E

mergence agitation (EA) during recovery from general anesthesia has been identified as a frequent problem in the pediatric population. In children, EA has been described as a mental disturbance that consists of confusion, hallucinations, and delusions manifested by moaning, restlessness, involuntary physical activity, and thrashing about in bed. The overall rate for EA in children is in the range of 10% to 67%, which includes a period of severe restlessness, disorientation, and/or inconsolable crying during anesthesia emergence.

The age at which children are more likely to display signs of EA ranges from 2 to 5 years old and then begins to decline at age 62 months. Additionally, the incidence of EA may be affected by individual variations in developmental level within an age group, mental disease, or neurologic conditions. These age groups are defined by the American Academy of Pediatrics in its Recommendations for Preventive Pediatric Health Care. Definitions are as follows: early childhood (15 months to 4 years old), middle childhood (5 to 10 years old), and early adolescence (11 to 12 years old). In this literature review, the most information was available on EA in the age groups of early and middle childhood, with additional studies that included early adolescents.

Clinical History of Emergence Agitation

- Epidemiology and Anesthetic Technique. In 1961, Eckenhoff et al described the phenomenon of EA, reporting signs of hyperexcitation in patients emerging from ether, cyclopropane, or ketamine anesthesia. Most often EA is seen in the pediatric population, especially prevalent in early to middle childhood. Children, especially at an early age, are limited not only by their lack of experience but also by developmental issues that restrict understanding and heighten fears. A rapid recovery in conjunction with psychological immaturity of these young patients has been postulated for this emergence event.

Emergence agitation was reported as a problem in general anesthesia recovery before the development of the modern inhalational agents (sevoflurane and desflurane), and EA has been shown to occur with the use of all anesthetic gases. The increased use of sevoflurane and desflurane in recent years has been associated with a higher incidence of EA compared with isoflurane and halothane (Table 1). This phenomenon is thought to be due to the low blood-gas solubility and rapid recovery characteristics of sevoflurane and desflurane. This pharmacokinetic prediction is borne out by real-world experience (see Table 1). It is suggested that substituting sevoflurane with isoflurane for maintenance of anesthesia significantly reduces the incidence of EA in preschool children. In addition, adjunctive agents such as propofol added to sevoflurane have been demonstrated to reduce the incidence of EA compared with sevoflurane alone. Currently, sevoflurane is the inhalational...
agent of choice for pediatric anesthesia because of its rapidity of induction and pleasant, nonirritating odor. Propofol (2,6-diisopropylphenol) is an intravenously administered general anesthetic released for use in 1989, with its mechanism of action enhancement of γ-aminobutyric acid (GABA)-activated chloride channels. The blood-brain equilibration half-life is approximately 2 to 3 minutes, with a distribution half-life of 2 to 4 minutes. Propofol use has been studied in adult populations as well as in pediatric surgical, ophthalmologic, urologic, radiologic, gastrointestinal endoscopy, and dental procedures. Propofol has several advantages and can be used in many settings in anesthesia, including inpatient and outpatient procedures. General anesthesia with propofol is characterized by a rapid recovery and a calm, sometimes euphoric state.

• Diagnosis of Emergence Agitation. The assessment of EA in children has been reported in the literature using 18 different clinical rating scales. Some are numeric rating scales, some are visual analog style (for use in young children), and not all are validated. Some scales were originally intended to assess pain and were adapted to assess EA; more recently, others were developed to specifically assess EA. Examples of validated scales include the Pediatric Anesthesia Emergence Delirium (PAED) scale and the Post Anesthetic Behavior Assessment (PABA) scale. Examples of nonvalidated scales include study-specific scales, the Modified Objective Pain Scale, and the 4-point scale of Aono and colleagues. In the more recent literature, the PAED scale has emerged as a leader in EA research (Table 2).

Possible Pathophysiologic Mechanisms of Emergence Agitation
Possible causes of postanesthetic problematic behaviors in children include physiologic compromise such as metabolic disturbances, hypoxemia, or bladder distention. Other contributing factors may be related to intraoperative and postoperative pain, preexisting psychosocial pathology, physiologic abnormalities, low adaptability, residual drug effects, rapid emergence, a hostile or unfamiliar environment, preoperative anxiety, and an increase in the use of specific inhalational agents.

Review of the Literature
The current literature review was conducted using multiple search engines, including CINAHL, MEDLINE, GOOGLE, and OVID. Articles were selected based on the following 3 criteria for inclusion: sevoflurane inhalational general anesthetic, propofol as an adjunct to sevoflurane general anesthetic, and propofol TIVA techniques.

Clinical Factors Related to Development of Emergence Agitation
Populations studied for EA included the following characteristics: sex, age, ethnicity, type and length of surgery, preoperative psychological status, and ASA class. Most studies failed to differentiate EA in male and female populations. Some studies did separate age cohorts; for instance, a higher rate of EA has been seen in preschool boys anesthetized with sevoflurane compared with school-aged boys.

The age of the child has been considered to be a factor in the development of EA postoperatively, perhaps because of the expected confusion and fright in this age group in response to perioperative events. Aono et al concluded that preschool-aged boys showed a higher rate of emergence agitation than did school-aged boys when anesthetized with sevoflurane.
that young age and anxiety level preoperatively were associated with EA. Many studies have confirmed that a younger age is a contributing factor in the development of EA, and most studies now target the ages of 2 through 6 years old when studying EA.\textsuperscript{2} When EA was first described by Eckenhoff\textsuperscript{8} in 1961, it was speculated that patients undergoing head and neck procedures may have a sense of suffocation during emergence from anesthesia, thus increasing the chance of EA. Surgical procedures that have been found to increase the risk of developing EA are otorhinolaryngology, ophthalmology, and neck procedures, all of which may produce a sense of suffocation.\textsuperscript{2,20,24} The length of surgery in at least one study was found to be a factor associated with increased incidence of EA.\textsuperscript{24} In most studies, patients have been excluded if they were above ASA classes I and II, which is one limitation of the current literature.\textsuperscript{22} Exclusion criteria also included children with psychological or emotional disorders, developmental delay, and patients who needed sedative medication before induction.\textsuperscript{14}

**Perioperative Measures to Prevent Emergence Agitation.** Undertreated pain can contribute to behaviors that are similar to those of anesthetic-induced EA. Cohen et al\textsuperscript{25} demonstrated a reduction in EA after the administration of fentanyl when used with desflurane. Aouad and Nasr\textsuperscript{2} also demonstrated, in children undergoing inguinal hernia repair under sevoflurane anesthesia, that there was adequate pain relief with a caudal block compared with intravenous fentanyl, which resulted in a very low incidence of EA when other triggering factors such as preoperative anxiety were excluded. Weldon et al\textsuperscript{26} indicated the combination of premedication with midazolam and the use of a caudal block for pain control minimized EA after sevoflurane anesthesia. Postanesthesia agitation with sufficient analgesia has been cited in the literature. Cole et al\textsuperscript{3} demonstrated that the use of caudal blocks or intraoperative narcotics for urologic surgeries did not decrease the risk of agitation in the postoperative period.

Preoperative identification of the child at greater risk of EA has been studied using various preoperative psychometric instruments. Examples include the Preoperative Observation Scale (POS),\textsuperscript{4} Child Behavior Check List (CBCL),\textsuperscript{27} and the modified Yale Preoperative Anxiety Scale (mYFAS). A high level of preoperative anxiety has been associated with an increase in emergence delirium (agitation).\textsuperscript{28} Preoperative interventions to reduce stress include attention to patient temperature, providing a quiet, calm environment with dim lighting, and encouraging the patient to bring comforting items from home. Interventions to treat or prevent childhood preoperative anxiety include behavioral preparation programs, hypnosis, and music therapy.\textsuperscript{28} It was found by Cole et al\textsuperscript{3} that a difficult separation of a child from their parents is associated with a higher risk of developing postoperative agitation. Some healthcare facilities have begun to allow loved ones to accompany the child to the operating room for the start of the child’s anesthetic induction.\textsuperscript{20} Parents may also be allowed to accompany the patient in the postanesthesia care unit.\textsuperscript{2}

In the early and middle childhood age groups, intravenous access was often delayed until the child is in the operating room and general inhalational anesthesia has been induced.\textsuperscript{2} For the early childhood, middle childhood, and early adolescent age groups, EMLA (eutectic mixture of local anesthetic) cream placed on the site of intravenous insertion reduced the pain of intravenous cannulation and preoperative distress.\textsuperscript{30}

There is conflicting evidence in the literature regarding preoperative medication and its benefit in preventing EA. Preoperative anxiety in children is considered to be a contributing factor in the development of EA, and medications such as clonidine and midazolam have been studied as potential aids for reducing EA. Clonidine premedication has been found to reduce the incidence of EA by 20% to 35% when compared with midazolam premedication\textsuperscript{21} (Table 3). Midazolam given preoperatively has reduced EA, possibly because of slowed awakening rather than anxiety reduction.\textsuperscript{24} Breschan et al\textsuperscript{31} demonstrated no significant difference in emergence behavior after midazolam was preoperatively administered with sevoflurane. Cohen et al\textsuperscript{13,25} demonstrated that midazolam administered any time before extubation produced longer wake-up times but did not significantly reduce the incidence of EA. It has also been reported that children who were premedicated with midazolam had a ninefold higher risk of developing EA over children who were not premedicated.\textsuperscript{3} The use of midazolam premedication during sevoflurane inhalational general anesthesia produced an EA incidence of 38% to 60% in 2 studies.\textsuperscript{9,21}

**Sevoflurane Inhalational General Anesthesia.** In a study in which a sevoflurane inhalational general anesthetic was compared with a sevoflurane induction and isoflurane maintenance, EA was noted to be 19.7% higher in the sevoflurane inhalational general anesthetic group\textsuperscript{6} (see Table 3). The incidence of EA in children who receive a sevoflurane anesthetic was noted to be as low as 20% for ear, nose, and throat surgery\textsuperscript{15} but as high as 60% in circumcision populations.\textsuperscript{21} An effort was made by Ozdemir et al\textsuperscript{16} to control for premedication and analgesia by omitting both premedication and analgesia in their study of children undergoing MRI. It was noted that the mean PAED scores were significantly lower for the propofol TIVA group compared with a sevoflurane anesthetic. In other studies, a sevoflurane inhalational general anesthetic was found to produce EA at rates of 50% to 60%, even in surgeries not normally known to produce EA—circumcision\textsuperscript{21} and subumbilical surgery.\textsuperscript{6}

**Propofol Adjunct.** The beneficial effects of a propofol anesthetic on the incidence of EA have been well documented in the literature during the last decade (see Table
Propofol has been demonstrated to be effective as an adjunct to sevoflurane inhalational general anesthesia in reducing the incidence of EA.5,14 Aouad et al5 demonstrated that propofol as an adjunct (a bolus of 1 mg/kg at the end of surgery) decreased the incidence of EA in children to 19.5% of study participants compared with 47.2% in patients who received sevoflurane only (saline as a control). In the same study, Aouad et al5 found that PAED scale scores were significantly decreased in the propofol group, as well as an improvement in parental satisfaction rates. A study on the effect of a subhypnotic dose of propofol (1 mg/kg bolus at completion of the procedure) also demonstrated a significant decrease in EA. This study demonstrated a significant reduction in the incidence of EA, with the propofol group having a 4.8% incidence versus a 26.8% incidence in the sevoflurane-only group. The PAED scores were significantly lower in the propofol group as well.14

- **Propofol Total Intravenous Anesthesia.** Propofol TIVA techniques have also demonstrated a reduction in EA in children. In the study by Cohen et al13 of sevoflurane inhalational anesthesia versus a propofol TIVA technique, there were significantly higher rates of EA in the sevoflurane group compared with the propofol group (23.1% versus 3.7%; see Table 3). In the study by Picard et al17 of the quality of recovery in children, a sevoflurane inhalational anesthetic and propofol TIVA techniques were compared, with a reduction in EA rates observed in the

### Table 3. Emergence Agitation (EA) Studies Divided by Anesthetic Technique With EA Incidence

<table>
<thead>
<tr>
<th>Study design</th>
<th>Population</th>
<th>Premedication</th>
<th>Analgesia</th>
<th>EA incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevoflurane only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevoflurane vs propofol induction/halothane maintenance10</td>
<td>322 children Age 3-12 y Day surgery or ENT surgery</td>
<td>None</td>
<td>Alfentanil, fentanyl, or regional blocks</td>
<td>Sevoflurane 25.7% Propofol/halothane 9.4%</td>
</tr>
<tr>
<td>Sevoflurane vs sevoflurane induction, isoflurane maintenance6</td>
<td>128 children Age 1-6 y Subumbilical surgery</td>
<td>None</td>
<td>Penile, caudal, or ilioinguinal/iliohypogastric block</td>
<td>Sevoflurane 51.8% Sevoflurane/soflurane 32.1%</td>
</tr>
<tr>
<td>Sevoflurane only21</td>
<td>68 children Age 1-6 y Circumcision</td>
<td>Midazolam 0.5 mg/kg, or clonidine 2 or 4 µg/kg</td>
<td>Penile block and rectal paracetamol 30 mg/kg</td>
<td>Midazolam 2% Clonidine 60% 40%, 4 µg/kg 25%</td>
</tr>
<tr>
<td>Sevoflurane vs propofol TIVA13</td>
<td>53 children 2-36 mo Ambulatory surgery</td>
<td>None</td>
<td>Fentanyl 2 µg/kg or caudal block</td>
<td>Sevoflurane 23.1% Propofol 3.7%</td>
</tr>
<tr>
<td>Sevoflurane vs propofol TIVA15</td>
<td>186 children Age 2-11 y ENT surgery</td>
<td>None</td>
<td>Fentanyl 2 µg/kg</td>
<td>Sevoflurane 20%-42% Propofol 5%-11%</td>
</tr>
<tr>
<td>Sevoflurane vs propofol TIVA16</td>
<td>88 children Age 2-6 y MRI</td>
<td>None</td>
<td>None</td>
<td>Mean PAED scale score significantly lower for propofol group</td>
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<tr>
<td>Sevoflurane vs propofol TIVA17</td>
<td>50 children Age 3-10 y Tonsillectomy</td>
<td>None</td>
<td>Alfentanil 20 µg/kg, acetaminophen 20 mg/kg, or ibuprofen 10 mg/kg, and local infiltration of site</td>
<td>Sevoflurane 46% Propofol 9%</td>
</tr>
<tr>
<td>Sevoflurane vs propofol TIVA9</td>
<td>16 children Age 1-5 y Eye surgery</td>
<td>Midazolam 0.5 mg/kg PO</td>
<td>Acetaminophen 30 mg/kg prn</td>
<td>Sevoflurane 38% Propofol 0%</td>
</tr>
</tbody>
</table>

Table 3. Emergence Agitation (EA) Studies Divided by Anesthetic Technique With EA Incidence

ENT indicates ear, nose, and throat; PAED, Pediatric Anesthesia Emergence Delirium; MRI, magnetic resonance imaging; prn, as needed; PO, orally; IV, intravenously.
propofol TIVA group (46% versus 9%, respectively). A reduction in EA from 42% to 11% was seen in children 2 to 5 years of age with propofol TIVA compared with sevoflurane inhalational general anesthesia.15 In a small study of children presenting for eye surgery (n = 16), propofol TIVA technique had an EA incidence of 0%, in contrast to a cohort managed with sevoflurane inhalational general anesthetic, which produced an EA incidence of 38%.9

The studies summarized in Table 3 compare EA rates in sevoflurane alone, propofol TIVA alone compared with sevoflurane alone, and propofol adjunct together with sevoflurane compared with sevoflurane alone. The study findings demonstrate that either using propofol adjunctively or using propofol TIVA results in lower rates of EA compared with either sevoflurane alone or sevoflurane with adjunctive propofol.

Discussion
Emergence agitation has been reported and studied in the literature for the last half century.8 Emergence agitation is an important issue in pediatric anesthesia and has increased in occurrence with the use of sevoflurane inhalational anesthesia. The goal of this literature review was to compare 3 general anesthesia techniques in children and their associated incidence of EA. The 3 techniques were sevoflurane inhalational general anesthetic, propofol as an adjunct to sevoflurane inhalational general anesthetic, and propofol TIVA techniques.

The literature review revealed the incidence of EA to be reduced with the use of a propofol TIVA technique compared with a sevoflurane inhalational general anesthetic. Also, the incidence of EA was reduced significantly with propofol as an adjunct to a sevoflurane inhalational general anesthetic.2,5,14 The results cited from the studies described in this literature review provide a rationale for the use of propofol TIVA, or propofol as an adjunct to sevoflurane inhalational technique, to reduce the rate of EA in children.

In the current literature review, a major limitation discovered is the need for the consistent use of a validated scale for assessing EA across all studies. Numerous studies of EA have used a variety of scales, which measure EA by different criteria. According to Sikich and Lerman,1 the PAED scale is a reliable and valid tool based on the scale’s reliability, content, and initial construct validity profile determined in their study. Aouad and Nasr2 recommended that the PAED scale be used as a reliable and valid tool that would minimize measurement error in the clinical evaluation of EA.

A further limitation of the current literature is the lack of a large scale multicenter study evaluating some of the confounding factors involved in studying EA. Future recommendations for further research on EA include the following: comparing many different anesthetic techniques, measuring environmental factors (body temperature and operating room temperature), measuring physiologic factors such as oxygenation (using arterial blood gases or other measures), using preoperative laboratory diagnostics as predictive factors, and measuring psychological preventive measures such as preparation and emergence support.

Summary
The reviewed literature suggests that there are advantages to the use of propofol TIVA techniques and adjunctive propofol anesthetics when combined with a sevoflurane inhalational technique. This reduction in EA with propofol use in conjunction with or separately from sevoflurane has been widely documented throughout the literature.5,14 A major limitation of this literature is that numerous EA assessment scales are used to compare various anesthetics. If future studies use the same validated assessment scale (such as the PAED), results can be more easily compared and strengthened. To better delineate the pathophysiology and causative factors regarding EA, more structured and multicenter studies with larger populations should be performed. Current research supports the use of propofol as discussed above; however, a continuation of current research with consistent and strengthened methodologies will help justify its use and application to clinical practice.

REFERENCES


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