Preoperative Anxiety Management, Emergence Delirium, and Postoperative Behavior

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KEYWORDS
- Anxiety
- Children
- Distraction
- Emergence delirium
- Parental presence
- Pediatric
- Premedication

KEY POINTS
- Preoperative anxiolysis is of utmost importance for children undergoing surgery.
- Preoperative educational materials, parental presence at induction of anesthesia (PPIA), distraction, and pharmacologic interventions are effective anxiolytics.
- Emergence delirium (ED) resurfaced with the newer insoluble anesthetics, sevoflurane and desflurane, as a nuisance and potentially serious sequela in young children in the recovery room.
- Research and investigation into the treatments of ED was stymied by the absence of a validated scale for ED until the Pediatric Anesthesia Emergence Delirium (PAED) scale was published.
- Causative factors for ED have not yet been elucidated, but several strategies have been described to attenuate ED, including propofol infusion and use of α2-agonists, opioids, and others.

INTRODUCTION
As the views and understanding of the factors that affect a child’s anesthetic experience evolve, preoperative anxiety, postoperative behavior, and parental participation in the child’s health care experience have become important considerations. In
children, preoperative anxiolysis is important not only for compassionate reasons but also for improving postoperative behavior such as ED. Parents and society expect not only effective but also patient- and family-centered care. This review summarizes the current state of the art of perioperative management of children.

PREOPERATIVE ANXIETY

Framework

Parental separation and induction of anesthesia is one of the most stressful experiences for a child undergoing a surgical procedure. Stress may be manifested not only during the induction period but also during the postoperative period.1 Although all children are vulnerable to stress, preschool children and toddlers aged 1 to 6 years seem to be the most vulnerable. Evidence suggests that children who are anxious in the holding area and during the induction experience a greater distress during the immediate postoperative period.1–4 Preoperative anxiety is an independent predictor for postoperative negative behaviors.2 Common postoperative negative behavior include nightmares, waking up crying, separation anxiety, and temper tantrums,2,5 whereas more serious behavioral changes such as new-onset enuresis are uncommon.5 The risk of postoperative negative behavior is 3.5-fold greater in children who experienced preoperative anxiety.2 Of these children, 67% will develop negative behaviors on the first day after surgery, 45% on the second day, and 23% within 2 weeks.2 Negative behaviors persist for up to 6 months in 20% of the children and for up to 1 year in 7.3% of the children.5 In addition to a surgical procedure, any other health care encounter that proves to be traumatic may increase the likelihood of an anesthesia phobia when the child returns to the hospital. How perioperative anxiety affects later emotional and intellectual development remains unclear, but negative memories of hospitalizations and anesthetic care may persist well into adulthood.6

Measuring preoperative anxiety in a child is challenging. However, quantifying the degree of anxiety experience by a child may be a worthy pursuit to understand the magnitude of the problem and to stratify appropriate therapeutic interventions to mitigate its effects. Several scales have been developed to measure preoperative anxiety and have been used for both clinical and research purposes. However, because self-reporting scales are unsuitable for preverbal children, there are currently no scales for children younger than 2 years. Clinical parameters such as heart rate and blood pressure have been used in the past to assess anxiety, but these clinical parameters have shown a low validity and reliability. Plasma cortisol concentrations7 after induction have also been used to quantify perioperative anxiety, but these are also insensitive measurements and impractical for every pediatric clinical practice.

Factors that Contribute to Preoperative Anxiety

Several factors contribute to preoperative anxiety and postoperative behavioral changes in children, including age, gender, temperament and ethnicity, previous hospital experience, type of anesthetic induction, type of surgery, and postoperative pain.

Age

The studies of the effects of age on anxiety during the induction of anesthesia have yielded inconsistent results. Younger children seem to be more anxious at separation from their parents8 and less cooperative during induction of anesthesia than older children.9,10 They also suffer from a greater incidence of postoperative behavioral disturbances,9,11,12 which may last up to 6 months after surgery.5 However, an observational study of 2122 children undergoing ambulatory surgery determined that distress at induction did not vary significantly with age.15 Infants younger than 1 year may or
may not express anxiety on separation from their parents and, depending on the in-
fants, may be easily distracted. Paradoxically, another study noted that children older
than 7 years were actually more anxious in the preoperative holding area than those
aged 4 to 7 years, although anxiety was not measured during induction of anesthesia. The
inconsistent results regarding the relationship between anxiety and distress and
age may, in part, be attributed to imprecise metrics that were used to measure the
anxiety in children, a paucity of prospective randomized controlled trials, and small
sample sizes.

Perioperative anxiety in children may depend primarily on their stages of develop-
ment. Each age group roughly correlates with a stage of development, and each
stage manifests different psychological issues that require different and specific ther-
apeutic approaches. Infants are less likely to experience separation anxiety, children
1 to 3 years experience separation anxiety but respond positively to distraction and
comforting measures, and children aged 4 to 6 years seek explanations and a desire
to maintain control of their environment. Furthermore, older children between the ages
of 7 and 12 years have strong desires to be involved in the decision-making process. Adolescents fear losing face and are concerned with their inability to cope. The last
2 age groups respond well to explanations, to maintain control of events, and to pre-
serve their privacy and independence as coping mechanisms to decrease anxiety.

Gender
Gender has not been found to be a factor involved in preoperative anxiety or in
postoperative behavioral problems in prepubescent children.

Temperament and ethnicity
Perioperative anxiety is influenced by a child’s temperament. Temperament is the
behavioral makeup of a child that influences the reaction to surrounding stimuli and
stressful environments. Four temperament components have been identified: emotionality, activity, sociability, and impulsivity. Temperament has been measured
using the EASI scale (emotionality, activity, sociability, impulsivity scale), which is an
observer-based measurement tool that uses the parents to assess their child’s
temperament. Parents score each of 5 patterns of behavior between 1 and 5 for a
total score between 5 and 25. In a prospective study of 183 children aged 2 to 10 years
undergoing elective surgery, situational anxiety of the mother, temperament and age
of the child, and quality of previous medical encounters significantly correlated with
preoperative anxiety. Previous surgery, premedication, and lack of enrollment in a
day care were predictors of child’s anxiety at separation from the parents. The Post-
hospitalization Behavior Questionnaire (PHBQ) is a tool to assess behavioral changes
in children after health care encounters. The PHBQ is a parental questionnaire that in-
cludes 27 items in 6 categories: general anxiety, separation anxiety, sleep anxiety,
eating disturbances, aggression toward authority, apathy, and withdrawal. Each
item is graded on a scale from 1 to 5. Low scores indicate a positive behavioral change
and high scores indicate a negative behavioral change. The PHBQ has good test
validity and reliability, although it has not been studied in all age groups and is subject
to parental bias.

Recent evidence suggests that cultural differences, including language and
ethnicity, may contribute to changes in behavior, specifically behavior during the
recovery period.

Previous hospital experience
A previous health care experience may influence a child’s preoperative level of anxi-
ety. Children who have had previous negative health care encounters experience
greater anxiety in the holding area and at separation from parents. Reducing a child’s anxiety during the preoperative period may not only benefit the current perioperative process but also decrease anxiety at subsequent anesthesia encounters. Stressful life experiences close in time to a hospital admission can also affect how a child reacts to anesthesia and the overall surgical experience.

**Type of anesthesia**
The effects of the type of anesthesia induction on preoperative anxiety and other behaviors are unclear. In children aged 2 to 7 years who were premedicated with midazolam, anxiety was least in those anesthetized by inhalational anesthesia compared with an intravenous (IV) or rectal induction with methohexitone. Postoperative behavior was similar among the 3 groups, although negative memories occurred more frequently in the inhalational group compared with the other 2 groups. At present, there is insufficient evidence to determine whether one type of anesthesia decreases perioperative anxiety any more or less than another.

**Type of surgery**
Whether the type of surgery influences the incidence of preoperative anxiety and postoperative behavior is unclear. Several studies concluded that the type of surgery does not increase the risk of postoperative maladaptive behaviors, whereas other studies found that surgery of the genitourinary system and inpatient surgery were associated with an increased risk of postoperative behavioral changes. Preoperative anxiety is similar for elective and emergency procedures. The effect of postoperative pain on the risk of postoperative maladaptive behavior is not well understood either. Using the PHBQ, one study found that pain was a significant predictor of behavioral changes that lasted up to 4 weeks, whereas another reported a poor correlation between the severity of postoperative pain and behavioral changes. The effect of the type of surgery on preoperative and postoperative anxiety and behavior remains unresolved.

**INTERVENTIONS**
The purpose of preoperative anxiolysis is to reduce a child’s anxiety and decrease the risk of negative postoperative behavioral changes. Preoperative anxiolysis also improves cooperation during induction and may contribute to increased parental satisfaction. Several strategies have been used to reduce preoperative anxiety, including PPIA, preoperative educational programs, sedative premedication, and distraction techniques. Additional studies are needed to determine the optimal intervention for each age group. Several tools have been used to assess preoperative anxiety. The Yale Preoperative Anxiety Score (YPAS) is an observer assessment tool designed for children between the ages of 2 and 6 years. The YPAS has shown good validity and reliability in several clinical trials. A modified version of the YPAS, the modified Yale Preoperative Anxiety Score (mYPAS), has been developed for children between the ages of 5 to 12 years. The mYPAS is based on the total score from 5 behavioral categories: the child’s activity, facial expressions, alertness and arousal, vocalization, and interaction with adults. The mYPAS has shown good validity and intraobserver and interobserver reliability in numerous clinical trials. Cooperation of a child during the induction phase of anesthesia has also been used as a surrogate measure of anxiety. The Induction Compliance Checklist (ICC) measures the cooperation of a child using a checklist of 10 items. The ICC has excellent interobserver and intraobserver variability, but the validity of this scale to measure preoperative anxiety has not been validated. A visual analog scale has also been used to assess cooperation of a child at induction.
PPIA

PPIA is a common practice in many countries but more common in Europe than in the United States. In a survey of US and UK anesthesiologists, 58% of US anesthesiologists agreed with PPIA but in only 5% of the cases were parents routinely allowed in the operating room. In contrast, 84% of British anesthesiologists allowed PPIA in more than 75% of the cases. Contrary to US anesthesiologists, most British anesthesiologists believed that PPIA decreased children’s anxiety, increased their cooperation, and benefited both the parent and the anesthesia provider. Fear of litigation has often been cited as an impediment to PPIA. Apart from isolated anecdotal cases, there is no evidence to support the notion that PPIA increases the risk of a lawsuit should an untoward event occur. Safety has also been cited as an impediment to PPIA.

Concerns over the safety of a child during PPIA are generally not substantive, although even when PPIA is routinely practiced, unusual circumstances may occur. Acceptance of PPIA is mainly a function of a provider’s experience, expertise, and available operating room logistical support. The level of anxiety of an experienced anesthesiologist is not increased by the presence of a parent at induction. The unavailability of an induction room or of an operating room staff member to accompany the parent back to the holding area is often cited as the main cause preventing the routine presence of parents at induction. Several studies concluded that perioperative anxiety is decreased by the presence of a parent during induction.

However, these studies have been criticized for their lack of randomization and the use of tools to assess anxiety that had not been previously validated. A total of 8 additional trials assessed PPIA, and none showed a significant difference in anxiety or cooperation during induction when parents were present. One study showed that PPIA was significantly less effective than midazolam in reducing children’s anxiety at induction. In a study using a visual analog score for cooperation, PPIA did not improve cooperation in children during induction. PPIA does not affect anxiety in infants younger than 1 year. In 2 studies of PPIA and preoperative anxiety in the holding area, on entering the operating room and during induction of anesthesia, the investigators found no correlation between parental presence and anxiety. A single measurement after induction showed reduced plasma cortisol levels in children of calm parents, shy and inhibited children, and in children older than 4 years. PPIA does not reduce the risk of postoperative behavioral changes as determined by the PHBQ, even with 6-month follow-up evaluations.

Several reasons may in part explain the lack of effect of PPIA on preoperative anxiety.

1. First, many studies have not addressed high anxiety levels experienced by parents, which are known to affect a child’s anxiety level and overall temperament.
2. The simple presence of a parent may be insufficient to decrease a child’s anxiety.
3. Even if a parent were present, the lack of a specific active role for the parent may actually contribute to the child’s anxiety.

It has also been shown that parents experience preoperative anxiety when they witness their child in distress. Parent anxiety has been well documented using a visual analog score and the State Trait Anxiety Inventory (STAI), which is a gold standard for measuring anxiety in adults. There are several sources of anxiety for parents. These include the following:

1. Concerns about how their child reacts to a new environment
2. Concerns about their child’s well-being
3. Concerns on witnessing their child’s loss of consciousness and immobility
4. Concerns that they are abandoning their child when they leave the operating room after the induction

Parents who are particularly vulnerable to experiencing anxiety during PPIA include:

1. The parents of young children
2. Parents of a single child
3. Parents in the health care field
4. Mothers of a child undergoing a surgical procedure

If given a choice, parents generally prefer to accompany their child during the induction of anesthesia, regardless of their level of anxiety. Parents believe their presence benefits their child. However, parental anxiety could actually negatively affect their child. Using the Global Mood Scale and the STAI, several studies have shown that children of anxious parents experience more anxiety than those of calm parents. A child’s anxiety in the holding area and after separation from the parent is greater if the parent is anxious. A child of an anxious parent is 3.2 times more likely to have persistent behavioral problems up to 6 months after a surgical procedure, compared with a child of a calm parent.

Although the role of PPIA in decreasing a child’s anxiety during induction is still debated, what is clear is that PPIA does not decrease the parent’s level of anxiety. In a study of parental anxiety, the level of anxiety was the same when measured in the holding area (control group) or after PPIA (intervention group). Some anxious parents found that separation from their child actually relieved their own anxiety. Only parents who were calm before induction of anesthesia felt less anxious when participating in their child’s induction. A single study demonstrated that PPIA reduces parental anxiety, but this study has been criticized for a lack of randomization. In the current environment of family-centered care, many advocate for parental involvement in all aspects of a child’s hospital experience as a strategy to increase overall parental satisfaction. However, even this assertion has been challenged as 2 studies noted that satisfaction with the perioperative experience did not improve with PPIA.

PREOPERATIVE PREPARATION PROGRAMS

Preoperative preparation programs to decrease preoperative anxiety have had mixed results, stemming from the inherent immaturity and lack of reliability in children and the variability of interventions needed to successfully address every age group, temperament, and baseline personality. In a study of 143 children aged 2 to 6 years, children who were randomized to the preoperative interactive book exhibited greater anxiety on the day of surgery but fewer behavioral changes 2 weeks after surgery than those who received the routine preoperative treatment. Parents in the intervention group reported that preoperative interactive book helped their child (87%) and themselves (83%). Children who were randomized to routine preoperative preparation were significantly more aggressive postoperatively than those who received the interactive teaching book preoperatively. In another study, children were randomized to either a preoperative preparation program that consisted of information, a tour and role play with child-life specialists, or no intervention. The anxiety of the children in the preoperative period was significantly less in the intervention group but did not reach statistical significance for the induction and postoperative periods. Children aged 2 to 3 years, those who were emotionally labile and those with previous hospital experience, were more anxious after the preoperative preparation program. Children older than 6 years were least anxious if they participated in the preoperative preparation program more than 5 days before surgery and most anxious if they participated...
1 day before surgery. Anxiety increased in children younger than 8 years who had a previous hospital experience and who viewed a preoperative videotape of hospital-related material the night before their surgery compared with those who viewed a nonmedical video. Children older than 8 years did not experience this increase in anxiety. Younger children become more anxious after participating in preoperative preparation programs because they have difficulty distinguishing fantasy from reality. Reality-based preparation programs may sensitize young children undergoing surgical procedures. To stratify the effects of different interventions on perioperative anxiety, one study compared the effects of a tour of the operating room plus a videotape plus role play with a tour of the operating room and video and with a tour alone in children aged 2 to 12 years. Those who participated in a tour of the operating room plus a videotape plus role play exhibited reduced anxiety in the holding area compared with the other 2 groups. However, beyond the holding area, the interventions did not affect perioperative anxiety. The investigators also determined that preoperative preparation program exerted no effect on postoperative behavior in children 2 weeks after their surgical experience.

Anxiety has also been measured in children after their parents read to them an age-appropriate interactive teaching book explaining the anesthesia process 1 to 3 days before surgery. Perioperative anxiety in the study and control groups was similar. The investigators reported a significant decrease in aggressive behavior after surgery in the teaching book group compared with the control group. Children who have undergone a psychological intervention—targeted behavioral strategy for surgery supervised by a pediatric psychologist are less anxious and more cooperative in the preoperative period and during the induction of anesthesia than controls. This psychological program has also shown to be more efficient in reducing a mother’s anxiety and increasing her satisfaction.

A novel preoperative preparation program is the ADVANCE family-centered behavioral preparation program which is an acronym for Anxiety-reduction, Distraction, Video modeling and education, Adding parents, No excessive reassurance, Coaching, and Exposure/shaping. This program is a multicomponent behavioral preparation program that in addition to standard preoperative management provides strategies and instructions to reduce preoperative anxiety, teach parents distraction techniques, video modeling and education before the day of surgery, PPIA, avoid excessive reassurance at induction of anesthesia, coach to reinforce the skills needed to succeed during induction, and exposure/shaping to familiarize the child with induction by mask. The effectiveness of ADVANCE, family-centered behavioral preparation, on preoperative anxiety and postoperative outcome measures was compared with PPIA alone, oral midazolam, and control groups. Anxiety in parents and children in the ADVANCE group was significantly less than that in the other 3 groups in the holding area. Furthermore, anxiety in children in the ADVANCE group was less than in those in the control and PPIA groups during induction of anesthesia. Anxiety and compliance in children in both the ADVANCE and midazolam groups were similar during induction of anesthesia. In terms of postoperative recovery, the incidence of ED and analgesic requirements in the recovery room in children in the ADVANCE group were less than those in the other groups. Discharge times for children in the ADVANCE group were less compared with times in the 3 other groups. In a postscript, the investigators conceded that a major obstacle in operating a program like ADVANCE was the large operational costs.

The effects of information or preparation programs for parents have also been studied. In a randomized study, discussing either routine or detailed anesthetic risk information and discussion regarding their child’s anesthetic did not affect anxiety levels
before the surgical intervention, on the day of surgery in the holding area, after separation from their child, or immediately after the intervention. The results were unaffected by both parental educational level and baseline parental anxiety.

Preoperative preparation programs to decrease preoperative anxiety in children can also reduce parental anxiety. Parents who watched a preanesthetic video to facilitate parental education and anxiolysis before pediatric ambulatory surgery were less anxious compared with the control group. Preoperative preparation programs also increase parental satisfaction. For example, children of parents who had acupuncture demonstrated more anxiolysis and were more cooperative during the induction of anesthesia compared with those whose parents had sham acupuncture. Moreover, the parents who received acupuncture were significantly less anxious than parents in the sham group. However, in 2 trials that reported the impact of audiovisual aids on preoperative and postoperative outcomes, preoperative videos did not significantly affect the anxiety of either the child or the parent.

PERIOPERATIVE INTERVENTIONS

The perioperative dialogue is a holistic intervention aimed at reducing perioperative anxiety in children. Perioperative dialogue is based on the beneficial effects of dialogue and continued support throughout the perioperative encounter. In children undergoing ambulatory surgery, perioperative dialogue reduces perioperative anxiety as determined by salivary cortisol concentrations and decreases postoperative morphine consumption.

PHARMACOLOGIC ANXIOLYSIS

Midazolam

The use of pharmacologic premedication varies widely among practices, age groups, and geographic location. The most commonly used agent for anxiolysis is midazolam. The major appeal of oral midazolam stems from its safety record, effectiveness, and reliability in reducing preoperative anxiety in children. The only substantive drawback of oral midazolam is its bitter taste, which may cause children to refuse to finish drinking it or to cause them to expectorate it.

Randomized controlled trials have established midazolam’s effectiveness as a preoperative anxiolytic in children. The dose of oral midazolam has not been clearly understood over the ages of children who need it, and this has led to underdosing or prolonged times to reach maximum effect. Most clinicians administer doses of 0.5 mg/kg without regard for the child’s age. The dose of oral midazolam for anxiolysis, analogous to inhalational anesthetics, increases with decreasing age. That is, a dose of 0.5 mg/kg will suit children aged 3 to 5 years, but for children aged 1 to 3 years, doses as large as 0.75 or 1 mg/kg may be required to achieve anxiolysis in 95% of children. This point has been studied from at least 2 perspectives, the pharmacologic and the neurobehavioral. To ensure a greater than 95% success in anxiolysis for children 3 years or younger, a dose of 0.75 mg/kg should be administered. This dose usually achieves a maximum effect within 10 to 15 minutes. For older children, an oral dose of 0.4 mg/kg is suitable for children 6 years or older and a dose of 0.3 mg/kg for those 10 years or older.

In addition to decreasing perioperative anxiety, midazolam decreased the incidence of negative behavioral changes, including separation anxiety and postoperative eating disturbances, although in one study, it actually increased negative postoperative behaviors. Preoperative midazolam may decrease the incidence of negative behavior by 2 postulated mechanisms, either by reducing preoperative anxiety or by causing
anterograde amnesia. Midazolam has been shown to confer anterograde amnesia in as little as 10 minutes. No serious complications have been reported after oral midazolam administration in doses between 0.2 and 1.0 mg/kg, although 2 children experienced dysphoric reactions after 0.75 and 1.0 mg/kg oral midazolam. Children with sleep-disordered breathing undergoing tonsillectomy have been given premedication with oral midazolam, 0.5 mg/kg, without serious sequelae. In an observational study, one of the 70 children who were enrolled experienced a transient desaturation to 77% for 5 seconds, awakening from the midazolam spontaneously, without stimulation or other intervention.

The effects of midazolam on the quality of emergence, discharge times, and postoperative behavioral disturbances have also been studied yielding conflicting results. Oral midazolam in a dose of 0.5 to 0.75 mg/kg delayed recovery from anesthesia in 3 studies but another study found no delay in recovery and hospital discharge after 0.2 to 0.3 mg/kg of oral midazolam in surgeries lasting 10 minutes. In a study that compared oral midazolam, 0.5 mg/kg, with PPIA, children who received midazolam were less anxious on entering the operating room and at induction of anesthesia compared with those with PPIA. The times to recover from anesthesia and the incidence of negative behavioral changes were similar in the 2 groups. Parental anxiety was significantly less when children who received midazolam were separated from their parents. In children undergoing an inhalational induction, oral midazolam was more effective in reducing preoperative anxiety than PPIA. When oral midazolam (0.5 mg/kg) was compared with oral midazolam plus PPIA, the incidence of perioperative anxiety was similar in the 2 groups. Parental anxiety postinduction was reduced and satisfaction with the perioperative process increased in the midazolam/PPIA group compared with the midazolam only group.

Midazolam has also been administered intranasally (IN) in a dose of 0.2 to 0.3 mg/kg in a 0.5 mL volume, with a time to peak effect of 15 minutes but a 2.5-hour elimination half-life. The most serious problem with this route of administration is a burning sensation in the nasopharynx after recovery from anesthesia. Midazolam has also been administered sublingually, rectally, and intramuscularly (IM), although these routes offer no particular advantages in children.

Midazolam interacts synergistically with propofol to reduce the propofol requirements during induction of anesthesia, a characteristic attributed to midazolam’s effects on the γ-aminobutyric acid (GABA) receptors. Midazolam also provides more favorable conditions for inserting laryngeal mask airways in the presence of propofol. Both characteristics have been cited as advantages to using midazolam for anxiolysis in the perioperative period.

Other Pharmacologic Agents

Clonidine, dexmedetomidine, ketamine, and sufentanil have all been used as anxiolytics in the preanesthetic period. Clonidine is an α2-adrenergic agonist with analgesic, anxiolytic, and sedative properties and decreases the anesthetic and postoperative analgesic requirements. Despite these properties, children who were scheduled for tonsillectomy surgery and who were premedicated with clonidine (4 μg/kg) exhibited more anxiety during separation from their parents, increased opioid requirements postoperatively, and greater postoperative pain scores compared with those who were premedicated with oral midazolam (0.5 mg/kg). In a meta-analysis of 10 studies of healthy children undergoing ambulatory surgery who were premedicated with oral clonidine, a dose of 2 to 4 μg/kg decreased both anxiety at induction of anesthesia and the incidence of ED. This meta-analysis neither addressed the effects of preoperative clonidine for surgeries of prolonged duration nor did it stratify for
confounding factors such as the effects of clonidine on postoperative nausea and vomiting (PONV). The major advantages of the $\alpha_2$-agonists include an absence of respiratory depression and fewer paradoxical reactions compared with midazolam. However, there are several major disadvantages of clonidine use, including its slow onset of action (>60 minutes), prolonged duration of action, and its sedation effects. At a dose of 4 $\mu$g/kg, the clinical effects and peak blood concentration of oral clonidine occur at 60 and 90 minutes, respectively. This slow onset of action precludes the use of clonidine in many busy ambulatory pediatric anesthesia practices.

Dexmedetomidine is another $\alpha_2$-adrenergic agonist that has also been used for preoperative anxiolysis. Its $\alpha_2$ receptor specificity is 8-fold greater than for clonidine, reducing the frequency of side effects. Despite dexmedetomidine’s slow onset time (30–60 minutes), its duration of action (85 minutes) is less than that of clonidine, which makes it a candidate for use in ambulatory surgery. IN dexmedetomidine has also been used for premedication in children. IN dexmedetomidine, 1 $\mu$g/kg, provides more effective sedation than oral midazolam, 0.5 mg/kg, or oral dexmedetomidine, 1 $\mu$g/kg. In a dose response study of IN dexmedetomidine, 2 $\mu$g/kg provided better sedation in children 5 to 8 years old than 1 $\mu$g/kg. In children 1 to 4 years old, 1 or 2 $\mu$g/kg provided equivalent anxiolysis. To further exploit combination premedications, the combination of IN dexmedetomidine (2 $\mu$g/kg) and oral ketamine (3 mg/kg) provided easy separation from their parents, accepted IV cannulation, and did not lead to side effects and postoperative complications when compared with smaller doses of IN dexmedetomidine, larger doses of ketamine, and oral ketamine alone (5 mg/kg).

Ketamine has been developed as a premedication for cognitively impaired children who are uncooperative and for healthy unimpaired children. For cognitively impaired children, IM ketamine, 2 to 5 mg/kg, is administered from a stock solution of 100 mg/mL. It has an onset time of approximately 10 minutes. The children should be seated on a gurney before IM ketamine is administered to avoid having to lift the child from the recumbent position once the child is completely unconscious. Oral ketamine (5–6 mg/kg) was developed as an alternative to oral midazolam, although emesis has proven to be a problem with ketamine. Some prefer a 50–50 mixture of midazolam (0.3 mg/kg) and ketamine (3 mg/kg) to mitigate the side effects of the medications.

IN sufentanil (2 $\mu$g/kg) is an effective premedication, although one study reported a 23% incidence of desaturation (<90%). Chest wall rigidity occurred in 45% of children after administration of 4.5 $\mu$g/kg IN.

**ADDITIONAL NONPHARMACOLOGIC STRATEGIES**

Several nonpharmacologic strategies have been found to be effective for anxiolysis in children. Clowns, hypnosis, low sensory stimulation, and handheld video games all reduce preoperative anxiety. In a systematic review of 17 trials involving 1796 children, anxiolysis after several nonpharmacologic strategies was evaluated. Video games given to children in the preoperative period significantly reduced anxiety at induction compared with no intervention or premedication. Clowns have also been shown to reduced anxiety in children. In contrast, hypnosis and music therapy did not reduce anxiety at induction of anesthesia. PPV caused no anxiolysis in 8 trials and was significantly less effective as an anxiolytic than oral midazolam in one study. Other distraction techniques such as playing with a favorite toy, viewing animated cartoons, listening to humorous stories, role playing, creative reinterpretation of the environment, and magic tricks reduced anxiety and increased the level of
cooperation compared with controls.\textsuperscript{80–82} Certain provider behaviors have been shown to exacerbate anxiety. Repetitive reassurance, excessive talk, apologizing, and adult-appropriate medical explanations all increase perioperative anxiety in children.\textsuperscript{83} although parental reassurance may not prove to be as harmful as originally believed.\textsuperscript{84} Other language such as empathy, distraction, and assurance may be effective to promote coping.\textsuperscript{83} To address this issue and to train health care providers to improve their behaviors, the Provider-Tailored Intervention for Perioperative Stress (P-TIPS) was developed to promote children’s coping and decrease behaviors that may exacerbate children’s distress. In a trial of the effectiveness of P-TIPS, the rate of desired behaviors increased and the rate of undesired behaviors decreased in participants compared with control.\textsuperscript{85} Furthermore, parents who were in contact with trained providers also demonstrated an increase in their rates of desired versus undesired behaviors.\textsuperscript{85} The study of the effectiveness of P-TIPS in preventing anxiety and improving the recovery process (in terms of postoperative pain, recovery room stay, nausea and vomiting, ED, maladaptive behavioral change, and parental anxiety and satisfaction) in children undergoing surgery is currently underway.\textsuperscript{86}

**ED**

**Definition and Incidence**

ED is a complex of perceptual disturbances and psychomotor agitation that occurs most commonly in preschool-aged children in the early postanesthetic period. The term ED is often used interchangeably with emergence agitation and postanesthetic excitement. For the purposes of this review, the authors refer to this complex as ED.

ED has been defined as a dissociated state of consciousness\textsuperscript{87} in a child who is crying, inconsolable, and thrashing. In this state, children typically do not recognize familiar objects or people such as parents or caregivers.\textsuperscript{87} It occurs in the recovery room, in the early recovery period. Wells reported paranoid ideation as a component of ED in an adult and children.\textsuperscript{88} In general, combative behavior more aptly describes the behavior found in children with ED rather than restlessness and incoherence.\textsuperscript{89} The authors define ED as “a disturbance in a child’s awareness of and attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate postanesthesia period.”\textsuperscript{90} The time course of ED usually begins as the child awakens from general anesthesia (typically in the first 30 minutes of recovery), lasts 5 to 15 minutes, and resolves spontaneously. The incidence of ED ranges from 5.3% to 50% and depends on several factors: the metric used to measure it, age group, anesthetic technique, and type of surgery.\textsuperscript{91}

ED is a cause for concern because it may result in injury to the child, disruption of the surgical site, and accidental removal of the IV catheter and surgical drains. In addition, a child experiencing ED requires extra nursing care and may require the use of supplemental sedatives that may delay discharge from the recovery room. The underlying cause of ED has not been clearly elucidated. Several factors have been suggested as potential causes of ED, including factors related to patient characteristics, anesthetic technique, and type of surgery.

**Assessment Tools**

More than 16 rating scales have been used to measure ED. The lack of consensus on a single tool with which to assess ED demonstrates the inherent difficulty in interpreting maladaptive behavior in small children, and especially in children who are not able to verbalize pain or anxiety. Most scales assess emotional distress and agitation, which are associated features rather than core features of a true ED.\textsuperscript{92} Crying, agitation, and
lack of cooperation have been included in several scales, but these behaviors are not specific to ED. They may also characterize children who are in pain, as many are after surgery, or who are frightened during the early emergence period from general anesthesia. These behaviors do overlap with behaviors measured in behavioral pain scales such as the Faces Legs Activity Cry and Consolability scale, the Children’s and Infants’ Postoperative Pain Scale, and the Children’s Hospital of Eastern Ontario Pain Scale. Hence, it is fair to state that agitation does not always indicate ED. However, agitation and thrashing requiring restraint are the most frequently used parameters to define ED in children.

The PAED scale was developed to specifically assess ED in young children. It consists of 5 psychometric items: the child makes eye contact with the caregiver, purposeful movement, awareness of the surroundings, restlessness, and whether the child is inconsolable. Items are each scored on a scale from 0 to 4. When the total score exceeds 10, ED is likely present, although some have suggested that a score greater than 12 more likely confirms ED. The PAED scale has good reliability and validity, having been used in more than 90 studies to date. A PAED score of 5 does not mean there is half a chance of ED, but rather any score less than the threshold of 10 (or 12) has no meaning in terms of ED. PAED has been compared with other scores with variable results.

Efforts have been undertaken to further refine the behaviors associated with ED. Activity; nonpurposefulness; eyes averted, stared, or closed; no language; and nonresponsivity appears to be significantly associated with ED. These behaviors are not significantly associated with pain or tantrum and are believed to reflect the true Diagnostic and Statistical Manual of Mental Disorders IV/V diagnostic criteria for delirium. A logistic regression showed that eyes averted or stared and nonpurposefulness were significant predictors of ED, whereas no language and activity did not significantly predict ED.

**Causative Factors**

**Age**

Children between the ages of 2 and 5 years are more likely to experience ED on recovery from general anesthesia, with no gender predilection. The psychological immaturity of a child’s nervous system and the rapid awakening from general anesthesia in an unfamiliar environment may be responsible for the genesis of ED. It has also been proposed that delirium in children and in the elderly may have a similar pathway. Immaturity of the cholinergic centers and the hippocampus and low levels of neurotransmitters may provide an explanation for the susceptibility of younger children to ED. It has been suggested that the GABA receptor could be excitatory rather than inhibitory in early infancy, explaining this paradoxic reaction to anesthesia in young children. As the child matures, the GABA receptor transforms into an inhibitory neurotransmitter, and the reaction no longer occurs, as in the adult. These receptors could be excitatory rather than inhibitory in early infancy because of a switch from high to low chloride content in the neurons. Other evidence, however, provides a conflicting view leaving the mechanism behind the ED behavior unexplained.

**Preoperative anxiety and temperament**

Preoperative anxiety has been associated with an increased likelihood of a restless recovery and postoperative maladaptive behaviors. However, a clear relationship between preoperative anxiety and ED has not been established. The odds of experiencing ED increases 10% for each increment of 10 points in a child’s preoperative anxiety score (mYPAS). The odds ratio of having new-onset postoperative maladaptive
behavior is 1.43 for children with marked ED, as compared with children with no symptoms of ED. A 10-point increase in the preoperative anxiety scores increase the odds that a child will have a new-onset maladaptive behavior after surgery by 12.5%. Despite these data, a statistically significant relationship between preoperative anxiety and postoperative maladaptive behaviors such as ED remains unconfirmed. It is likely that the underlying emotional temperament of a child determines his responses to outside stimuli and the degree to which preoperative anxiety and postoperative agitation are manifested. Children who are emotional, impulsive, or withdrawn are at increased risk for developing ED.

**Anesthetic technique**

ED has been reported in children after both inhalational and intravenous anesthesia. Sevoflurane, desflurane, isoflurane, and to a lesser extent halothane have all been implicated as causative agents for ED. Most of the intravenous agents (midazolam, remifentanil, propofol, ketamine, and barbiturates) have also been associated with ED, although the incidence with these latter agents is far less than it is with inhalational anesthetics. Research into the etiology of ED has been made difficult when investigators have selected a surgical model that is associated with pain in the recovery room, a behavior that is often difficult to distinguish from ED, and when scales are used to diagnose ED that have not been validated to measure ED.

In children undergoing magnetic resonance imaging (MRI), the incidence of ED after use of sevoflurane may be up to 7-fold greater than with that of halothane. ED occurs more commonly after ether inhalational anesthetics than after alkanes like halothane, suggesting that this is a class action. Considering that the electroencephalogram changes that are associated with sevoflurane are similar to those observed with either desflurane or isoflurane but different from halothane, it is possible that ED is related to the interference with the balance between neuronal synaptic inhibition and excitation in the central nervous system produced by the ether anesthetics.

Sevoflurane has been shown to potentiate GABA\(_A\)-receptor-mediated inhibitory postsynaptic currents at high concentrations and to block these currents at low concentrations. This biphasic effect of sevoflurane on GABA\(_A\)-receptor-mediated postsynaptic currents may be a contributing factor to the genesis of ED in young children.

Specific brain metabolites may also contribute to ED in young children. The metabolic signature of sevoflurane shows greater brain concentrations of lactate and glucose than that of propofol. Lactate and glucose correlate positively and total creatine negatively with ED. The association between ED and serum lactate concentration suggests that anesthesia-induced enhanced cortical activity in the unconscious state "may interfere with rapid return to coherent brain connectivity patterns required for normal cognition upon emergence of anesthesia."

Several other factors have also been implicated as causes of ED. Depth of anesthesia and rapid awakening were postulated as contributing factors, but subsequent studies determined they were not associated with ED. Although some have suggested that the type of surgery (such as head and neck) may be associated with ED, there is no evidence to support this claim either.

**Pain**

The presence of postoperative pain may contribute to the genesis of ED in preschool-aged children. Several studies reported that the incidence of ED in children decreased after analgesic/sedatives were administered intraoperatively. For example, the incidence of ED in children who were anesthetized with halothane or sevoflurane...
decreased 3- to 4-fold when ketorolac was administered intraoperatively. Similarly, ED was prevented when fentanyl, 1 or 2.5 μg/kg, was administered intraoperatively to children undergoing ambulatory surgery, although the fentanyl preserved the rapid recovery associated with desflurane anesthesia. The incidence also decreased after IN fentanyl was administered intraoperatively. The incidence of ED decreased after administration of clonidine 3 μg/kg IV or via the caudal space or 2 μg/kg IV and dexmedetomidine 0.2 μg/kg IV. The possibility that these analgesics sedate the child to prevent or attenuate ED rather than provide pain relief has not been clarified. To further investigate the role of pain in this phenomenon, the incidence of ED has been determined in children aged 1 and 6 years undergoing inguinal hernia repair. Two studies demonstrated that agitation occurred significantly more frequently after use of sevoflurane anesthesia than that of halothane anesthesia despite the presence of an effective but preemptive caudal block. Similarly, the incidence of ED after sevoflurane or desflurane was similar when analgesia was provided by a caudal block. However, to completely remove pain as a confounding variable, the incidence of ED was determined in children undergoing diagnostic MRI. ED occurred in 33% of young children anesthetized with sevoflurane compared with 0% of those anesthetized with halothane. The same group determined that the incidence of ED decreased from 56% to 12% when IV fentanyl, 1 μg/kg, was administered to children anesthetized with sevoflurane for MRI 10 minutes before discontinuation of the anesthetic suggesting the sedative effect of fentanyl may be contributory to attenuating ED.

Inadequate pain control remains a potential cause of or contributor to the incidence of ED after brief surgical procedures for which the peak analgesic effect of the agent administered is delayed until the child is awake. Although pain cannot be entirely excluded as a contributing factor to the presence of ED, current evidence suggests the influence of other mechanisms in the cause of ED. It is likely that several factors combined and specific characteristics of a child’s temperament contribute to the development of ED.

PREVENTION AND TREATMENT OF ED

The only strategy that could prevent ED from occurring at all is to use a total intravenous anesthetic approach for the anesthetic procedure. The authors generally use a propofol infusion, supplemented with opioids and/or midazolam, with analgesia provided by either a regional block or opioid. This approach may be supplemented with nitrous oxide as well. Using this technique, the incidence of ED approaches zero. Propofol, either as a single bolus or administered as an infusion has been shown to decrease the incidence of ED after sevoflurane anesthesia. Preoperative administration of midazolam may decrease the incidence of ED, although the evidence is still conflicting. Clonidine and dexmedetomidine have also been noted to decrease the incidence of ED. Clonidine may exert its effect centrally by reducing the noradrenaline content in adrenergic areas of the brain observed with all the inhaled anesthetics. This increase in noradrenaline content is prominent during sevoflurane or isoflurane anesthesia and persists in some areas of the brain during the recovery phase. Magnesium sulfate infusion reduces the incidence of ED during tonsillectomy in children with a number needed to treat of 3. Chloral hydrate has not shown to decrease the incidence of ED. Preemptive analgesia with opioids, ketorolac, and α2-agonists and regional anesthesia have all been shown to decrease the incidence of ED in children. Their effects may be due to combinations of analgesia and sedation.
ketamine, and oral transmucosal fentanyl citrate have also been used to decrease the incidence of ED. Remifentanil however, has yielded conflicting effects on the incidence of ED. A meta-analysis of the pharmacologic prevention of ED after sevoflurane and desflurane in children reported that propofol, ketamine, fentanyl, and preoperative analgesia successfully prevented ED.

The decision to treat ED in the recovery room is often influenced by the severity and duration of the symptoms and by concerns over the safety of the child, disruption of the surgical site, and the accidental removal of IV access and drains. There is no evidence, however, that if left untreated ED has long-term sequelae in children. However, steps should be taken to protect the child from self-injury and to provide a quiet and dark environment where the child can recover. Parental presence has not been shown to affect either the incidence or the severity of ED, except in one study. If parents are present during ED, they should be appropriately reassured and be made aware that the situation is self-limiting and that the child will return to his or her normal behavior in due course. If treatment of ED becomes necessary, a single bolus of propofol (0.5–1.0 mg/kg IV), fentanyl (1–2.5 μg/kg IV), or dexmedetomidine (0.5 μg/kg IV) has been successful in decreasing the severity and duration of the episode.

REFERENCES


