22 Nakayama S, Furukawa H, Yanai H. Propofol reduces the incidence of emergence agitation in preschool-aged children as well as in school-aged children: a comparison with sevoflurane. *J Anesth* 2007; **21**: 19–23.
23 Hasani A, Ozgen S, Baftiu N. Emergence agitation in children after propofol versus halothane anesthesia. *Med Sci Monit* 2009; **15**: CR302–CR306.
24 Pieters BJ, Penn E, Nicklaus P *et al*. Emergence delirium and postoperative pain in children undergoing adenotonsillectomy: a comparison of propofol vs sevoflurane anesthesia. *Pediatr Anesth* 2010; **20**: 944–950.
25 Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. *Pediatr Anesth* 2010; **20**: 704–711.
26 Malarbi S, Stargatt R, Howard K *et al*. Characterizing the behavior of children emerging with delirium from general anesthesia. *Pediatr Anesth* 2011; **21**: 942–950.
27 Kapila A, Glass PS, Jacobs JR *et al*. Measured context-sensitive half-times of remifentanil and alfentanil. *Anesthesiology* 1995; **83**: 968–975.
28 Cohen IT, Drewsen S, Hannallah RS. Propofol or midazolam do not reduce the incidence of emergence agitation associated with desflurane anaesthesia in children undergoing adenotonsillectomy. *Paediatr Anaesth* 2002; **12**: 604–609.
29 Faulk DJ, Twite MD, Zuk J *et al*. Hypnotic depth and the incidence of emergence agitation and negative postoperative behavioral changes. *Pediatr Anesth* 2010; **20**: 72–81.