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Emergence delirium in monochrome

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CONTENT

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MAKING SENSE OF THE CHAOS

Emergence delirium (ED) is a common phenomenon in paediatric anaesthesia. It was first described in the early 1960's by Eckenhoff et al.(1) in patients emerging from ether, cyclopropane or ketamine. The incidence of emergence delirium decreased due to two important factors:

1. The above mentioned anaesthesia agents were replaced with halothane.
2. Recognizing the importance of postoperative pain management in children and treatment with appropriate analgesia.

The introduction of the short-acting volatile agents into clinical practice contributed to emergence delirium's "return" to the recovery room. Currently we are faced with "Many questions, Few Answers" as described by Vlajkovic (2) with the description and definition filled with heterogeneity and lack of consensus. It is referred in the literature as postanaesthetic excitement, delirium and agitation while the definition varies between the different authors(2).

The cause appears to be multifactorial and some authors refer to it as a syndrome(3) consisting of biological, pharmacological, psychological and social components.

The focus of this review is to investigate the risk factors for emergence delirium.

THE CONFOUNDING FACTOR NIGHTMARE

Emergence delirium has a very wide reported incidence (10-80%). This can be explained by the different risk factors and confounding variables such as pain and assessment tools for measuring emergence delirium(2).

The clinical presentation of postoperative pain and emergence delirium overlaps (4). A study by Somaini suggests that the only clinical findings to differentiate between the two are no eye contact and no awareness of surroundings (5). The only assessment tool that uses these clinical signs is the PAED scale.

There is several studies illustrating that adequate analgesia reduces emergence delirium in the recovery room (6). This raises the question if pain is a contributing variable or if emergence delirium is incorrectly diagnosed.

The scales and assessment tools offer little assistance in the differentiation process with most lacking specificity (7). The criticism of these scales is that behavior such as crying, agitation and failure to cooperate are not specific to emergence delirium (5). Some of these scales were developed for adolescents and are not appropriate for smaller children. A comparison of the common scales in practice is illustrated in table 1.

Scale	Advantages	Disadvantages
Paediatric Anaesthesia Emergence Delirium (PAED) (Table 2)	Validated by studies to be useful and reliable Better in differentiation between ED and pain	Authors did not define the ED threshold More complex
Cravero (Table 3)	Easy to use Clear ED threshold	Does not differentiate between ED and pain
Watcha (Table 4)	Some authors suggest it has the highest sensitivity and specificity Easy to use Clear ED threshold	Does not differentiate between ED and pain

Table 1: Comparison of emergence delirium scales

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

Table 2: PAED scale

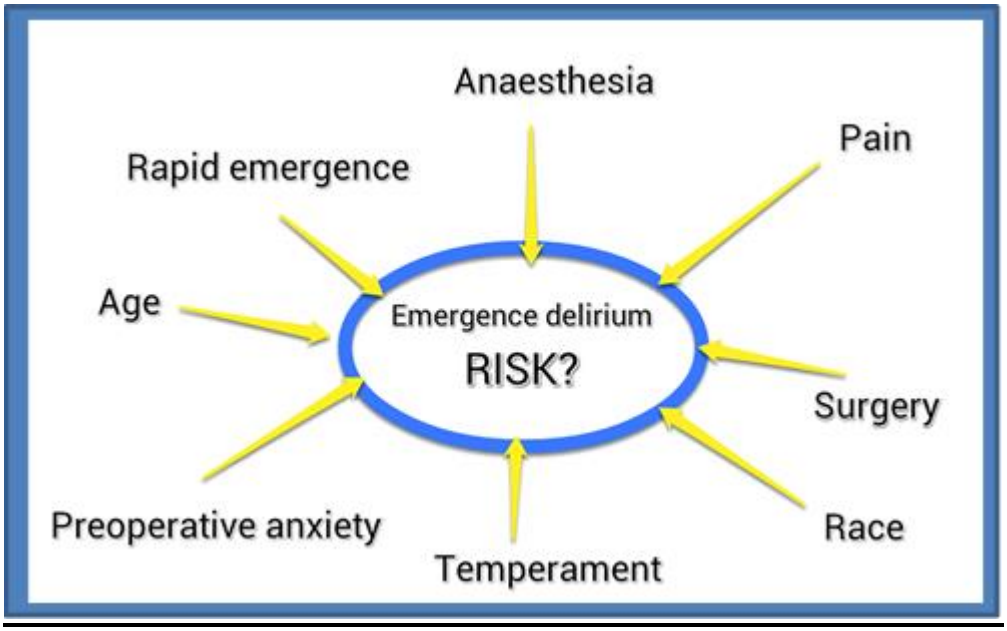
Level	Description
1	Obtunded with no response to stimulation
2	Asleep but responsive to movement or stimulation
3	Awake and responsive
4	Crying (for >3min)
5	Thrashing behavior that requires restraint

Table 3: Cravero scale

	Score
Asleep	**0**
Calm	**1**
Crying, but can be consoled	**2**
Crying, but can't be consoled	**3**
Agitated and thrashing around	**4**

Table 4: Watcha scale

PREDICT THE UNPREDICTABLE



The exact etiology of emergence delirium is still unknown. The difficulty with clarifying the exact etiology is due to major variation in prevalence, different measurement scales, definitions, risk factors and a variety of anaesthetic techniques between studies. Since the etiology is still uncertain, investigating the predictors that are described in the literature hopefully will assist with unveiling the mechanism of action.

Rapid emergence

The introduction of less soluble inhalational agents led to an increase of emergence delirium. A postulated mechanism for this is rapid awakening worsens a child's apprehension when finding himself in an unfamiliar environment. This is thought to be supported by the evidence illustrating a higher incidence of emergence delirium in preschool-aged children whose inability to cope with environmental stresses tend to make them more vulnerable for postoperative agitation(8).

A possible theory is that inhalational agents inhibit different parts of the central nervous system. This inhibition is non-uniform and leads to the earlier recovery of auditory and locomotor areas compared to the cerebral cortex. This usually leads to drowsiness but may be expressed by disorientation(9).

However, this risk factor has been questioned. Propofol also provides rapid emergence but several studies illustrate a lower incidence of emergence delirium compared to sevoflurane(10-12).

Also, a slow, stepwise decrease in sevoflurane concentration to create a delayed emergence was not found to be protective(13). This raises the question that the intrinsic characteristics of sevoflurane might be the culprit.

Anaesthesia technique

Some authors belief that the increase of emergence delirium in modern day anaesthesia is due to the introduction and increase use of sevoflurane. This is highlighted by several studies and there are some postulated mechanisms for this difference:

1. Sevoflurane can causes irritating CNS side effects(14).
2. Possible interaction with sevoflurane degradation products with other medications.

These mechanisms are not supported by definitive evidence and are speculative. The irritating CNS side effects are thought to be caused by the following characteristics of sevoflurane:

- Sevoflurane induce electroencephalogram changes(15, 16) (also seen with desflurane and isoflurane administration), which are not seen with halothane administration. These EEG changes are similiar to changes seen with night terrors. This might illustrate affectation of the balance between synaptic inhibition and excitation which influences normal brain activity.
- Sevoflurane has a biphasic effect of GABA-A inhibitory effect. It increases GABA activity at high sevoflurane concentrations but blocks the effect at low concentrations(17, 18).
- Sevoflurane at low concentrations blocks the “resting functional connectivity network” which is responsible for thought processing(9).

Age

The most vulnerable age group for developing emergence delirium is preschool toddlers (2-5 years). Martini addressed the role of brain maturation in the pathophysiology of this phenomenon(19). The paediatric brain is almost a mirror image of normal age-related regression process with a decline in noradrenaline, acetylcholine, dopamine and ɣ-aminobutyric acid (GABA) which may explain the higher susceptibility in younger children.

Preschool children and toddlers are also more vulnerable to stress/anxiety due to parenteral separation and induction of anaesthesia(18) which has been identified as an independent predictor for postoperative negative behaviours.

Surgery type

Ear, nose and throat (ENT) surgery stand out as the surgery type most associated with emergence delirium. Eckenhoff et al. described the sense of suffocation as the contributor. Number of studies illustrated ENT surgery as an independent predictor of emergence delirium. Mousavi et al. reported that 42.2% of patients with emergence delirium undergone ENT or other forms of head and neck surgery(20).

Race

Human diversity remains a fascinating field for modern biologists and studies investigating human genetic predisposition of various diseases are growing. Multiregional continuity hypothesis by Thorne and Wolpoff proposes that Homo sapiens migrated from the African continent about 1.5 million years ago and distributed throughout the Old World(21). Regional populations were connected by gene flow but different geographical regions developed recognizable regional morphologies in the continents of Africa, Europe and Asia. New emerging DNA markers have important implications in determining population diversity, human migration pattern and evolutionary relationship.

An observational study done at Grey's hospital illustrated a significant different incidence of emergence delirium between African patients and non-African patients (3.1% versus 10.4%, p=0.007)(22). The reason for this difference is unclear, but it is speculated that the difference can be due to genetics.

African population illustrates distinctly different mitochondrial DNA, human leukocyte antigen (HLA) and human Toll-like receptor genetic haplotypes which influences protective mechanisms against certain diseases. Studies by Yani and Liu discovered that higher preoperative serum IL-6 levels in older patients were associated with significant increased risk for developing delirium(3, 23, 24). Another by Leung et al. demonstrated that individuals with one copy of the e4 allele (responsible for inflammatory markers – Apolipoprotein E e4) had an increased risk of early postoperative delirium (OR 3.64; 95% confidence interval 1.51-8.77)(25).

Another possible mechanism is linked to P-450 cytochrome system and volatile metabolism(26). It is speculative but although sevoflurane degradation products appear to cause no organ damage, their possible interactions with other medications and CNS irritating side effects might be problematic. A person can't help to ponder if this can be a contributor factor to the cases of emergence delirium that lasted for 2 days(2) since emergence delirium usually resolves spontaneously within 15-30 minutes.

Preoperative anxiety

One of the most stressful experiences for a child undergoing surgery is parenteral separation and induction of anaesthesia. Evidence suggests that children with anxiety in the holding area and during induction experience greater distress in the recovery period(18).

Preoperative anxiety is determined by several factors including:

Age

There are no consistent results if age influences the degree of anxiety. Infants younger than 1 year are less likely to experience separation anxiety while toddlers between 1-3 years are more prone. Children 4-6 years seek explanations and older children (7-12 years) have a strong desire to be part of the decision-making process. Adolescents fear losing control and an inability to cope. Each stage has different psychological issues and need specific therapeutic approaches appropriate to the age group (distraction, comforting versus explanations, providing choices)(27, 28).

Gender
It has not been found to influence the degree of preoperative anxiety and emergence delirium.

Temperament

Ethnicity
Some evidence suggests that cultural differences (which include language and ethnicity) may contribute to behavior patterns especially during the perioperative period(29). A study done by Fortier et. al. found a difference in negative behavioural patterns in English- and Spanish-speaking White and Hispanic patients.

Previous hospital experience
Children with previous negative health care system encounters experience more anxiety during separation from their parents and in the holding area(30). The importance of reducing the child's anxiety in the preoperative period will not only benefit the current perioperative period but subsequent anaesthesia encounters.

Type of anaesthesia
There is currently insufficient evidence to determine whether the anaesthesia technique decreases perioperative anxiety, but an isolated study illustrated more anxiety at induction with an inhalational technique compared to an intravenous or rectal induction(31).

Pain

Temperament
Temperament is the behavioral makeup that influences reaction to surrounding stimuli and stress(32). A child with a temperament that is more emotional, more impulsive, less social and less adaptable to environmental changes has an increased risk for emergence delirium and other adverse perioperative complications. This is due to a child most likely having a fearful response to external stimuli.

Pain
Postoperative pain is the most important confounding variable when diagnosing emergence delirium. The overlapping clinical picture and lack of ability to verbalize pain, make formulating an accurate assessment tool immensely difficult(5).

Inadequate pain relief may contribute to postoperative agitation especially in short surgical procedures where peak analgesic effect is not present at emergence. Several studies illustrated that adequate analgesia reduces emergence delirium. This suggests that pain may be a major contributor to the phenomenon(2, 6).

The other side of the coin is that emergence delirium has been observed when pain was efficiently treated or not even present. Emergence delirium was reported in patients undergoing non-painful intervention such as magnetic resonance imaging scanning and eye examinations(33, 34). This suggests a clinical phenomenon separate from pain.

PREVENTION IS THE KEY

The natural path of emergence delirium is spontaneous resolution but it is still considered a serious complication because of the risk of self-injury and stress caused to caregivers and families. In some hospitals, the incidence is as high as 80% with the clinicians' focus shifting on finding prophylactic treatment.

A meta-analysis by Dahmani and collegues evaluated the efficacy of pharmacological prevention of emergence agitation in patients receiving sevoflurane and desflurane(35). They studied the following pharmacological treatments: midazolam, propofol, fentanyl, ketamine, α2-agonist (clonidine and dexmedetomidine), local anaesthetics, caudal analgesia and 5HT3 inhibitors (ondansetron).

- Midazolam - not prophylactic

Midazolam (premedication or given after induction) was not proven to be effective (OR=0.88 (0.44, 1.76); I^2=47%, P=0.11).

- Propofol – prophylactic

Propofol showed a protective effect (OR=0.21 (0.16, 0.28), I^2= 52%, P=0.01). The timing was noted to be important during subgroup analysis where continuous administration and a bolus dose at the end of anaesthesia were protective. A bolus of propofol at induction was ineffective in preventing emergence delirium.

- Ketamine – prophylactic

Despite ketamine's hallucinating side-effects, it was found to prevent emergence delirium (OR=0.28 (0.13, 0.6), I^2=0%, P=0.68).

- α2-agonist (clonidine, dexmedetomidine) – prophylactic

α2-agonist were protective (OR=0.23 (0.17, 0.33), I^2= 24%. P=0.2). The route of administration (IV versus caudal) and the agent used (clonidine versus dexmedetomidine) did not influence the efficacy of α2-agonsit against emergence delirium.

- Fentanyl – prophylactic

Perioperative fentanyl provided protection against emergence delirium (OR=0.31 (0.18, 0.56), I^2=47%, P=0.06). Subgroup analysis demonstrated that intranasal fentanyl was prophylactic while intravenous fentanyl was not.

- Perioperative analgesia – prophylactic

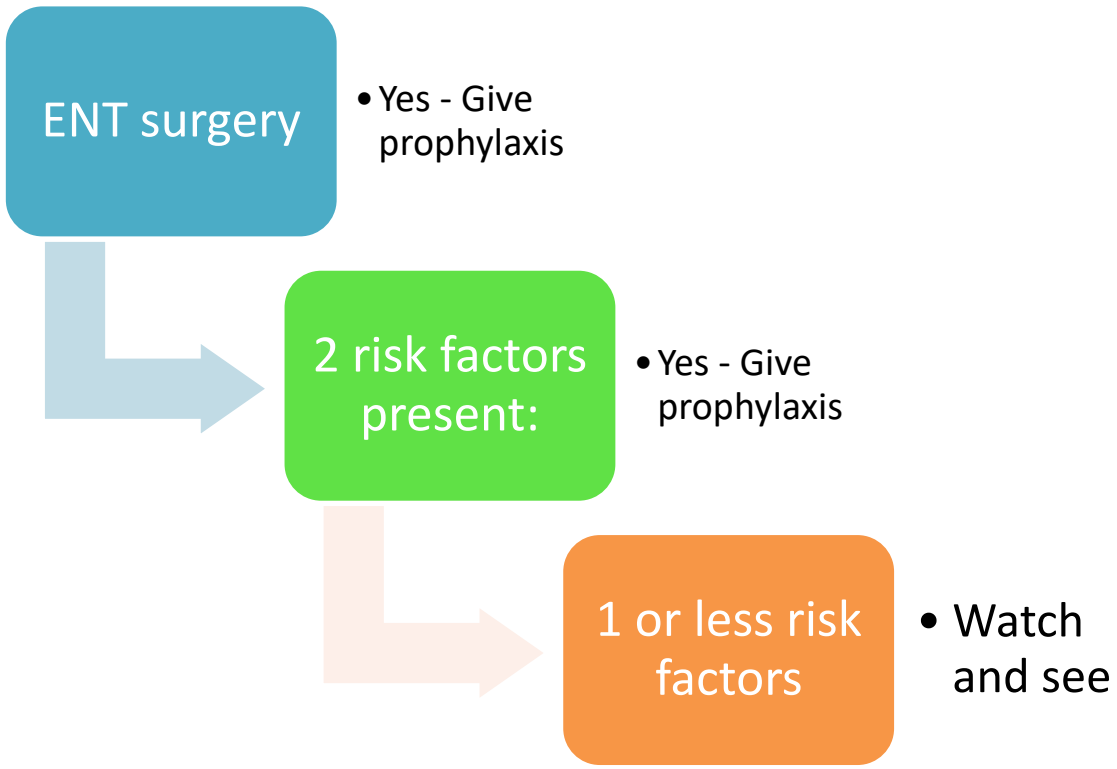
Perioperative analgesia protected against emergence delirium (OR=0.15 (0.07, 0.34), I^2=8%, P=0.36). There was only one study of caudal analgesia.

- 5HT3 antagonist – not prophylactic

Serotonin antagonists were ineffective (OR 0.39 (0.12-1.31), I^2=0%, P=0.56).

CONCLUSION

Emergence delirium remains a relevant complication in paediatric anaesthesia and despite that there are “few answers, many questions”, recent studies are shining light on this common recovery room phenomenon with the importance of biological, pharmacological, psychological and social components being emphasized. There is currently no predictive scoring system in practice but flow diagram 1 illustrates a guideline. The risk factors excluding ENT surgery are sevoflurane maintenance, white/indian race, preoperative agitation and 1-3 years.



Flow diagram 1: Prevention guidelines

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