Section A -Research paper

Emergence Agitation in Pediatric Anesthesia: Risk Factors, Pathophysiology and Management

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Abstract:

Emergence agitation following general anesthesia in children is an evolving problem, since sevoflurane has become a popular anesthetic for pediatric anesthesia. Several studies comparing incidence of emergence agitation between halothane and sevoflurane showed that sevoflurane anesthesia would result in higher chance of emergence agitation. The reasons of higher incidence of emergence agitation following sevoflurane anesthesia remain unknown. The avoidance of sevoflurane use for maintenance of anesthesia could be a major contributing factor to reduce the risk of emergence agitation. Other risk factors of emergence agitation include age of patients, operative procedure, pain, preoperative anxiety and so on Several methods are advocated to prevent emergence agitation. The aggressive treatment of surgical pain is essential to avoid screaming on emergence. In addition, varieties of medication, including opioid, sedatives and alpha-2 agonist, have been tried with various success. Emergence agitation should be treated appropriately, since it could injure the patient him/herself or caregiver. The calm wake-up from general anesthesia will greatly enhance the parental satisfaction to anesthesia and surgery.

Keywords: Emergence Agitation, Anesthesia, Pediatric.

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Introduction:

Emergence agitation (EA) is often seen in children during recovery from general anesthesia. EA is defined as "a disturbance in a child's awareness of and attention to his or her environment with disorientation and perceptual alterations, including hypersensitivity to stimuli and hyperactive motor behavior in the immediate post-anesthesia period**(1).**

In cases of EA, patients often remove drains or catheters, causing self-harm. Thus, sedation or restraint by health care providers may be required. Furthermore, this EA is often a particularly unpleasant experience for parents or caregivers. Therefore, various approaches allowing uneventful emergence from anesthesia have been studied**(2).**

EA was first reported in the early 1960s. According to this retrospective study of 14,436 cases, EA was shown to be significantly more common among children aged 3–9 years, but it occurred in all populations, including in adults. EA was not very common in the era of halothane use prior to the advent of sevoflurane and desflurane**(3).**

Risk factors

Although the exact causes and underlying mechanisms of EA in children

are yet to be determined, several factors are thought to be involved.

A. Patient related :

- **Age**

It has been reported a high rate of EA(40%) in preschool aged who underwent minor urological surgery with sevoflurane-induced anesthesia compared to 11.5 % in the school-age sevoflurane group. In general, preschool-aged children of both genders are considered to be at risk of EA. It was noted that the pediatric brain is almost a mirror image of normal age-related regressive processes, with a consequent decline in norepinephrine, acetylcholine, dopamine, and γ-aminobutyric acid (GABA), with younger children therefore more likely to develop EA after general anesthesia**(4).**

- **Mental state**

Children who have strong anxiety upon entering the operating room and in whom anesthesia is induced by mask ventilation in an anxious state (i.e., preoperative anxiety) have a higher incidence of EA. In addition, children with emotional, active, impulsive, and unsociable personalities were shown to have a higher incidence of emergence agitation **(5).**

B.Anesthesia related

Sevoflurane and desflurane have become commonly used for general anesthesia. Sevoflurane and desflurane have low blood/gas partition coefficients, and the use of these agents for anesthesia maintenance has been shown to increase the risk of EA. A meta-analysis was conducted comparing sevoflurane and halothane anesthesia, and demonstrated that sevoflurane anesthesia is a risk factor for EA**(6).**

Sevoflurane and desflurane anesthesia are thought to increase the risk of EA as awakening often occurs too early with the use of these agents anesthesia.

C. Surgery related

Ophthalmological and otorhinolaryngological surgeries are considered to be risk factors for EA, also duration of surgery**(7).**

Table 1. Possible Risk Factors for Emergence Agitation in pediatrics (8).

Risk factor	**Children**
Patient related	Preschool age (2–5 years)
	No previous surgery
	Hospitalization or high number of previous interventions
	Poor adaptability
	Attention-deficit hyperactivity disorder
	Patient preexisting behavior
	Psychological immaturity
	Preoperative anxiety
	Parental anxiety
	Patient and parent interaction with healthcare providers
Anesthesia related	Lack of premedication (with midazolam)
	Paradoxical reaction to midazolam stated in child's medical history
	Use of inhalational anesthetics with low blood–gas partition coefficients (e.g., sevoflurane and desflurane)
	Excessively rapid awakening (in a hostile environment)
	Pain

Surgery related	Type of surgery

Pathophysiology of emergence agitation

The precise pathophysiological mechanism of EA after general anesthesia is unknown. In children, proposed causes of EA include high levels of anxiety regarding surgery, new environments, separation from parents, and encounters with unfamiliar medical staff. These may lead to increased sympathetic tone and prolongation of the excited state during anesthesia recovery**(9).**

Halothane, isoflurane, desflurane, and sevoflurane can all serve as triggers of EA; however, EA is more common with inhalational anesthetics with low blood–gas solubility, such as sevoflurane and desflurane. A proposed explanation for this is that sevoflurane and desflurane cause differential recovery rates in brain function, due to differences in clearance of inhalational anesthetics from the central nervous system; whereas audition and locomotion recover first, cognitive function recovers later, resulting in EA. In addition, elevated lactate and glucose concentrations in the parietal cortex due to sevoflurane anesthesia, and the occurrence of clinically silent sevoflurane-induced epileptogenic activity have been proposed to induce EA**(10).**

Functional magnetic resonance imaging has been used to study the mechanisms underlying the alteration of consciousness during anesthesia. Studies have reported that alterations of brain network connectivity vary with the level of sedation. During emergence from general anesthesia, thalamocortical connectivity in sensory networks, and activated midbrain reticular formation are preserved. However, delayed recovery of impaired functionality of subcortical thalamoregulatory systems could contribute to defects in cortical integration of information, which could lead to confusion or an agitated state**(11).**

Assessment tools for emergence agitation

Although several scales and their variants have been proposed as tools for assessing EA in children, the most commonly used in pediatric EA studies is the Pediatric Anesthesia Emergence Delirium (PAED) scale developed in 2004 (Table 2). It provides a score from 0 to 20 and reportedly shows validity for assessment of EA in children. However, the PAED scale has disadvantages of inherent subjectivity in assessing each behavior item and suboptimal interrater reliability. In addition, the cutoff point for defining the presence of EA is controversial (**12).**

Lee et al (2020) reported that PAED score > 12 had greater sensitivity and specificity than PAED score ≥ 10 in the assessment of EA PAED. In another study, PAED score ≥ 16 was adopted as an indicator of EA without an obvious rationale**(13).**

Table 2. Pediatric anesthesia emergence agitation scale(PAED)(14).

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 surrounding	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

Emergence agitation will be considered mild if score (≥ 10), moderate (<16), sever ≥(16) .

Management of emergence agitation

EA is a self-limiting phenomenon, which lasts for only a short period (1–15 minutes) if The elimination of causative factors (e.g., pain, anxiety, presence of invasive devices) is the mainstay of EA management. Differential diagnosis and prompt treatment should also be performed for conditions that can lead to disorientation, such as increased intracranial pressure, bladder distention, upper airway obstruction, hypo- and hyperglycemia, hypotension, hypoxia, and hypercarbia. Two web-based surveys conducted by pediatric anesthesiologists in Canada and Germany revealed that sedatives (e.g., propofol and midazolam) and opioids (e.g., fentanyl and morphine) were preferred therapeutic pharmacological treatments for EA. Rarely, some anesthesiologists chose "wait for spontaneous resolution" and/or "parental presence" as the first choice of therapy for EA **(8)**.

Pharmacological agent used in EA

Appropriate drug administration may reduce the incidence of EA. Various drugs can be used at different times during anesthesia to prevent or treat EA, such as prior to induction of general anesthesia (premedication), during maintenance of general anesthesia, upon anesthesia completion, and upon the development of EA **(15).** Such as :

- **Opioids**

Opioids are frequently used as preventive and/or therapeutic agents for EA. A single intravenous bolus of 2 μg/kg fentanyl at anesthesia induction has been shown to significantly reduce the incidence of EA after short surgical procedures. Although small doses of opioids have demonstrated efficacy in the prevention and treatment of EA, opioids are associated with respiratory depressant effects and postoperative vomiting **(16).**

- **Midazolam**

Midazolam, a sedative from the benzodiazepine class of drugs, is often primarily used as premedication. Oral administration of premedication is effective for preoperative sedation; however, it has been reported to be ineffective for the inhibition of EA following surgery. On the other hand, intravenous doses of 0.03 mg/kg at the end of surgery have been reported to reduce the incidence of EA following squint surgery. The combined use of midazolam with other agents may lead to prolonged patient stays in the operating and recovery rooms, meaning that follow-up observations are imperative **(17).**

- **Ketamine**

Ketamine, an N-methyl-D-aspartate receptor blocker, has demonstrated efficacy in preventing EA and has analgesic and sedative activities with minimal respiratory depressant effects. Ketamine can provide dissociative sedation without prolonging emergence time following general anesthesia **(18)**.

- **Alpha-2 agonist sedatives**

Clonidine and dexmedetomidine exhibit sedative and analgesic effects by acting on alpha-2 receptors with minimal respiratory depressant effects. The efficacy of dexmedetomidine has been demonstrated

with nasal administration as a premedication and intraoperative continuous infusion **(19).**

- **Propofol**

Although a low risk of EA has been noted in children who received general anesthesia as well as propofol at the end of surgery, it is unclear whether administering propofol at the induction of general anesthesia suppresses EA. The use of propofol to maintain anesthesia after induction has demonstrated benefit as it reduces EA **(20)**.

- **Non steroid anti inflammatory drugs**

It is reported that the use of ketorolac, a NSAID, reduces EA by 12 % in patients undergoing halothane anesthesia and by 14 % in patients undergoing sevoflurane anesthesia**(21).**

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