EMERGENCE AGITATION IN CHILDREN

- A Review -

VIVIANE G. NASR[*] AND RAAFAT S. HANNALLAH[**]

Introduction

Eckenhoff et al first described emergence agitation (EA) in the early 1960's. Children anesthetized with ether, cyclopropane, or ketamine undergoing tonsillectomy, thyroidectomy and circumcision experienced crying, thrashing and disorientation during emergence from anesthesia[1].

Today, approximately 4 million children undergo anesthesia each year and EA has been identified as a significant problem in children recovering from anesthesia with a reported incidence ranging between 10-80%[2-5]. EA manifests with restlessness and disorientation and may cause injury to the child, disruption of the surgical site and dressing, drains, or even removal of intravenous catheters. Extra nursing care especially in the PACU is needed. Medication given to treat EA may delay discharge from the PACU and sometimes from the hospital.

Since 1960, this topic has been studied and investigated with multiple comparative studies of inhalational and intravenous anesthetics, effects of adjuvants to general anesthesia; and different assessment tools have been described. In this review, we will discuss the most recent updates on the topic and point out the controversies present despite ongoing clinical research.

Definition

The term "emergence agitation" has been interchangeably used with "emergence delirium (ED)" and "excitement" in order to describe an irritable, uncooperative, and inconsolable child upon emergence[6,7]. However there are differences in definitions and clinical presentations of agitation and delirium.

"Agitation", which is simply excessive motor activity, is quite common in the postoperative period in children as well as in adults. It is a nonspecific symptom resulting from any type of internal discomfort including pain and anxiety. Agitation resulting from pain or anxiety is relatively easily treated with reassurance and the appropriate use of analgesics and benzodiazepines.

"Delirium", however, is more difficult to diagnose, prevent, or treat, and the clinical outcome of patients with delirium is much different. Delirium, like anxiety, is characterized by an unpleasant alteration of mood. Unlike anxiety, delirium is an acute state of confusion accompanied by cognitive impairment (perceptual

* Resident, Department of Anesthesiology, Tufts-Medical center, Tufts University School of Medicine, Boston, MA, USA.

** Professor of Anesthesiology and Pediatrics, The George Washington University Medical Center, Division of Anesthesiology, Children's National Medical Center, Washington, DC, USA.

Corresponding author: Raafat S. Hannallah, MD, Division of Anesthesiology, Children's National Medical Center, 111 Michigan Avenue, N.W, Washington, DC 20010, USA. Tel: (202) 476-2025, E-mail: rhannall@cnmc.org

disturbances and hallucinations).

Unfortunately, the distinction of cognitive impairment, which is critical to making the proper diagnosis and prescribing appropriate therapy for EA, is difficult to differentiate in children. Therefore the terms emergence agitation and emergence delirium are used interchangeably in the literature.

When present, EA occurs within the first 30-minutes of recovery from anesthesia, is usually self-limited but can last up to 2 days. The incidence ranges between 10-80%. Many studies have been done in order to determine the etiology of EA. These point to surgical and patient related factors, as well as anesthesia related factors such as rapid emergence and type of anesthetic.

Assessment tools of emergence agitation

EA have been widely described, several factors have been implicated and studied and controversies continue to exist. Comparing studies have been difficult due to the lack of a uniform definition of emergence agitation and the lack of a universal assessment scale.[8] Therefore, many tools have been described and studied in order to define, grade the "agitation" and treat accordingly. As many as 16 different scales and two visual analog scales have been used. None of these tools can differentiate between pain and emergence agitation. Przybylo et al devised tool that assesses behaviors separate from pain-induced agitation[9]. Also, Sikich et al developed the Pediatric Anesthesia Emergence Delirium (PAED) scale incorporating cognitive and agitation assessments and proved its reliability and validity (Fig. 1)[10]. However, they did not define the threshold for ED making it difficult to calculate its incidence. Aouad et al by assessing ED using two different scales found that the threshold score of 10 on the PAED scale was the best discriminator between presence and absence of agitation correlating with the agitation and nonagitation scores on the four-point scale[11]. In contrast to all previous studies, Pieters et al did not find a difference in ED following propofol versus sevoflurane anesthesia when measured by the PAED scale attributing this to a low cutoff >10 on the PAED scale[12]. Bajwa et al have compared three different emergence delirium scales and have found a reasonable correlation between all three scales despite the individual limitations. More importantly the subjective assessment by an experienced anesthesiologist is highly likely to score positive on all three scales[13].

Fig. 1
PAED scale

1. The child makes eye contact with the caregiver.
2. The child's actions are purposeful.
3. The child is aware of his/her surroundings.
4. The child is restless.
5. The child is inconsolable.

Items 1, 2, and 3 are reversed scored as follows: 4 = not at all, 3 = just a little, 2 = quite a bit, 1 = very much, 0 = extremely. Items 4 and 5 are scored as follows: 0 = not at all, 1 = just a little, 2 = quite a bit, 3 = very much, 4 = extremely. The scores of each item were summed to obtain a total Pediatric Anesthesia Emergence Delirium (PAED) scale score. The degree of emergence delirium increased directly with the total score.

Factors contributing to emergence agitation

Several factors have been implicated in the etiology of emergence agitation and their effect has been extensively studied in the literature through randomized clinical trials.

1-Patient and parent related:

Age:

Aono et al have shown in 1997 that preschool boys aged 2-6 years have higher rate of EA compared to schoolboys[14]. This finding was embraced by most studies focusing on EA. The authors attributed this to rapid awakening and psychological immaturity. In fact, Martini's commentary addresses the role of brain maturation and suggests a role of physiologic development to the susceptibility of the young age group to delirium[15].

Preoperative anxiety; patient and parent:

Preoperative anxiety has been associated with increased postoperative agitation[16,17]. Kain et al in a retrospective database search of 791 children have shown that high levels of preoperative anxiety in the child are predictive of the development of adverse postoperative behavior including emergence delirium[18]. The odds of ED increased by approximately 10% with each increment of 10 points in children's state anxiety score. No clear relationship was demonstrated between parental anxiety and ED. However, in a recent study, Fortier et al have shown that parental anxiety is a risk factor for high levels of child anxiety across the perioperative setting, from the preoperative holding area, up to two weeks postoperatively and therefore could be a contributing factor to ED[19].

Kain et al have shown recently in a prospective controlled study recruiting 241 children that preoperative anxiety is related to increased postoperative pain and behavioral changes[20]. However; it remains to be determined if this relationship is an association or a cause-effect.

Temperament of the child:

Premedication or preparation programs as discussed later in this review can modify preoperative anxiety of the child and the parent. However, temperament of the child including emotionality, activity, sociability and impulsivity cannot be modified. Voepel-Lewis et al found that low adaptability in children is associated with increased incidence of EA[3]. Kain et al have also shown that ED was higher among children who are more emotional, more impulsive and less sociable[18]. Therefore this innate temperament of the child undergoing anesthesia might cause him to react differently to the outside environment and therefore could cause EA[21].

Parental presence during recovery:

Most of the studies focus on the preoperative anxiety of the parent and the presence of the parent prior to the anesthetic and the effect of these two factors on the child's EA. However, only few studies mention the effect of the parent as the child awakens in the postanesthesia care unit (PACU). Weldon et al have shown that the incidence of EA decreased as the parent joined the child in the PACU[22]. Demirbilek et al observed that the parental presence decreased the agitation despite the presence of surgical pain[23]. Aouad et al have also related the low incidence of EA in children undergoing inguinal hernia repair under caudal block to the parental presence in the PACU in addition to the lack of pain[24]. The positive effect of parental presence in all above mentioned studies was only a noticeable observation and was not the studied outcome. Many hospitals today welcome early parental presence in the PACU as the child is recovering from anesthesia. And therefore, a prospective study rating EA prior to arrival of the parent and after their arrival to the PACU would be of interest.

2-Surgical procedure:

Type of procedure:

Surgical procedures involving the ears, eyes, tonsils, thyroid and urological surgeries have been associated with higher rates of EA. When Eckenhoff at al first described the EA in 1961, he attributed the increased incidence among otolaryngologic procedures to the "sense of suffocation" [1]. Later, in 2003, Voepel-Lewis in a prospective study has shown that the otolaryngologic procedures are an independent risk factor for EA[3]. The increased incidence during ophthalmologic procedures could be related to the distortion or lack of ability to see the outside environment.

Pain:

Most of the above mentioned procedures are painful and pain has been acknowledged as a major risk factor for EA. Several studies have been done in order to study the causal effect of pain and EA and to decrease the incidence of EA by treating pain with different modalities including NSAID, ketorolac,[25] α2-agonist such as clonidine,[26-28] dexmedetomidine,[29-31] regional anesthesia including caudal blocks[22, 24] and narcotics. The incidence of EA in these studies has decreased after adequate pain control compared to controls but was not abolished. This suggests the presence of EA despite adequate pain control. In fact, Cravero et al have found that the incidence of EA was higher in sevoflurane anesthetized patients compared to halothane in children undergoing nonpainful interventions such as MRI[4]. Therefore, pain cannot be pointed out as the sole contributing factor to EA.

3-Inhalation and intravenous anesthetics:

Sevoflurane's high incidence of emergence agitation has led to numerous studies evaluating the incidence of emergence agitation following inhalation and intravenous anesthetics. It was found that sevoflurane is not the only anesthetic implicated in agitation. Desflurane as well as isoflurane have been shown to have a comparable incidence ranging between 50% and 80%[3,9,31]. In fact, the electroencephalogram changes occurring in patients under sevoflurane are similar in patients under isoflurane and desflurane[32]. However, most studies have shown that sevoflurane causes more agitation than halothane with different electroencephalogram changes[4,13,33]. Kuratani et al have shown in a meta-analysis identifying 23 studies comparing sevoflurane and halothane that emergence agitation occurs more frequently with sevoflurane[34].

The rapid emergence following sevoflurane has been speculated to be the cause of EA. Awakening in an unfamiliar environment could cause EA. Patients who have decreased ability to cope with environmental stresses tend to become more agitated. Studies have compared sevoflurane and propofol on the quality of recovery[35-37]. Cohen et al compared emergence from sevoflurane and propofol, which allows a fast recovery[38]. They found that rapid emergence from propofol was smooth and pleasant compared to sevoflurane and concluded that EA was not related to the speed of recovery. In fact, delaying emergence by stepwise decrease of sevoflurane did not reduce the incidence of EA as shown by Oh et al[39].

Similarly, Grundmann et al have shown that in children, TIVA with remifentanil and propofol is a well-tolerated anesthetic method, with a lower perioperative heart rate and less postoperative agitation compared with a desflurane-N_2O based anesthesia[40].

Therefore, EA is not related to the rapid recovery but could be related to the intrinsic property of inhalation anesthetics.

4-Premedication:

The possible association of midazolam, a commonly used premedicant in children with ED has been a controversial topic. Few studies have shown that midazolam decreases agitation postoperatively following sevoflurane;[2] while others have shown no effect or even noted an increase in agitation[34,41]. We can suggest that midazolan may decrease agitation by its residual sedative effect at the end of surgery for short procedures as noted by Lapin et al or by decreasing anxiety score preoperatively[2].

Other premedicant drugs has been used and compared to midazolam. Oral clonidine 4 mcg/kg given thirty minutes prior to sevoflurane anesthesia induction in preschool children is associated with a significant reduction in EA compared to midazolam 0.5 mg/kg (25% vs. 60%)[27].

Premedication with melatonin have been proven to be superior to midazolam in reducing excitement following emergence from sevoflurane and similar in decreasing preoperative anxiety[42]. In contrast to the above mentioned drugs, oxycodone, a long acting opioid did not decrease agitation in children who received sevoflurane anesthesia but decrease the frequency in children who received halothane[43].

5-Adjuvants to GA including pharmacological and nonpharmacologic tools:

- Pharmacological adjuvants:

Several drugs have been used as adjuvants to general anesthesia, aiming to decrease the incidence of emergence agitation[44,45].

Propofol delays or modifies emergence and decreases emergence agitation depending on the time of administration. Being a short acting medication, propofol given at induction could not prevent emergence agitation[46]. Aouad et al as well as other studies have shown a decrease in EA following propofol administration (1 mg/kg) at the end of surgery, as plasma concentration of propofol can be effective[11].

Fentanyl, α2-agonists including clonidine and dexmedetomidine, ketamine have been shown to be effective measures in decreasing the incidence of EA.

Fentanyl is a potent opioid, which can decrease EA following sevoflurane and desflurane anesthesia by its high efficacy on preoperative analgesia as well as its sedative effect[47-50]. Cravero et al have shown that fentanyl 1 mcg/kg IV given 10minutes before the discontinuation of the anesthetic in patients undergoing nonpainful procedure such as magnetic resonance imaging decreased the incidence of EA from 56% to 12%[48]. Inomata et al studied the effect of fentanyl infusion on the intubating conditions as well as emergence agitation in children anesthetized with sevoflurane[50]. They recommended a bolus of 2 mcg/kg followed by an infusion of 1 mcg/kg/hr for a smooth emergence. Intranasal fentanyl 2 mcg/kg for moderately painful procedures can also decrease agitation[51,52].

Dexmedetomidine, a selective α2-agonist has sedative, analgesic and anxiolytic effects after IV administration[53]. Isik et al as well as two other studies have shown a reduced incidence of emergence agitation ranging between 4.8% and 17% with no hemodynamic effects after IV administration of 0.3-1 mcg/kg dexmedetomidine after induction of anesthesia[29,30,54].

Similarly, because of its sedative and analgesic effects, clonidine 2-3 mcg/kg IV after induction decreases agitation on emergence down to 0%-10% as documented respectively by Bock et al and Kulka et al. [28, 55] Bock et al have also noted that the effect of clonidine is independent of the route of administration: intravenous or caudal[28]. In fact α2-agonists decrease EA by their analgesic effect as well as by decreasing the anesthetic requirements.

Ketamine, a N-methyl-D-aspartate receptor antagonist, produces both analgesic and opioid sparing effects when used at low doses[56-58]. Dalens et al showed that administration of 0.25 mg/kg of ketamine at the end of the MRI in children reduced agitation with no delay in discharge[56]. In fact, Lee et al compared ketamine 0.25 mg/kg and 0.5 mg/kg showing similar incidence of EA however less pain score with the higher dose of ketamine[57].

It has also been shown that tropisetron, a 5HT3 antagonist, decreases emergence agitation compared to placebo (32% vs. 62%) however; the mechanism of action is unclear as described by Lankinen et al. [59] In summary; most adjuvants studied have decreased ED postoperatively in painful and nonpainful procedures through their analgesic and sedative effects. A recent meta-analyses by Dahmani et al have shown that propofol, opioids such as fentanyl, pain prevention, ketamine and α2-agonists have a preventative effect on ED while midazolam and serotonin inhibitors did not have a prophylactic effect[44]. However, comparison between the different drugs using the same scale remains of benefit for more definitive conclusion.

- Nonpharmacologic tools including child life and preoperative preparation programs:

Holding the child and physical restraint may be necessary sometimes to protect the child. A very effective method is reuniting with the parent/caregiver during awakening. It is also important to maintain a quiet environment for the child.

Demirbilek et al was not able to decrease the incidence of EA further by the use of fentanyl if the parents and the child's anxiety were controlled[23].

Relationship between EA and long-term postoperative maladaptive behaviors:

Long-term maladaptive behavior can occur following anesthesia in children. It has been hypothesized to be related to the hypnotic depth, the duration of the anesthetic, type of anesthetic as well as the incidence of emergence agitation. Kain et al suggests that patients with emergence delirium are seven times more likely to have new onset postoperative maladaptive behavioral changes including eating problems, sleep disturbances, separation anxiety and apathy[18,60]. This is in contrast to Sikich and Lerman who were unable to find a statistically significant relation between emergence agitation and negative postoperative behavioral changes[10].

Recently, Faulk et al revealed no correlation between the length of time under deep hypnosis defined as BIS<45 and the incidence of EA or negative postoperative behavioral changes[61].

In addition, there is no conclusive relationship between the type of anesthetic and the maladaptive behaviors. In fact, Keany et al have shown no relationship between sevoflurane and maladaptive behavior and Kain et al found no difference in behavior between children exposed to sevoflurane or halothane[62,63].

Kain et al have reported that 54% of all children undergoing general anesthesia exhibit negative behavioral responses 2 weeks after the surgery and continues up to 6 month in 20% and up to one year in 7%[16]. He reports in a later study the benefit of premedication with midazolam 0.5 mg/kg on decreasing this incidence during the first week as decreasing preoperative anxiety decreases the incidence of emergence agitation[60]. In view of these results, we cannot establish a theory associating emergence agitation and long-term maladaptive behavior or type of anesthetic and behavioral changes.

Prevention and treatment:

As previously described in details, numerous medications have been studied to prevent or reduce emergence agitation in children. No one effective method has been shown to be highly superior. It is very difficult to compare studies as each uses different assessment tools, type of surgical procedure, or even anesthetic techniques.

However, it is no doubt that a young anxious preschool child undergoing a painful surgical procedure without adequate pain control will most likely suffer from emergence delirium. As studies are ongoing trying to discover the underlying causes or trying to treat and prevent the occurrence of emergence agitation, it is the role of the anesthesiologist to recognize patients at risk, involve the parents preoperatively as well as postoperatively and use adjuvants drugs as deemed necessary.

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