



Emergence delirium: an overview with an emphasis on the use of electroencephalography in its management

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Emergence delirium remains a clinically significant issue, often leading to short-term distress among pediatric patients, parents, and staff, and potentially resulting in postoperative maladaptive behaviors persisting for weeks to months. Although several diagnostic tools are available, the Pediatric Anesthesia Emergence Delirium Scale is most often utilized. Many risk factors contributing to the likelihood of a pediatric patient developing emergence delirium have been identified; however, its accurate prediction remains challenging. Recently, intraoperative electroencephalographic monitoring has been used to improve the prediction of emergence delirium. Similarly, it may also prevent emergence delirium if the anesthesiologist ensures that the at-risk patient rouses only after the onset of appropriate electroencephalogram patterns, thus indicating a change to natural sleep. Prediction of at-risk patients is crucial; preventing emergence delirium may begin early during patient preparation by using non-pharmacological methods (i.e., the ADVANCE program). Intraoperative electroencephalographic monitoring can predict emergence delirium. This review also discusses a range of pharmacological treatment options which may assist the anesthesiologist in preventing emergence delirium among at-risk patients.

Keywords: Emergence agitation; Emergence delirium; Emergence excitement; Electroencephalogram; Electroencephalography; Pediatric anesthesia; Post operative delirium.

INTRODUCTION

In 1945, Levy first described a phenomenon whereby some children who had come for an operative procedure subsequently suffered from behavioral problems [1]. Eight years later, Eckenhoff investigated the link between anesthesia induction and postoperative personality changes [2]. In 1960, he described this phenomenon as "emergence excitement", which was characterized by restlessness, disorientation, crying, moaning, and irrational talking [3].

Emergence delirium (ED) and emergence agitation (EA)

have been extensively studied to identify risk factors as well as anesthetic techniques and management regimens to reduce their incidence. However, an increasing move towards personalized anesthesia has led researchers to investigate the process of wakefulness, particularly for predicting which patients would experience ED or EA with greater certainty.

In this review, we summarize the risk factors for ED or EA, examine the latest evidence for their prediction among pediatric patients, and discuss practical strategies for their management.

ARE ED AND EA THE SAME?

The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) defines “agitation” as excessive motor activity associated with feelings of inner tension; “delirium” is defined as a state in which a person has disturbances in attention and awareness (i.e., reduced ability to direct, focus, sustain, and shift attention), with associated cognitive changes (i.e., disorientation and language disturbance) and perceptual disturbances. ED is an acute state of confusion after emergence from anesthesia, in which patients experience hallucinations, restlessness, disorientation, and hyperexcitable behavior [4].

“ED and EA are often used interchangeably [5], although they are not the same. After anesthesia, a child may have EA, but not ED (e.g., when they are anxious, in pain, or uncomfortable, but without changes in cognition). A child may have ED without EA, also referred to as “hypoactive delirium”, which may be easily missed as the child appears “quiet.” Finally, children may experience both EA and ED. However, EA, which is much more apparent, can be seen in children who are in pain, tired, or angry, but not delirious.

INCIDENCE AND DIAGNOSIS OF ED

The incidence of ED ranges from 10 to 89% [6-8]. This variability is due to the heterogeneity in studies investigating the incidence, particularly the various rating scales and cut-off points used for diagnosis.

Several scales have been used, including the Riker Sedation-Agitation Scale, Richmond Agitation-Sedation Scale, WATCHA Scale, and CRAVERO scales [4,5]. One of the most commonly used scales is the Pediatric Anesthesia Emergence Delirium Scale (PAEDS); it is one of the few validated tools used to assess ED in pediatric patients undergoing general anesthesia. The PAEDS is a five-point scale whereby higher scores correlate with an increased likelihood of ED [9]. Even when using the PAEDS for diagnosing ED, various cut-off values of < 10 , ≥ 10 , and ≥ 12 have been used, thereby adding to the complexity in diagnosing ED.

Han et al. [10] used PAEDS score cutoffs to compare EA and ED. They used a PAEDS score > 10 to diagnose patients with ED, whereas those who scored > 2 were diagnosed with EA. In their study on electroencephalogram (EEG)-guided anesthesia, the incidence of EA was similar between the groups; however, ED was lower in the EEG-guided group than in the control group.

A meta-analysis by Russell et al. [11] evaluating the diagnostic accuracy of PAEDS for ED found that its pooled sensitivity and specificity were 91% and 94%, respectively, thus indicating a robust diagnostic scale. However, an observational study in a cohort of 4,424 children found that the incidence of ED was 1.7%, of which 23% of all ED were hypoactive in nature [12]. None of these cases were identified by the PAEDS scale, but by the Cornell Assessment of Pediatric Delirium.

The clinical implications of hypoactive delirium in children remain unclear. While hypoactive delirium has been widely studied in adults in the intensive care unit setting, it has been studied less frequently in children, particularly in the post-anesthesia care unit (PACU). In a prospective longitudinal study of 1,547 patients, 267 were diagnosed with delirium, of whom 46% were hypoactive, 8% were hyperactive, and 45% had mixed subtypes. Delirium is an independent predictor of mortality among critically ill children. It is also associated with morbidity, increased length of hospital stay, and long-term cognitive impairment [13]. However, these were studies on critically ill children, which are a different population from those in the PACU.

RISK FACTORS OF ED

Patient factors

Patient and parental anxiety as well as negative patient or parent interactions with healthcare providers have been found to contribute to ED risk [14]. A child’s behavior and temperament were also identified as risk factors for ED. Those who were more emotional, impulsive, and less adaptable to change were more likely to develop ED, wherein preschool ages of 2–5 had the highest incidence [8].

Surgical factors

The type of surgery has been implicated in ED, particularly ophthalmic and otorhinolaryngological surgeries. In particular, strabismus and adenotonsillectomy surgeries have been shown to have high rates of ED [15].

Postoperative pain was strongly associated with ED [5,16]. Pain control is suggested to be one of the mainstays of ED treatment and prevention. However, it is important to differentiate between ED and postoperative pain to prevent delayed treatment and inadequate analgesia [17].

Certain components of the PAEDS are descriptors in the

pain assessment tools (i.e., Face, Legs, Activity, Cry, and the Consolability Scale [FLACC]), thus complicating accurate diagnosis. For example, a restless child would score points on the PAEDS for an ED diagnosis. The same child would also score points on the FLACC under “Activity”, which describes a child squirming, moving back and forth, or having an arched back and jerking, and under “Legs”, which describes a child with restless legs. In addition, “Inconsolability” was a component of both scales. Somaini et al. [17] conducted a retrospective analysis of observational studies to differentiate ED from postoperative pain by simultaneously applying the PAEDS, FLACC, Children’s and Infants’ Postoperative Pain Scale (CHIPPS) and the Children’s Hospital of Eastern Ontario Pain Scale (CHEOPS). They found that in PAEDS, two components were particularly important: having no eye contact and no awareness of the surroundings. These components had 99% sensitivity and 63% specificity for identifying ED, but only 32% sensitivity and 39% specificity for pain detection [17]. However, other studies have found that regional anesthesia or pre-emptive analgesia reduces the incidence of ED. Il-Sook et al. [18] found that sub-Tenon injections reduced the incidence of EA in patients undergoing strabismus surgery.

It is likely that pain worsens ED. As such, pain may be a confounder rather than a risk factor for ED; it is difficult to differentiate between the two entities during diagnosis due to overlapping clinical features. ED was also observed in a significant proportion of pediatric patients undergoing general anesthesia for non-painful procedures such as scans [19,20].

Anesthetic factors

Volatile anesthetics, particularly those with low blood-gas solubility coefficients such as sevoflurane and desflurane, have been identified as risk factors for emergence delirium [8]. In a prospective, observational, cohort study by Zhang et al. [21], the sevoflurane end-tidal area under the curve-exposure time was independently associated with EA in a dose-response relationship. Anesthesiologists should aim to use the minimum effective concentration and duration of sevoflurane anesthesia to achieve adequate depth of anesthesia for their patients. Nitrous oxide was also not associated with EA in children. A prospective, observational study by Park et al. [22] compared the incidence of EA in two groups of children undergoing adenotonsillectomy using sevoflurane anesthetic alone versus sevoflurane plus ni-

trous oxide. They found no statistically significant difference in EA diagnosed using PAEDS between the two groups [22]. Another study by Kilic [23] also found no significant difference in EA diagnosed using PAEDS between the sevoflurane air and the sevoflurane plus nitrous oxide groups undergoing elective ophthalmic surgery.

Reversal agents for muscular paralysis, such as neostigmine, atropine, and sugammadex, are commonly administered at the conclusion of surgery. In adult studies, anticholinergics have been shown to be associated with ED [24,25]; however, there is insufficient data among pediatric populations. A randomized, placebo-controlled, clinical trial comparing atropine to normal saline showed slightly higher rates of ED among children administered atropine [26]; however, more studies are required to draw definitive conclusions. A retrospective, case-control study comparing the use of neostigmine with atropine and sugammadex in patients undergoing strabismus surgery found no significant differences in the incidence or severity of EA [27]. A subsequent, small randomized controlled trial (RCT) of 70 children undergoing adenotonsillectomy found that the use of sugammadex resulted in less EA [28].

SHORT- AND LONG-TERM EFFECTS OF ED

ED is generally self-limiting, resolving within 15–30 min. However, its occurrence is distressing. Physical harm, such as dislodgement of intravenous sites, surgical dressings, and drains, may occur. This may result in increased bleeding or pain at surgical sites. It can also cause both physical and emotional harm to those caring for the patient, such as hospital staff or caregivers. In a qualitative research done on 16 adult caregivers and one child regarding their postoperative experiences during and after ED, a parent described the child as “the devil having jumped into him – he was pitch black”; another felt fear and insecurity, and said that “he was distant”, and “we weren’t connected at all” [29]. Feelings of powerlessness and guilt were also dominant; many parents expressed their lack of knowledge on how to address the situation or that none of their management strategies alleviated the ED symptoms.

Although ED is self-limiting and lasts for only a short period postoperatively, studies suggest that patients with ED are at an increased risk of postoperative maladaptive behaviors [4]. Kain et al. [30] prospectively studied children undergoing surgery under anesthesia and collected data on proper-

ative anxiety, emergence status, and postoperative behaviour. They found that in children with ED, there was an odds ratio of 1.43 of having new-onset postoperative maladaptive behavior changes, as compared to children without ED. Postoperative maladaptive behaviors include general anxiety, nighttime crying, enuresis, and sleeping and eating problems. In a separate study, the authors found that postoperative negative behavioral changes could persist for a long time; 54% of children exhibited negative behavioral responses at 2 weeks postoperatively, where 20% continued to demonstrate these behaviors at 6 months and 7.3% persisted at the 1-year follow-up [31].

PREDICTION OF ED

Recently, interest in the use of EEG to predict ED has surged. In 1937, Gibbs et al. [32] found marked EEG alterations following drug administration, including analgesic and anesthetic agents. Since then, EEG monitoring has been of interest in controlling the depth of anesthesia and sedation; EEG monitoring during anesthesia has gradually risen in popularity.

Emergence from anesthesia is not the reverse of anesthesia induction. General anesthesia is often compared to natural sleep, with EEG waves observed after anesthetic administration resembling those seen during sleep. Transitions in the brain's arousal state occur daily after sleeping. Sleep inertia, a state of transition characterized by a temporary reduction in performance, sleepiness, and confusion, often occurs. There is a concept of "neural inertia", described after anesthesia, in which the brain has a tendency to resist change in its arousal state; this is seen when emergence from anesthesia occurs at much lower anesthetic doses than those required for induction. Even when awakening from natural sleep, waking from slow-wave sleep appears to have the most profound negative impact on subsequent vigilance and performance [33].

Guidelines recommend routine EEG monitoring in paralyzed patients undergoing total intravenous anesthesia with propofol [34]. The popularity of EEG has extended to pediatric patients. However, while there are numerous processed "depth of anesthesia" index available for use in adults which have been adapted for use in children, it remains unclear whether their proprietary algorithms can be applied to pediatric patients [35]. Preliminary evaluation studies suggest that utilizing the bispectral index (BIS) may be possible in infants and children [36], although its use remains contro-

versial. Paradoxically, BIS has been seen to increase with the depth of sevoflurane, rising from 3.0 to 4.0% [37]. Expert guidance has suggested utilizing raw EEG waveforms and spectrogram monitoring to adjust anesthetics in children [38].

Martin et al. [39] previously used EEG monitoring to characterize the EEG signals in ED patients. Results showed attenuation of delta activity after the cessation of sevoflurane, with a subsequent indeterminate state characterized by diffuse, mixed alpha, and beta activity. In the ED group, patients arose from anesthesia in this indeterminate state before the onset of natural sleep-like EEG patterns. In contrast, those in the control group awoke from EEG patterns suggestive of sleep-like or drowsy states (i.e., theta or delta activity with spindles) after this indeterminate state [39].

A recent small RCT found that using spectral edge frequency (SEF), density spectral array (DSA), and raw EEG data for pediatric anesthesia reduced the incidence of ED. In their study, sevoflurane anesthesia was adjusted by titrating the SedLine SEF to 10–15, in addition to monitoring the DSA power spectra and raw EEG in the interventional group versus standard care (blinded to the SedLine screen). The PAED scores within 5 mins after extubation were lower in the interventional group [10]. Another RCT found that children undergoing BIS-guided endoscopic adenoidectomy under general anesthesia developed ED less frequently, with 12.8% (11/86) in the intervention group ($P=0.001$) developing ED as compared to 35.1% (27/77) in the control group. The intervention group also had lower overall PAED scores than the control group [40]. This was similar to the findings in adults; intraoperative neuromonitoring and a reduction in extremely low BIS values were associated with a lower incidence of delirium [41]. However, intraoperative burst suppression, although predictive of postoperative delirium in adults [42], has not been shown to predict ED in children in a prospective, observational study of 97 children aged 0.5–8 years [43]. A larger observational study of 648 patients aged 36 months and younger, which analyzed isoelectric events occurring during general anesthesia, confirmed no association with emergence behaviour [44].

In a study published in 2020 by Kim et al. [45], the relative power of the delta wave, the power ratio of low-to high-frequency EEG waves, and the ratio of delta to alpha EEG waves had a positive linear relationship with the occurrence of ED. As upper alpha oscillations in thalamocortical feedback loops indicated search and retrieval of memory processes [46], this led to the speculation that the low relative power of

alpha waves with high relative power of delta waves observed during emergence from anesthesia might impair cognitive and memory functions, thus leading to ED [45]. This suggested that EEG monitoring and pattern observation may help predict patients who were likely to develop ED.

PREVENTION OF ED

In search of ways to prevent ED, studies have looked into non-pharmacological measures as well as pharmacological interventions with midazolam, opioids, alpha2-agonists, melatonin, and the choice of anesthetic agent to prevent ED, either as a monotherapy or in combination with other therapies.

NON-PHARMACOLOGICAL MANAGEMENT OF ED

The ADVANCE program also resulted in significantly lower anxiety levels and a reduced incidence of ED after surgery; “ADVANCE” represents anxiety reduction, distraction on the day of surgery, video modeling and education before the day of surgery, adding parents to the child’s surgical experience and promoting family centered care, no excessive reassurance, coaching of parents by researchers to help them succeed, and shaping of the child via induction mask practice [47].

PHARMACOLOGICAL MANAGEMENT OF ED

In the following sub-sections we introduce some drugs used for the management of ED, of which, a summary table and suggested dosing can be found in [Table 1](#).

Midazolam

Midazolam has been extensively studied; however, its monotherapy has not been shown to reduce EA/ED [48]. However, midazolam shows promise as a combination therapy [49], likely due to its anxiolytic effects.

Opioids such as fentanyl and remifentanyl

A meta-analysis by Tan et al. [50] in 2015 suggested that fentanyl could significantly decrease the incidence of EA, albeit prolonging emergence time. Studies examining sevoflu-

rane anesthesia with or without remifentanyl infusion have found that EA was significantly lower with the addition of remifentanyl; however, it was uncertain whether this was due to the requirement for decreased sevoflurane concentrations when adding remifentanyl intraoperatively [51,52].

Alpha-2 agonists

In a double-blind RCT comparing dexmedetomidine to normal saline in patients undergoing adenotonsillectomy, dexmedetomidine was found to significantly decrease the incidence of ED and reduce negative postoperative behavioral changes measured at 1 and 7 days after discharge; however, it also significantly prolonged extubation time [53]. A meta-analysis of dexmedetomidine on EA in children after sevoflurane anesthesia concluded that dexmedetomidine reduced EA as compared with placebo; however, it also resulted in a significantly delayed effect on emergence time, time to extubation, and time to discharge from the recovery room. There was also no significant difference in EA risk between dexmedetomidine and fentanyl or midazolam [54].

In a small RCT done in patients undergoing magnetic resonance imaging (MRI), comparing dexmedetomidine 0.3 mcg/kg at induction against propofol 1 mg/kg at the end of general anesthesia against a normal saline bolus, there were

Table 1. Summary of Suggested Pharmacological Interventions to Prevent Emergence Delirium

Intervention	Examples for dosing
Midazolam	Not shown to be useful as monotherapy; however, it has a role as a pre-medication with Oral Midazolam, 0.5 mg/kg (maximum 20 mg), to decrease pre-operative anxiety or when used as part of a combination therapy with dexmedetomidine and an antiemetic or with propofol and an antiemetic.
Dexmedetomidine	Intraoperative infusion of dexmedetomidine, 0.2–1 mcg/kg/h or 0.3–0.5 mcg/kg bolus, prior to reversal
Clonidine	Intraoperative, 1–3 mcg/kg
Propofol	Intraoperative maintenance with propofol (total intravenous anesthesia) or transition to Intravenous (IV) propofol, 3 mg/kg in divided doses over 3 mins at the end of sevoflurane anesthesia
Opioids	Preoperative or intraoperative intranasal Fentanyl, 2 mcg/kg, or IV Fentanyl, 1–2.5 mcg/kg
Melatonin	Preoperative Oral Melatonin, 0.3–0.5 mg/kg

no significant differences in the incidence or severity of ED among the three groups. The only significant predictor found was the time to awaken from general anesthesia, with every minute increase in wake-up time reducing the odds of ED by 7% [10].

Single-dose dexmedetomidine administration in children undergoing adenotonsillectomy [55] and lower abdominal or genital surgery [56] was found to reduce the incidence of ED; however, in these studies, opioids are likely to have also been administered, which would not have been given to children undergoing MRI scans in the study by Bong et al. [19]. In addition, Pickard et al. [57] performed a systematic review and meta-analysis showing that the use of alpha-agonists reduced ED as compared to placebo. A recent randomized, controlled, multicenter trial in Denmark, the PREVENT AGITATION, found that Clonidine 3 mcg/kg was useful to reduce postoperative agitation in boys - 30 of 150 boys (20.0%) in the clonidine group were agitated versus 69 of 147 (46.9%) in the placebo group. However, the number of girls (75 of 379 children recruited) was too small to draw conclusions [58].

Melatonin

A recent network meta-analysis found that high-dose melatonin was the most effective monotherapy for reducing ED [49]. A separate systematic review and meta-analysis by Zhang et al. [59] also concluded that melatonin significantly reduced the incidence of EA as compared to placebo. Zhang et al. [59] also suggested that dexmedetomidine was better than melatonin at decreasing the incidence of EA; however, this may have been confounded by the majority of the included studies which also administered fentanyl.

Combination therapies

The most effective combination for reducing ED incidence was dexmedetomidine/midazolam/antiemetic, followed by the combination of midazolam/propofol/antiemetic [49]. This suggests that although midazolam monotherapy has not been shown to reduce EA/ED [48], it may be effective as part of a combination therapy.

Choice of anesthetic agent

Volatile anesthesia is commonly implicated as a risk factor for ED. A RCT among adults undergoing nasal surgery

showed that total intravenous anesthesia (TIVA) with remifentanyl and propofol reduced the risk of ED as compared to sevoflurane and nitrous oxide. Among 80 patients included in the analysis, EA occurred in 20% of the volatile anesthesia group as compared to 2.5% in the TIVA group [60].

Although Bong et al. [19] found that propofol 1 mg/kg did not significantly influence the incidence of ED, another study in children aged 1–12 years, where a transition to propofol 3 mg/kg in divided doses over 3 minutes at the end of sevoflurane anesthesia, found a significant reduction in EA [20]. Additionally, in a previous study of children aged 18 months to 7 years undergoing MRI, in whom sevoflurane anesthesia was compared with propofol bolus and infusion, it was found that the propofol group had less EA [48,61].

A meta-analysis of children who experienced EA after propofol versus sevoflurane anesthesia also found that propofol resulted in a lower incidence of EA [62]. Despite the benefits that propofol seems to confer for ED prevention, challenges remain for TIVA anesthetic in pediatric practice. Children are more prone to propofol infusion syndrome (PRIS) because of their low weight, low glycogen storage, high fat metabolism, and sedation requirements [63]. PRIS is a feared complication, especially in neonates; there have been reports of PRIS even with single-dose administration [64]. As such, caution should be exercised when using TIVA at doses of > 4 mg/kg/h for more than 48 h, > 10 mg/kg/h for more than 8 h, or for prolonged neonatal anesthesia [63]. Patients who were also at greater risk included those with ongoing critical illness, elevated catecholamines, steroid or glucocorticoid therapy, excess lipids, or a lack of carbohydrates [65]. Where sevoflurane is chosen for use, EEG monitoring might help predict ED.

CONCLUSION

Pediatric ED has been observed for decades; however, we are only beginning to understand anesthesia emergence. The risk factors associated with ED have been widely described; however, they cannot reliably predict which children will develop ED. Therefore, apprising the patient and parents remains helpful for preventing ED. A range of pharmacological options have also shown promise.

With the increase in the usage and study of EEG patterns associated with ED, we may be able to better identify children at risk for ED and to utilize pharmacological means to reduce its occurrence.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Writing - original draft: Lucy Jennifer Davies, Shu Qi Tham. Writing - review & editing: Agnes Ng. Conceptualization: Agnes Ng. Supervision: Agnes Ng.

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