

## Emergence Delirium in Paediatric Anaesthesia

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### Abstract

*Emergence delirium (ED) in children is a well-documented clinical phenomenon with incidence ranging from 25 to 80%. It is characterized by confusion, mental irritability, disorientation, inconsolable crying, and thrashing. No single factor can be identified as the cause of postoperative agitation, which should therefore be considered a syndrome made up of biological, pharmacological, psychological and social components. Possible causes and risk factors include child's personality, inhalation anaesthetics, surgery of head and neck, rapid awakening and pain. Many scales have been proposed to evaluate the incidence and severity of ED and a variety of scales are used in clinical practice and for research purposes in children. Preventive measures include the co-administration of propofol, midazolam, or fentanyl, but the risks associated with their use must be weighed against the self-limiting nature of ED. Once ED is established, the most common interventions are pharmacological. Treatment options are clam environment in recovery and with agents having sedative and analgesic effect, such as propofol, fentanyl, ketamine and alpha-2 receptor agonists (clonidine and dexmedetomidine). ED may increase the incidence of new-onset postoperative maladaptive behavior changes such as general anxiety, night-time crying, bed wetting, general anxiety and loss of appetite for up to 14 days after surgery. A standard diagnostic, preventable and treatable guideline should be required for adverse outcomes in the paediatric populations.*

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### Introduction

Postoperative agitation, also referred to as emergence delirium (ED) in international literature, is a well-documented clinical phenomenon, particularly in children. ED has been described as "a mental disturbance during the recovery from general anaesthesia consisting of hallucinations, delusions and confusion manifested by moaning, restlessness, involuntary physical activity, and thrashing about in bed."<sup>1</sup> It has been considered a common postanesthetic problem in children as well as adults.<sup>2,3</sup> ED first identified in the 1960's when Eckenhoff et al. studied over 14,000 patients who experienced unusual post-operative behavioral disturbances which they termed "excitement".<sup>4</sup> This occurred in 5.3% of the sample patients.

ED occurs during the first 30 minutes after emergence that the greatest incidence of agitation is observed, and duration is generally limited and recovery spontaneous.<sup>5</sup> However, prolonged episodes of agitation lasting for up to 2 days have been described.<sup>6</sup> During an ED reaction, children risk injuring their surgical repair, themselves, and their caregivers. Their behaviour is disruptive to the postanesthetic care unit and often requires constant nursing supervision. When an ED reaction occurs, all members of the healthcare team as well as the parents express dissatisfaction with the quality of the child's recovery.<sup>5</sup> These negative effects of ED have motivated clinicians to investigate possible etiologies prevention and potential treatments for ED.

## Prevalence

This condition has been shown to occur in 5% to 10% of general surgery patients of all ages.<sup>7</sup> The prevalence of ED in children generally ranges from 25 to 80%, depending on the definition of ED used to measure this phenomenon,<sup>8</sup> but may be as high as 80%.<sup>8,9</sup> The incidence of ED largely depends on age, anaesthetic technique, surgical procedure, and application of adjunct medication.<sup>10</sup>

## Presentation

It is characterized by mental confusion, irritability, disorientation, inconsolable crying, and thrashing behavior. ED increased recovery time in the post anaesthesia recovery room, increasing parents concern and anxiety with respect to the clinical condition of their children.<sup>11</sup> Typically, these children do not recognize or identify familiar objects or people. Combative behaviour has been more often described than simple restlessness and incoherence.<sup>10</sup>

## Mechanism

### Neurophysiology

The first sense to return during emergence from anaesthesia is hearing, a sense that is made possible by the synapse between the acoustic thalamus and the lateral nucleus of the amygdala.<sup>12</sup> During post-anaesthesia recovery, this connection is also responsible for auditory fear conditioning by exaggerating an inappropriate response to auditory stimuli.<sup>13</sup> Disturbance of other important neurotransmitters that regulate sleep and arousal, specifically serotonin and noradrenaline, have also been associated with delirium.<sup>14</sup> To date, there have been a limited amount of studies investigating the neurophysiology basis behind ED. A study by Yasui et al., investigated that inhalation anaesthetics have been known to exert transient paradoxical "excitatory" effects in the animals

and human patients, more predominantly in children.<sup>15</sup> Another study, by Lim et al., attempted to explain the neurophysiology behind hyperexcitatory behaviors occurring after sevoflurane anaesthesia.<sup>16</sup> They postulated that the excitation may result from the potentiation by sevoflurane of GABAergic depolarization/excitation in neocortical neurons, cells implicated in the genesis of arousal and consciousness.

Further, a study by Murrin showed that neurotransmitter levels in pediatric brains were analogous to levels in brains that had undergone normal age-related changes. Diminished levels of ACh, dopamine, norepinephrine and aminobutyric acid were neurophysiological findings characteristic of both the geriatric and pediatric populations.<sup>17</sup>

Studies have identified cases of elevated serum cortisol levels postoperatively. This cortisol surge has been correlated with an increased incidence of post-operative confusion.<sup>18</sup> Intraoperative reduction in carbon dioxide (CO<sub>2</sub>) levels can decrease cerebral blood flow via vasoconstriction. Extended periods of hypocapnia causes damage to the caudoputamen and may be responsible for some of the characteristic symptoms of postoperative delirium.<sup>19</sup> Perioperative hypoventilation results in elevated CO<sub>2</sub> levels, promoting an acidotic state that alters consciousness. Importantly, altered blood oxygen levels may also contribute to the symptoms associated with ED.

## Risk Factors

### Genetics

There are theories that support the ED is predicated, in large part, on the interaction between genes and factors imposed by surgery and anaesthesia.<sup>20</sup> Agnoletti et al., hypothesized that certain genetic polymorphisms play an important role in the immune response and inflammatory pathways that may predispose a patient to ED.<sup>21</sup>

### **Age**

Studies have examined the role of brain maturation on delirium, with some relating ED susceptibility in children to the development of the hippocampus and cholinergic function.<sup>6,22</sup> Diminished level of neurotransmitters and disturbance to these neurotransmitters has been implicated as precipitating factors for ED in children and under the age of 5 years are vulnerable to altered behavior upon recovery from anaesthesia.<sup>6</sup>

### **Preoperative Anxiety**

Intense preoperative anxiety, both in children and their parents, has been associated with an increased likelihood of restless recovery from anaesthesia.<sup>23</sup> Younger children, those with impulsive and emotional behavior, those who are less sociable and whose parents are more anxious, appear to be more prone to developing this clinical phenomenon.<sup>24,25</sup> When children are separated from their parents and sent to the operating room alone, this is traumatic and increases the risk of agitation.<sup>5</sup>

### **Inhalation anaesthetics**

The recent surge in ED cases is a reflection of the gaining popularity of sevoflurane and desflurane.<sup>26</sup> It is believed that the low blood solubility characteristic of these newer inhaled anaesthetics promote a rapid awakening that concurrently increases susceptibility to ED.<sup>27</sup> The causative relationship between inhalation anaesthetics and ED is affected by the concurrent use of other medications. Supporting the findings by Aono et al., a study by Kuratini and Oi, found that children anaesthetized with sevoflurane exhibited a greater incidence of ED than those anaesthetized with halothane.<sup>28</sup>

### **Type of Surgery**

Surgical procedures that involve the tonsils, thyroid, middle ear, and eye have been reported to have higher incidences of postoperative agitation and restlessness.<sup>10,26</sup> Eckenhoff et al.<sup>4</sup>

speculated that a “sense of suffocation” during emergence from anaesthesia may contribute to ED in patients undergoing head and neck surgery.

### **Rapid Awakening**

It has been known that rapid awakening after the use of the insoluble anaesthetics may initiate ED by worsening a child’s underlying sense of apprehension when finding himself in an unfamiliar environment.<sup>26</sup> Some parents claim the patient’s behavior upon emergence was the same as when he was suddenly awakened from deep sleep.<sup>29</sup> Older children and adults usually become oriented rapidly, whereas preschool-aged children, who are less able to cope with environmental stresses, tend to become agitated and delirious.

### **Pain**

Inadequate pain relief has been one of the principal confounding factors when analyzing trigger factors for emergence agitation. ED observed particularly after short surgical procedures for which peak effects of analgesics may be delayed until the child is completely awake.<sup>30</sup> In several studies, the preemptive analgesic approach successfully reduced ED, suggesting that pain may be its major source.<sup>31</sup> It is recommended that postoperative pain be first removed to exclude the cause of ED who exhibit signs compatible with emergence agitation.

### **Diagnosis and Assessment Tools**

The diagnostic criteria for diagnosing ED are not well described. Several assessment tools have been established to guide diagnosis. Many scales have been proposed to evaluate the incidence and severity of ED and a variety of scales are used in clinical practice and for research purposes and measure ED in young children.<sup>32,33</sup> Agitation due to pain is a significant confounding factor for the evaluation of the presence or measurement of the degree of

ED.<sup>34</sup>The Cravero scale (Table I) has five steps from obtunded and unresponsive to wild thrashing behavior requiring restraint.<sup>8</sup> A score of 4 (from crying and difficult to console to wild thrashing) for a 5 or more min duration despite active calming efforts is regarded as indicative of ED.

**Table I:** Cravero Scale

Behavior	Score
Obtunded with no response to stimulation	1
Asleep but responsive to movement or stimulation	2
Awake and responsive	3
Crying (for>3 minutes)	4
Thrashing behavior that requires restrain	5

The Paediatric Anaesthesia Emergence Delirium (PAED) scale (Table: II) is validated but is difficult to use in routine clinical practice.<sup>34</sup>

**Table 2:** PAED Scale. Score is sum of all values.

Behavior	Not at all	Just a little	Quite a bit	Very much	Extremely
Make eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surroundings	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

The Watcha scale (Table:III) is a simpler tool to use in clinical practice and may have a higher overall sensitivity and specificity than = the PAED and Cravero scales.<sup>35</sup>

**Table 3:** Watcha Scale. Score is observed value.

Behavior	Score
Asleep	0
Calm	1
Crying but consoled	2
Crying but cannot be consoled	3
Agitated and thrashing around	4

### Preventive Measures

Prophylactic measures include the co-administration of propofol, midazolam, or fentanyl, but the risks associated with their use must be weighed against the self-limiting nature of ED. The efficacy of propofol is dependent on the timing of administration. Due to the rapid pharmacokinetics of propofol, a bolus may be given at the end of the procedure or continuous infusion used during maintenance of anaesthesia results in increased concentrations during emergence resulting in a decreased incidence of ED.<sup>36</sup> Perioperative analgesia has been shown to be effective in preventing ED. Several analgesics have been studied for the prevention of ED including: fentanyl intravenously 10 min before the end of a procedure, ketamine intravenously given at the end of procedure, or as an oral premedication and alpha2adrenoreceptor agonists such as clonidine caudally and dexmedetomidine intravenously.<sup>6</sup>

### Treatment

#### Non-Pharmacologic Treatment

There are a variety of non-pharmacological methods that may be effective in reducing the incidence of emergence delirium as well. These consist of a quiet induction environment with

decreased sensory stimuli, music therapy, and distraction by way of videos or touch screen games. Interestingly, parental presence at induction has not been found to be consistently effective, although parental presence following emergence is helpful.<sup>37</sup> The recovery area should be quiet. Parental presence in the recovery area may or may not help.

### **Benzodiazepine**

Despite the increased risk of ED in preoperative administration of benzodiazepines, several studies have demonstrated lower incidences of ED when benzodiazepines are administered in the perioperative stage.<sup>38</sup> Small intravenous dose of midazolam administered just prior to the end of surgery reduced ED without delaying the emergence time but risk is respiratory depression.<sup>37</sup>

### **Analgesics: NSAIDs and Opioids**

Pain is an important risk factor for ED, mainly in the pediatric population.<sup>5</sup> Adding a single injection of intravenous propofol and ketorolac to the end of a brief sevoflurane anesthetic for bilateral myringotomy with tube insertion was associated with a lower incidence of emergence agitation one study.<sup>39</sup> Fentanyl, given either intravenously or intranasally during moderately painful surgery, has also been shown to decrease emergence agitation in children.<sup>40</sup>

### **Clonidine**

The sedating effects of the alpha-2 receptor agonists clonidine reduced ED.<sup>41</sup> Administration routes were intravenous or caudal. This reduction was seen even with good analgesia from caudal. As inhalational agents raise noradrenalin levels in the brain, the alpha-2 receptor agonists may exert their effects centrally by reducing noradrenalin levels.<sup>41</sup>

### **Dexmedetomidine**

The more selective alpha-2 receptor agonist dexmedetomidine has a relatively more safety profile and improved efficacy relative to other medications has made a preferred agent of choice

for treatment of ED.<sup>42</sup> Studies also found that perioperative administration of dexmedetomidine significantly reduced the incidence of ED in children without increasing the risk of side effects.<sup>43</sup> The main disadvantage of dexmedetomidine is that it remains quite expensive.

### **Ketamine**

Ketamine has been one of the more extensively studied pharmacological agents in the management of ED. Debate about the efficacy of ketamine in the management of ED is largely driven by earlier studies that linked ketamine to an increased risk of ED.<sup>4,44</sup> Presently, emerging studies strongly favour treatment with ketamine, particularly in combination with dexmedetomidine. Yoon Sook Lee et al. found that ketamine was effective in the prevention of emergence agitation without delay in awakening and both subhypnotic doses of ketamine 0.25 and 0.5 mg/kg were effective.<sup>45</sup> Kararmaz et al. concluded that oral ketamine was effective in reducing incidence of emergence agitation.<sup>44</sup>

### **Long Term Consequences**

Although emergence delirium is transient, it has been found to be associated with postoperative maladaptive behavioural changes, with children who display emergence delirium being seven times more likely to develop postoperative maladaptive behaviors such as night terrors, bed wetting, general anxiety and loss of appetite for up to 2 weeks following surgery.<sup>24,46</sup> However, there is no evidence that ED has any impact on long-term outcome did not suggest a cause-effect relationship between these two phenomena.

### **Conclusion**

ED is a preventable and treatable condition in paediatric anaesthesia. It is distressing for children, parents, and staff. No single factor in isolation could be identified as causing postoperative agitation, and the condition should be considered to be a syndrome with biological, pharmacological, psychological and social

components. ED should be treated as the child can increase risk for injury, pain, hemorrhage, self-removal of intravenous cannula and catheters. Agitated children often face a more complicated and prolonged stay in the PACU, consisting of extensive medical regimens and additional ancillary staff. A reasonable number of diagnostic tools are currently available, each of which are not without limitations. A standard diagnostic, preventable and treatable guideline should be required for adverse outcomes in the paediatric populations.

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