Teary Tots, Yelling Youths, and Kicking Kids: A Synopsis of Pediatric Emergence Delirium/Agitation, Treatment and Prevention

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A Synopsis of Pediatric Emergence Delirium/Agitation

As with all areas of medical treatment, pediatric surgery rates are increasing annually. Coupled with this is the need for safe, effective anesthetic care. In 2006, about 2.3 million American youths under the age of 15 incurred anesthetics for ambulatory surgery.[1] In addition, approximately 450,000 American youths under the age of 18 underwent inpatient anesthetic/surgical care. An estimated 25% of these patients are 3 years of age or younger.[2]

The majority of pediatric procedures are performed under general anesthesia (GA), with/without local anesthetic, and initiated by way of inhalational induction with sevoflurane and oxygen (O_2), with or without nitrous oxide (N_2O). GA is predominantly maintained with the same agents. Upon emergence, and continuing for an average of 30 minutes postoperatively, 2-80% of these patients (approximately 55,000 to 2.2 million) will experience inconsolable crying, thrashing, and screaming, which creates a potential for harm to themselves or others, including healthcare providers. This behavior can delay hospital discharge, possibly resulting in unanticipated inpatient admission for follow-up care/treatment. Furthermore, new onset of maladaptive behaviors in the postoperative period lasting a month or longer have been documented.[3] Without proper prevention, diagnosis, and treatment, these patients fall subject to pediatric emergence delirium (ED), commonly termed emergence agitation (EA).

The phenomenon of ED was first referred to as hyper-excitation or post-anesthetic excitement by Eckenhoff et al. in the early 1960's.[4] They reported a 12-13% incidence, noting the irrational and sometimes dangerous behavior in children emerging from ether, cyclopropane, or ketamine general anesthesia, and most notably after tonsillectomy, thyroidectomy, or circumcision. Their study revealed significantly higher rates of ED in pediatric patients 3-9 years

of age, who received cyclopropane or ether anesthesia for tonsillectomy, along with barbiturate preoperative medication for sedation.[5]

Soon thereafter, the pediatric anesthetic community realized two major milestones. First, halothane, a halogenated inhalational anesthetic agent, was introduced and became the mainstay of pediatric anesthetic care. Next, pediatric pain gained recognition. The increased use of narcotics, and other analgesics, with halothane use abated ED occurrence. Unfortunately, ED resurfaced with the introductions of the newer, shorter-acting insoluble inhalational anesthetic agents, sevoflurane and desflurane.[6]

Statement of the Problem

Studies have produced widely variable incidence of ED/EA. Some report a 2-55% occurrence rate for all pediatric patients anesthetized with halothane, isoflurane, sevoflurane, and desflurane.[7] Yet others report an incidence as high as 10-80%.[3] Patients experiencing this phenomenon in the post-anesthesia care unit (PACU) risk harm to themselves, short- and long-term, as well as others. The restlessness and inconsolability present during an ED episode are commonly accompanied by thrashing, screaming, crying, and disorientation that can lead to dislodgment of drains, removal of intravenous (IV) catheters, damage/removal of other medical devices required for care,[5] and increased surgical site hemorrhage and pain.[7] Assigned healthcare personnel also risk injury, albeit rare and usually minor.

Most cases of ED/EA are considered self-limiting and patients recover within 30 minutes of anesthetic emergence, but cases lasting over 48 hours have been reported.[8] Additionally, long term sequelae from ED/EA have been noted, including new onset maladaptive behaviors, such as eating issues, sleep disturbances/night terrors, separation anxiety, and apathy.[3,9-10]

Pediatric Emergence Delirium/Agitation

Terminology

Although first described by Eckenhoff et al. as post-anesthetic emergence excitation, the phenomenon has many aliases. In available literature, the terms emergence delirium and emergence agitation are used interchangeably. This is largely due to the heterogeneous clinical presentation of the phenomenon,[6] however this causes confusion and mis-recognition.

Emergence is the period of recovery from general anesthesia when normal bodily functions return after a period of unconsciousness.[18] It is the time of discontinuation of anesthetic maintenance agents leading to the return of spontaneous respirations and airway reflexes, extubation, transport to the PACU, and wakefulness. The patient is returning to stage one (pre-anesthetic) functioning, however is still at risk of untoward effects from the stage two (excitement or delirium) anesthetic state. Stage two includes irregular respirations, increased muscle tone, involuntary/reflexive movements, dilated pupils, and the elevated risk of vomiting, aspiration, laryngospasm, and bronchospasm.[19]

Agitation is described as excessive motor activity. It is very common in the post-operative pediatric patient and is most commonly the result of pain or anxiety, which is often easily relieved.[3] Unfortunately, this definition fails to encompass the full clinical presentation of the phenomenon.

Delirium is a complex psychiatric condition characterized by perceptual disturbances, hallucinations, and psychomotor agitation.[6] This definition more completely describes pediatric ED, given the presentation of incoherence, irritability, and uncooperative/uncompromising behaviors, with screaming, crying, restlessness, and combative actions.[11] ED was defined by Sikich and Lerman[12] 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 post-anesthetic period."

While ED is a more complete definition/description, the ability to fully evaluate a pediatric patients psychological state during emergence from anesthesia is difficult, if not impossible.[13] Although the literature historically uses both terms interchangeably, for completeness and the purposes of this article, the phenomenon will be referred to as emergence delirium (ED).

Measurement Tools

Many ED measurement/diagnosis tools have been developed. The earliest tools utilized pain scales. As it was discovered that pediatric patients possess central nervous system (CNS) nociceptive systems mature enough to sense pain and mount a neuroendocrine response, anesthesia providers began treating pediatric surgical pain. The administration of narcotics managed pediatric pain effectively and further led to a precipitous drop in ED occurrence.[6] As a result, it was postulated that pain was the cause of ED. Pain scales for pediatric patients were then developed and utilized. These include visual analog scales, Baker-Wong FACES-type visual analog pain rating scales, and categorical point scales such as the Face, Legs, Activity, Cry, Consolability (FLACC) preverbal pediatric patient pain scale[14,15] (appendix A) or the Childrens Hospital of Eastern Ontario Pain Scale (CHEOPS)[20] (appendix B).

Although ED rates declined with improved pain management for pediatric patients, ED experienced a resurgence. Researchers were forced to abandon pain hypotheses and look in other directions. Abdelhalim and Alarfaj[16] stated,"..pain cannot be considered as the sole contributing factor to EA." As a result of the complexities of the phenomenon, researchers retained pain as an indicator on many scales but added further criteria including psychological components, such as

agitation and delirium. Currently, the most widely used tool is the Pediatric Anesthesia Emergence Delirium (PAED) scale (appendix C). It measures pediatric patient activity and mood in 5 areas to develop a score that rates the degree of ED present.[17] Although these tools are reliable, easily applied, and can aid in diagnosis and treatment of ED, they are unable to preemptively identify patients at risk.

Researchers have additionally employed parent survey methods. These tools have been used to assess patient recovery and behavioral characteristics from the immediate post-operative period through the first week after discharge. Reliable tools have been developed and have produced some insight as to possible causative agents of ED. The only predictive factor for ED incidence may be preoperative anxiety, measured by way of a three-point scale.[23] Further instruments are under development, but fail to sufficiently identify at risk patients preemptively.

CAUSATIVE FACTORS/AGENTS

Independent Risk Factors

After first describing the phenomenon of ED, Eckenhoff et al. reviewed 14,436 post-operative pediatric anesthetics. Statistically significant correlations were found between ED and 1) patients 3-9 years of age, 2) cyclopropane or ether anesthetics, 3) tonsillectomy, and 4) premedication with a barbiturate. They further proposed that a feeling of suffocation led to ED, specifically in pediatric ear, nose, and throat (ENT) surgery, especially tonsillectomy.[4] More recently, Voepel-Lewis, Malviya, and Tait identified 10 factors most closely associated with ED; 1) younger age, 2) first surgical experience, 3) poor adaptability, 4) ophthalmologic and 5) otorhinolaryngologic procedures, 6) sevoflurane, 7) isoflurane, 8) sevoflurane/isoflurane, 9) analgesics, and 10) rapid emergence.[8]

Pediatric Emergence Delirium/Agitation

Age. Research affirms that age is an independent risk factor for ED. Patients 3-5[25] or 2-5[26] years of age are at greatest risk of ED occurrence. However, Przybylo et al. concluded that ED incidence is greatest after 62 months of age.[27] It is generally agreed that younger children are more likely to exhibit ED than school-age children.[8,26,27]

Psychological and physiological immaturity coupled with rapid emergence from anesthesia in a foreign environment are the most likely causes in this subpopulation.[6] Furthermore, Martini suggests that the immature hippocampus and underdeveloped central nervous system (CNS) cholinergic function may be sites of ED susceptibility.[28]

Surgery Type. Eckenhoff et al. suggest increased rates of pediatric ED after head and neck surgery.[6] The greatest rates of ED have been reported following urologic,[3] tonsilar, thyroid, middle ear, and ophthalmologic procedures.[8,29]

Pain. Many mechanisms of action (MOA) have been proposed in an effort to understand the phenomenon of ED. The earliest hypotheses were related to nociceptive pain in pediatric patients. Inadequate treatment of pain, in patients once believed to be unable to sense pain and mount a normal pain response, has been blamed for ED occurrence. Treatment of pediatric pain was found to reduce the incidence of ED dramatically, identifying pain as the causative agent of ED.[6] However, this has been found to be untrue. Studies of analgesic agents have produced mixed results. Some report a decrease in ED incidence while others find no significant difference. For example, studies using IV ketorolac demonstrated no difference in ED occurrence when compared to placebo.[23] Furthermore, studies of pediatric patients reporting for non-painful procedures, most notably imaging procedures (MRI or CT)[30,31] or eye examinations[32] performed under general anesthesia have manifested symptoms of ED, despite the absence of painful

stimuli. However, further studies continue to conclude that children with higher pain scores most frequently present with symptoms of ED in the PACU.[15]

Rapid Emergence/Modern Anesthetic Agents. With the advent of the newer insoluble inhalational anesthetic agents, sevoflurane and desflurane, anesthesia providers have recognized a resurgence of ED. After rapidly emerging from anesthesia, feelings of confusion, apprehension, and disorientation in the unfamiliar immediate post-anesthetic environment coupled with the decreased adaptability of young pediatric surgical patients are often blamed for ED occurrence.[26,29,33,34] Younger children are unable to effectively cope with the newly presented environmental stresses and become more easily delirious and agitated as compared to older pediatric patients.[6]

Additionally, sevoflurane and desflurane may equally and intrinsically be responsible for ED versus rapid emergence.[35,36] Propofol anesthesia similarly produces rapid emergence, but smoother and more pleasantly in pediatric patients.[6] Studies of general anesthesia with sevoflurane versus propofol have shown statistically significant higher rates of ED in the sevoflurane treatment groups.[28, 37-39] The same results were found when comparing desflurane/nitrous oxide anesthetic maintenance with propofol/remifentanil total intravenous anesthesia (TIVA).[40] No further improvements have been achieved by slowly decreasing inspired sevoflurane concentrations at the conclusion of surgery[41] and there is no statistical difference in ED occurrence between young children entering the PACU still sleeping (deep extubation/emergence) versus fully awake.[42]

Pre-Operative Anxiety/Temperament. It is speculated that the emotional/psychological states and overall temperament of pediatric patients pre-operatively directly affect the severity and occurrence of ED post-operatively. An association between increased risk of ED and ED-

like behavior has been reported in pediatric patients who displayed high levels of pre-operative anxiety.[23,43,44] Preoperative anxiety manifested by parents/guardians further increases ED risk.[9] In contrast, studies have found no correlation between pre-operative anxiety levels of pediatric surgical patients and ED incidence.[15,27] These studies concluded that post-anesthetic behavior was more dependent upon patient age and anesthetic technique utilized rather than pre-operative anxiety level.[27]

Further studies, of pre-operative pediatric patient temperament, have demonstrated that patients who are more emotional and impulsive while less social[9] and less adaptable to environmental changes[8] were at higher risk of developing ED. Vlajkovic and Sindjelic[6] state, "It is likely that there is some substrate innate to each child that will elicit, to a larger or lesser extent, a fearful response to outside stimuli, depending on the interaction between the child and the environment. This reactivity, which describes excitability, responsivity, or arousability of the child, might be the underlying substrate from which both preoperative anxiety and ED arise." They further note that although factors related to temperament, emotional, and psychological states of pediatric patients pre-operatively are important sources of variability when studying ED occurrence, they are difficult factors to control.

Proposed Mechanisms of Action

The precise mechanism(s) of action for pediatric ED incidence/stimulation is unknown and highly debated. One preeminent theory describes the role of variable rates of neurologic recovery and stimulation/suppression in specific and unique regions of the brain.[45] A CNS subunit, known as a pontine nucleus and located near the pontomesencephalic junction, the locus coeruleus (LC), has become a predominant site of relevance. The LC is the major noradrenergic (noradrenaline) nucleus of the CNS responsible for regulation of autonomic activity and

arousal.[46] It is a primary wakefulness-promoting nucleus with excitatory projections to the cerebral cortex, cholinergic neurons of the basal forebrain, thalamus, serotoninergic neurons of the dorsal raphe, and cholinergic neurons of the pedunculopontine and laterodorsal tegemental nucleus. LC activation is also excitatory to the amygdala, resulting in increased levels of anxiety and enhanced formation and retrieval of emotional memories. Furthermore, the LC possesses inhibitory projections to gamma-aminobutyric acid (GABA) neurons of the basal forebrain and ventrolateral preoptic area. When stimulated, its complex network produces increased sympathetic activity and decreased parasympathetic activity, and is the sole source of cortical noradrenaline.[46]

LC stimulation promotes the release of noradrenaline in the CNS. The primary site of noradrenaline stimulation in the CNS is the alpha-1 adrenergic subunit. There are also less pronounced stimulations produced at beta-1 and alpha-2 CNS adrenergic sites.[46] Areas of the forebrain, diencephalon, brainstem, cerebellum, and spinal cord are stimulated resulting in an array of responses. These responses include 1) increased levels of cortical arousal, consciousness, and neuronal excitation via alpha-1 stimulation of neocortex (coeruleo-cortical pathway) and thalamic sites, stimulation of serotogenic neurons of the dorsal raphe nucleus, and inhibition of GABAergic basal forebrain and hypothalamic (ventrolateral preoptic) sites, 2) increased fear/anxiety responses and emotional memory formation/retrieval abilities via amygdala stimulation, 3) increased stress response via hypothalamic (paraventricular nucleus) sites, increased heart rate (HR) and blood pressure (BP) via inhibitory responses to the parasympathetic vagal nuclei (coeruleo-vagal pathway) and rostroventrolateral medulla (coeruleo-vasomotor pathway), 4) analgesia via alpha-2 stimulation of dorsal horn spinal cord and sensory nuclei (trigeminal sensory nucleus) sites, and 5) increased muscle tone and

responsiveness via alpha-1 stimulation of ventral horn spinal cord sites.[46] The final products of LC activation typify the clinical presentation of ED.

Activation of the LC further correlates with increased levels of arousal as evidenced by increased electroencephalograph (EEG) activity with a reduction of both slow wave and rapid eye movement (REM) sleep in subjects.[46] Sevoflurane has been shown to directly stimulate the LC in rats.[47] Furthermore, at high concentrations sevoflurane will potentiate and at low concentrations block $GABA_A$ receptor mediated inhibitory postsynaptic currents (IPSC).[48]

Additionally, sevoflurane produces unique EEG patterns in humans when compared to other volatile anesthetic agents, and causes cardiovascular excitation resulting in increased HR and BP.[49] This hyper-dynamic response is in direct proportion to EEG epileptiform activity.[49-51]

Cortical neuronal excitation from sevoflurane is capable of producing epileptiform activity as evidenced by convulsive-like movements and EEG patterns in patients with no history of seizures.[49-54] This most commonly occurs at high inhaled concentrations, greater than 6%, and is increased with hyperventilation.[49,51] In contrast, isoflurane and halothane are capable of producing convulsive-like movements but yield no changes in EEG patterns. However, desflurane produces no abnormal motor activity and no changes in EEG patterns.[49]

Additionally, each volatile inhaled anesthetic agent can cause ED[13,32-35,38,55-59]. An intrinsic stimulatory/excitatory, depressant, or metabolic factor related to these agents or stimulation/suppression of a unique bronchial receptor(s) may be responsible. This is supported by evidence that children given a combination of sevoflurane for induction and isoflurane for maintenance of general anesthesia were twice as likely to manifest ED when compared to other anesthetic treatments.[7] Furthermore, continuous IV propofol infusion for general anesthesia maintenance in pediatric patients, whether used as the sole anesthetic agent via TIVA or begun

after sevoflurane inhalational induction, produces little to no incidence of ED.[32, 37-40,61,62] In addition, a single IV bolus of propofol at the conclusion of surgery significantly reduces ED occurrence after volatile inhalational agent general anesthesia in pediatric patients.[62,63]

CNS neurologic immaturity is another theoretical MOA. Children less than 5 years of age are continuing to develop CNS function and maturity, most notably CNS myelination, hippocampal function, and cholinergic development.[28] This neuro-anatomic difference when compared to adult patients may result in ED occurrence.[47] There are age-related differences in CNS receptor activity. $GABA_A$ receptor subunits may be excitatory in the early postnatal period and become inhibitory with increasing age due to a change from high to low inter-neuronal chloride content.[64]

ED may also occur from CNS direct neuronal excitement or damage, indirect inhibition of neuronal reparative agents such as CNS glial cells, or metabolic factors from pharmacokinetic and pharmacodynamic properties of volatile inhaled anesthetics.

Current data corroborate the possibility of a link between inhalational anesthetic exposure and the development of neurotoxicity leading to transient and/or permanent CNS neuronal damage in neonatal and pediatric patients. During this critical period of rapid growth and development, this population is increasingly susceptible to long term neurologic insults and injuries resulting in neurocognitive dysfunction.[65-75]

Developmentally similar animal models have each demonstrated the presence of neurotoxicity, the effects of which can be related to dose/concentration effects and/or cumulative/exposure effects of inhalational agents. Single, prolonged anesthetic exposure at 0.5 to 1 MAC of volatile anesthetic agents has been shown to produce irreversible neurocognitive damage,[67-70] as well as exposing subjects to short anesthetics repeated over time.[73]

Neuronal gray and white matter is affected with specificity towards CNS glial cells, most notably oligodendroglia.[66] The resulting inhibition and apoptosis can directly impact synaptogenesis and CNS maturation by disturbing/preventing the formation and repair of neuronal myelin sheaths. Oligodendroglia cell death produces similar CNS demyelination patterns as seen in multiple sclerosis (MS), cerebral palsy (CP), and many leukodystophies.[74] Other later life neurocognitive concerns include educational and emotional impairments, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder. [65-75]

Sequelae

Harm/Injury. The manifestation of ED in pediatric patients recovering from general anesthesia may result in variable degrees of injury. ED usually resolves within the first 30 minutes post-emergence but can be associated with a prolonged post-anesthetic recovery, increased nursing care, and delayed reunion with family. Moreover, there are reports of ED symptoms and behaviors lasting more than two days post-discharge.[6]

During ED incidence, patients present as restless, incoherent, inconsolable, crying/screaming, and are often thrashing in bed. This behavior can result in increased pain and bleeding at operative sites, disruption of sutures/staples and dressings, and removal of drains, other medical devices, and IV catheters. Occasionally, the patient requires restraint to prevent harm. This may be accomplished by one nurse but is often performed by two or more nurses. Reports of minor injuries to nurses during this time include cuts, scratches, bruises, and abrasions.[5-8]

New Onset Maladaptive Behaviors. Sevoflurane anesthesia has been linked to new onset, long-term maladaptive behaviors in pediatric patients. Those presenting to the PACU with

ED are seven times more likely to develop non-characteristic behaviors that may include eating problems/difficulties, sleep disturbances/ night terrors, separation anxiety, and apathy.[9,10] Sevoflurane produced more frequent behavioral malignancies when compared to halothane,[23] and a more marked ED episode correlates with increasing risk for new behaviors.[76] Kain et al. maintain an odds ratio of incurring one or more new onset maladaptive behavior postoperatively of 1.43 for pediatric patients exhibiting marked ED symptoms when compared to pediatric patients reporting to PACU with no signs/symptoms of ED. However, they do not suggest a direct cause-effect relationship.[9]

TREATMENTS

The prevention and treatment of pediatric ED has evolved over many years but continues to be problematic. Many therapies, pharmacologic and non-pharmacologic, have been employed. Each has produced widely varying degrees of success, with studies supporting and refuting many claims. As of yet, there is no clear prescription for avoidance/prevention of ED in pediatric anesthesia.

Pharmacologic

Volatile Inhalational Anesthetic Agents. Sevoflurane represents the fundamental choice of volatile inhaled anesthetic agents among anesthesia providers for use in general anesthetic maintenance for pediatric surgery. This is primarily the result of the reliability and non-pungent nature of sevoflurane, making it an ideal agent for inhalational induction.[60] It is uncommon for pediatric surgical patients to have pre-operative IV access established, especially in out-patient/same-day surgery centers. Inhalational general anesthesia can be achieved safely,

quickly, and with minimal risks to the patient. Unfortunately, sevoflurane may also be the primary agent responsible for ED.

It is unclear which agent represents the best choice for GA maintenance in order to avoid/prevent ED. The anesthetic provider is faced with the choice after inhalational induction to continue sevoflurane for maintenance or switch to another agent, isoflurane or desflurane. Studies report mixed findings in the efficacy for each choice.[3,5,8,15,25,27,29,30,33,34-36,38,41-43,54,55,76-90]

When comparing the traditional inhalational volatile anesthetic agents, sevoflurane produces significantly more complications, higher frequency and more profound behavioral changes, and unique EEG changes when compared to halothane.[3,5,25,30,33,43,55,76-87] Lerman et al.[34] and Grundmann et. al.[41] report a three-fold increase in rates of ED when utilizing sevoflurane over halothane, but equivalent times to discharge. Furthermore, sevoflurane produces greater rates of ED in the absence of a painful stimulus when compared to halothane.[30]

A meta-analysis conducted by Kuratani et al. reviewed 23 randomized controlled trials (RCTs) and further confirmed these findings.[77] Additionally, sevoflurane produced EEG changes that differed from halothane.[78] These findings were confirmed despite any number of treatments utilized to prevent ED, including pharmacological and non-pharmacological preventative measures employed in the pre-operative and intra-operative areas, or pain control measures whether by IV or PO analgesics or regional blocks.[30,38]

Few studies refute these findings.[54,88,89] For instance, a study in 1999 by Davis et al. concluded that sevoflurane and halothane produced similar rates of ED,[79] while Weldon et al. in 2004 noted that sevoflurane only produced greater rates on ED during the first 5 minutes post-operatively when compared to halothane and rates remained equal after this time.[43] Finally, Lapin et al. concluded that when compared to halothane, sevoflurane was superior in its abilities

to produce shorter recovery and discharge times and causes significantly less post-operative agitation when pre-medicated with midazolam in the pre-operative area.[55]

Although studies confirm that halothane is responsible for increased rates of PONV when compared to sevoflurane,[82,83] there is dissent as to the effects on pain control and discharge times. Studies have found sevoflurane to produce faster recovery and discharge times,[55,81] halothane to be superior,[80,84] or equal to each other.[30, 33,82] One study noting delayed discharge after sevoflurane anesthesia reported increased pain and narcotic administration in PACU when compared to halothane[84] while another noted inverse results.[81]

Additionally, desflurane is noted to produce similar if not greater incidence of ED than sevoflurane and halothane in pediatric patients.[15,29,34-36] Sevoflurane and desflurane have been shown to produce similar rates of ED via the PAED and FLACC scales,[15] while desflurane provides a quicker emergence and shorter recovery period.[15,35,36] The shorter recovery period produced by desflurane also produces shortened total duration of ED occurrence when compared to sevoflurane.[36]

In contrast, desflurane causes increased rates of ED when compared to halothane.[29] However, Wellborn et al. demonstrated that while desflurane produced fastest emergence and significantly higher rates of ED when compared to sevoflurane and halothane, discharge times were equal between the three agents.[34]

Finally, isoflurane has been identified as an independent risk factor for ED. The rates of ED from isoflurane are similar to that of sevoflurane.[8,27,42,90] However, induction/maintenance with a combination of sevoflurane converted to isoflurane maintenance increase rates of ED two-fold.[27]

Pediatric Emergence Delirium/Agitation

Narcotics. As previously stated, narcotics have produced positive results in ED prevention and treatment. Unfortunately, it is unclear by what mechanism this is accomplished. The promotion of analgesia plays a role in ED prevention and treatment but is not the sole mechanism.[30-32] It is proposed that narcotics extend the period of emergence long enough to attenuate inhaled volatile anesthetic agent influenced ED occurrence via controlled out-gassing of agents, while also providing surgical analgesia. However, analgesia is not solely responsible for ED prevention or treatment and the difference between pain and delirium must be differentiated.[91] Numerous narcotic regimens have been trialed with assorted doses, timings, and routes, each with varied results.

Fentanyl. Fentanyl is the prototypical narcotic utilized in anesthetic delivery, and the most widely studied with regards to ED. Fentanyl when dosed at 2.5 mcg/kg IV at the beginning of surgery, most commonly given immediately after IV establishment, provides a significant reduction in ED occurrence post-operatively while also preserving rapid emergence.[13,35] There is no significant difference between sevoflurane or desflurane maintenance at this dose. Rates of severe ED were 24% and 18% for desflurane and sevoflurane respectively,[35] and smaller front-loaded doses, 1 mcg/kg IV, were found to be ineffective.[13]

In contrast, fentanyl when given towards the conclusion of surgery is beneficial in ED prevention.[16,31,92,93] When administering fentanyl 1 mcg/kg 10 minutes before surgery conclusion to pediatric patients under sevoflurane maintained general anesthesia without a surgical stimulus, the incidence of ED was 12% compared to 56% in a placebo controlled group.[31] The same results were reported when administered 15 minutes prior to procedural conclusion, without any delays in emergence, increased rates of PONV, or post-operative complications.[16,92,93]

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Fentanyl when administered intranasally (IN) also provides for significant reductions in ED post-operatively.[88,94] When dosed at 2 mcg/kg IN at procedural start, fentanyl significantly reduces the rate of ED occurrence when compared to placebo in children treated with sevoflurane and halothane for anesthesia maintenance, without any significant delays in emergence, recovery, or discharge times.[88]

Fentanyl has also been studied as to its effect on intubating conditions and ED prevention when used as an infusion for pediatric patients anesthetized with sevoflurane. Inomata et al. concluded that a bolus of 2 mcg/kg IV after IV access attainment followed by an infusion of 1 mcg/kg/hr provided optimal intubating conditions, better post-operative analgesia, and a smoother emergence.[95]

Finally, fentanyl may be utilized to treat episodes of ED in the PACU. Fentanyl has routinely and successfully been used for 'rescue dosing' in the PACU once a pediatric patient exhibits signs and symptoms (S/S) of ED. Typical dosing is 1 mcg/kg IV.[96]

Sufentanil. Although not widely used or studied, sufentanil has been shown to significantly reduce ED incidence when compared to fentanyl. When given IV after induction of general anesthesia maintained with sevoflurane in pediatric patients, sufentanil 0.2 mcg/kg significantly reduced ED when compared to fentanyl 2 mcg/kg and placebo without significant differences in time to extubation, emergence, or discharge between all groups. 12.5% and 70.6% patients exhibited ED via the PAED scale in the sufentanil and fentanyl groups respectively.[97]

Morphine. Morphine, when given at procedural start is advantageous in its ability to prevent ED.[98,99] Morphine, whether given at a dose of 0.1 mg/kg IV or intramuscular (IM), is equal to fentanyl 2 mcg/kg IV when given at procedural start for bilateral myringotomy and placement of ventilating tubes in preventing ED via the FLACC and PAED scales.[98] The

researchers further note the efficacy of IM morphine as it is the simplest route, avoids delays for establishment of IV access, and avoids the potential for laryngospasm from the passage of IN medication streaming from the posterior nasopharynx and irritating the vocal cords.

Other studies note inconsistent results with the routine administration of morphine by any route. Furthermore, morphine use has to be balanced by high rates of PONV produced.[8]

Meperidine. The use of meperidine has been studied in the prevention of ED. Unfortunately, while a placebo group exhibited the highest rate of ED occurrence, meperidine 0.5 mg/kg IV when given after morphine 50 mcg/kg IV administration did not significantly prevent ED when compared to morphine, dexamethasone 150 mcg/kg IV, granisetron 40 mcg/kg IV, or combinations of the three treatments. Only morphine was found to independently reduce the incidence of ED.[99] However, meperidine has been used to treat ED. For successful post-operative analgesia and treatment of ED, meperidine was dosed as 5 mg IV increments at the discretion of the PACU registered nurse (RN).[82]

Remifentanil. Remifentanil use, similarly to other narcotics, may reduce the incidence of ED in pediatric surgical patients. When used with a propofol IV infusion for TIVA, remifentanil IV infusions significantly reduce the incidence of ED when compared to desflurane, sevoflurane, and isoflurane for general anesthetic maintenance.[27,40,100] Furthermore, patients benefited from decreased post-operative pain[101] and stability in vital signs, most notably heart rate (HR) and blood pressure (BP).[40]

Oxycodone. Oxycodone may prevent or reduce ED occurrence. However, it has not been widely studied. Murray et al. studied the use of oxycodone 0.1 mg/kg PO given 30 minutes prior to surgery in pediatric patients and noted that patients receiving halothane anesthetics experienced a significantly reduced incidence of ED. However, there was no significant effect if

sevoflurane was administered. Times to discharge were similar between both groups and placebo, but the halothane/oxycodone group further experienced the highest rates of PONV.[83]

Oxycodone may also be able to treat ED occurrence. Viitanen et al. noted the successful used of oxycodone 0.05 mg/kg IV to treat post-operative pain/ED presence, as indicated by a pain/discomfort scale including 3 objective components, in pediatric patients.[58]

Nalbuphine. The opioid agonist/antagonist nalbuphine may prevent ED occurrence. Dalens et al. found that nalbuphine 0.1 mg/kg IV given at the end of an MRI procedure after receiving sevoflurane general anesthesia with laryngeal mask airway (LMA) was able to significantly reduce the incidence of ED. This was accomplished without delays in waking, recovery, or discharge times. The researchers also noted that nalbuphine offered the highest benefit-to-risk ratio when compared to placebo and other treatments groups in their study.[101]

Tramadol. The use of tramadol may prevent ED occurrence. Fan et al. administered a saline control or tramadol 1 mg/kg IV before surgery conclusion to pediatric patients reporting for ambulatory surgery. They found that tramadol significantly reduced ED occurrence and severity while providing greater analgesia and had no deleterious effects on emergence or discharge times.[102]

Benzodiazepines. The most commonly utilized benzodiazepine in current anesthetic practice is midazolam. Its short duration of action and PO formulation make it an ideal anxiolytic agent for use in pediatric anesthesia. The abilities of midazolam to provide anxiolysis and amnesia are believed to be beneficial in providing pediatric patient comfort and expedite transport to the OR. However, its ability to prevent/treat ED has been met with mixed results.

Midazolam. Various studies suggest pre-operative midazolam administration prevents ED. Lapin et al. found that pre-operative 0.5 mg/kg PO midazolam significantly reduced ED

occurrence in pediatric patients after sevoflurane and halothane general anesthetics when compared to a saline control group. Additionally, it produced significantly longer recovery times but without additional delay in discharge from PACU.[55] Viitanen et al. also found that 0.5 mg/kg midazolam PO given pre-operatively significantly delayed emergence and recovery times after sevoflurane general anesthesia but further noted 'arousal distress' and greater pain after 20 minutes in PACU when compared to saline or propofol groups.[103] Furthermore, Mountain et al. found that 0.5 mg/kg PO midazolam was equal to dexmedetomidine 4 mcg/kg PO in significantly preventing ED incidence, when each were given pre-operatively.[104]

In contrast to these studies, low dose midazolam premedication may produce a comparable effect on ED. Ko et al. premedicated pediatric patients with 0.2 mg/kg PO midazolam prior to sevoflurane general anesthesia. The incidence of ED occurrence post-operatively when compared to a control group was 47% and 81%, respectively, without delay in discharge.[105]

Premedication with midazolam may aid in the period after discharge. Viitanen et al. found that premedication with 0.5 mg/kg PO midazolam produced no significant reduction in post-anesthetic excitement and further delayed emergence, recovery, and discharge times when compared to placebo. However, the placebo group experienced significantly higher incidence of disturbed sleep on the first post-operative night when compared to the midazolam group, 30% vs. 4% respectively.[58]

Midazolam may further be beneficial when administered at the end of surgery. Kim et al. found that 0.05 mg/kg IV midazolam was equal to 1 mcg/kg IV propofol and superior to saline placebo IV in preventing ED occurrence when given 5 minutes prior to surgery end. The rates of ED in the midazolam and propofol groups were 42.9% and 48.4% respectively, while 74.3% in

the control group for children undergoing strabismus surgery under sevoflurane general anesthesia. They further compared children undergoing unilateral versus bilateral strabismus surgery and noted ED incidence was unaffected in the midazolam group but was higher in the bilaterally operated patients receiving propofol or saline.[47]

In contrast, midazolam use may produce no desirable effects on ED prevention, and could even cause an increased incidence.[10,42,48,58,106] Cohen et al. noted no benefit to midazolam in preventing ED incidence. Midazolam 0.1 mg/kg IV and propofol 2 mg/kg IV when given after induction of general anesthesia with halothane delayed emergence/recovery and were unable to significantly reduce ED occurrence when compared to a control group. They noted that ED incidence was initially decreased in the midazolam group post-operatively, but was short lived and significant ED was noted equally among treatment and control groups.[106] Other studies found that midazolam treated children experienced a significantly higher incidence of ED occurrence that lasted longer when compared to a control group.[103,107] This is supported by investigations of benzodiazepines that note paradoxical reactions and increased agitation[108,109] that may be successfully reversed by flumazenil administration.[110,111]

Finally, although not studied for efficacy in ED prevention, midazolam has been utilized IN. Davis et al. administered midazolam 0.2 mg/kg IN for pediatric patient receiving sevoflurane or halothane for pressure equalization tube insertion. Anxiolysis and amnesia were adequately achieved with pre-operative administration. However, ketorolac administration IV markedly reduced ED and/or pain behavior.[79]

Diazepam. The use of diazepam premedication in pediatric surgical patients has been seldom studied in current literature but may provide a better anesthetic experience while decreasing ED occurrence. Arai et al. premedicated children with midazolam 0.5 mg/kg PO or a

combination of midazolam 0.25 mg/kg PO and diazepam 0.25 mg/kg PO and then compared results against a group receiving no premedication for sevoflurane general anesthesia. They found that the combination group was more sedated pre-operatively, had a better quality of mask induction, and exhibited significantly less agitation post-operatively when compared to the midazolam alone or control groups.[112]

Propofol. Propofol provides for a rapid, pleasant recovery while possessing antiemetic and antipuretic properties. It exerts its effects via inhibition of GABA and $GABA_A$ glycoprotein receptor complex units. It is rapidly redistributed, requiring higher doses in children as a result of larger central volumes of distribution and higher metabolic rates.[74]

TIVA. The use of propofol in prevention of ED in pediatric patients has produced overwhelmingly positive results. Studies have demonstrated that propofol maintenance of general anesthesia (TIVA) notably reduces or prevents ED occurrence,[32,37,38,40,76] as well as produces greater analgesia post-operatively.[100] Uezono et al. compared recovery of preschool children reporting for painless, unilateral eye examination under general anesthesia with sevoflurane or propofol infusion for maintenance, after sevoflurane induction. Each child received the opposite maintenance agent when returning for contralateral eye examination. Each received 0.5 mg/kg PO midazolam pre-operatively and rate of propofol IV infusion for maintenance varied from 100-400 mcg/kg/min. Sevoflurane produced shorter post-operative recovery and discharge times, however it also produced significantly higher rates of ED when compared to propofol maintenance, 38% versus 0% respectively. Moreover, parent satisfaction was significantly higher in the propofol group.[32]

Picard et al. produced similar results. After no premedication and sevoflurane induction for general anesthesia, children age 3-10 randomly received sevoflurane or propofol IV infusion

(100-250 mcg/kg/min) maintenance for tonsillectomy. Both groups were similar with respect to times for extubation, response to verbal command, and discharge, but sevoflurane caused significantly higher rates of ED when compared to propofol, 46% versus 9% respectively.[37] Furthermore, Cohen et al. studied children age 2-36 months undergoing ambulatory surgery. Patients randomly received sevoflurane or propofol IV infusion (200 mcg/kg/min.) for general anesthesia maintenance after sevoflurane induction. Patients then randomly received fentanyl 2 mcg/kg IV or caudal block for post-operative analgesia. All treatments produced similar times to extubation and recovery, however sevoflurane caused significantly more ED, independent of analgesic technique.[38]

Finally, propofol TIVA produces greater ED prevention when compared to desflurane for general anesthetic maintenance. Grundman et al. studied children age 4-11 receiving either desflurane or propofol/remifentanil TIVA maintenance for general anesthesia after IV induction. Groups were similar in recovery times and absence of PONV, however the desflurane group exhibited significantly increased HR and ED incidence when compared to propofol TIVA, 80% versus 44% respectively.[40]

In contrast, Pieters et al. concluded that propofol maintenance had no effect on ED prevention. After sevoflurane induction, children undergoing adenotonsillectomy received sevoflurane or propofol IV infusion (100-300 mcg/kg/min.) for anesthetic maintenance. Recovery and discharge times were similar between groups and median PAED scores were only slightly lower in the propofol treated group. This difference was not statistically significant, however the propofol group had significantly greater analgesia and reduced PONV.[113]

IV Bolus. In contrast to the variability and unpredictability of TIVA general anesthesia, anesthetic maintenance with a volatile inhalational agent may be maintained and ED prevented

by a propofol IV bolus at the conclusion of surgery.[47,63,93] Aouad et al. randomly assigned children premedicated with midazolam and receiving sevoflurane LMA general anesthesia to receive either propofol 1 mg/kg IV or an equal volume of saline IV at surgery conclusion. Mean PAED scores differed significantly, 8.6 in the propofol group versus 11.5 in the control group. ED occurrence was significantly higher in the control group compared to the propofol group, 47.2% versus 19.5% respectively. Additionally, parents rated the anesthetic recovery as excellent significantly more frequently in the propofol treated group compared to the control group, 75.6% versus 41.7% respectively. However, the time to LMA removal was notably longer when compared to the control group.[63]

As previously discussed, propofol 1 mg/kg IV and versed 0.05 mg/kg IV 5 minutes before surgery end after routine sevoflurane general endotracheal anesthesia (GETA) are similar in their abilities to prevent ED occurrence while both also prolong times to extubation and emergence when compared to a control group.[47] However, Kim et al. concluded that IV propofol is superior to IV fentanyl in preventing ED and decreasing PONV when given at surgery conclusion. After sevoflurane induction and general anesthetic maintenance, at the conclusion of surgery, children 18-72 months of age randomly received either propofol 1 mg/kg IV, fentanyl 1 mcg/kg IV, or an equal volume saline control IV. Propofol and fentanyl produced significantly lower rates of ED as evidenced by their median PAED scale scores, 4.3 and 4.9 respectively, when compared to the control group, 9.0. Propofol treatment also produced the greatest effects on PONV prevention while fentanyl produced the highest rate of PONV.[93]

These results are further supported by the systematic review and meta-analysis performed by van Hoff et al. After reviewing 9 studies meeting inclusion criteria, including 997 pediatric patients, with low risk of bias, they noted that a prophylactic dose of IV propofol 1mg/kg given

at the end of volatile inhalational general anesthetic maintenance was effective in ED incidence reduction (29% vs. 58% respectively, RR=0.50, 95% CI 0.41-0.61, I^2=37%, 7 studies) and reduction of ED severity via PAED scale scores (WMD= -2.08, 95% CI -3.20 to -0.96, I^2=0%, 3 studies) when compared to placebo. Propofol administration did delay awakening (WMD=4.07 min. 95% CI 2.22-5.91, I^2=82%, 6 studies), however there was no significant increase in recovery time (WMD=2.91 min., CI -0.59 to 6.41, I^2=82%, 6 studies).[114]

In contrast to these findings, Cohen et al. studied midazolam 0.1 mg/kg IV and propofol 2 mg/kg IV versus a saline control given immediately after general anesthetic induction and maintenance with halothane. They noted that significant incidences of ED were present in both treatment groups and the control group. [106]

Centrally-Acting Alpha-2 Adrenoceptor Agonists. The centrally-acting alpha-2 adrenoceptor agonists, dexmedetomidine and clonidine, represent a relatively new class of adjuvants to anesthetic practice. Both possess sedative and analgesic properties, making them interesting adjuvants to an anesthetic whether as pre-operative or intra-operative agents, and that also produce narcotic-sparing effects.[74] Furthermore, through studies with clonidine, there is evidence that this drug class possesses the ability to reduce LC activity, in contrast to the alpha-2 antagonist yohimbine which is known to increase LC activity,[46] as well as sevoflurane.[45,47]

Dexmedetomidine. Dexmedetomidine represents a second generation of this drug class. By direct stimulation of alpha-2 receptors located post-synaptically at the dorsal horn and on or near unmyelinated peripheral nerve terminals, dexmedetomidine prevents the release of substance P and nociceptive nerve firing, producing analgesia. Sedation is produced by direct stimulation of CNS alpha-2 receptors.[74] Dexmedetomidine lacks potentiation of PONV, produces stability of vital signs, and does not delay emergence/discharge.[44] Noted decreases in HR and BP

from dexmedetomidine administration decrease oxygen consumption by 8% intraoperatively and 17% post-operatively.[115] Furthermore, with a half-life of 6 minutes, rapid redistribution, neuroprotective effects during periods of ischemia, and limited effects on hemodynamic and respiratory function,[115,116] dexmedetomidine is a useful anesthetic adjuvant and may aid in the prevention of ED, whether given as a PO premedication or intra-operatively as an IV bolus or infusion.[44,116]

As previously noted, Mountain et al. found no significant difference between premedication with midazolam 0.5 mg/kg PO or dexmedetomidine 4 mcg/kg PO in pediatric patients with regard to ED incidence, but a significant improvement over placebo.[104]

When given IV, by one time bolus at any time intra-operatively[44,116-121] or by infusion, [116,122-124] dexmedetomidine produces a 8-10 fold decrease in ED incidence with no negative effect on extubation, emergence, of discharge times independent of the volatile inhalational agent administered.[116] Ibacache et al. found that a IV bolus of dexmedetomidine (0.15 mcg/kg or 0.3 mcg/kg) immediately after induction of LMA general anesthesia with sevoflurane, no premedication, IV establishment, and caudal block for lower abdominal or genital surgery in pediatric patients significantly reduced ED incidence in PACU when compared to saline control, without delay in emergence or discharge. The 95% CI of ED incidence was 37% (20-54%) in the saline group, 17% (4-30%) in the 0.15 mcg/kg group, and 10% (0-21%) in the 0.3 mcg/kg group. They further noted the dose-dependent effect in ED prevention.[117]

Additionally, when given as a IV bolus at the conclusion of surgery, dexmedetomidine significantly reduces ED occurrence. Ali and Abdelatif compared the abilities of propofol 1 mg/kg IV and dexmedetomidine 0.3 mcg/kg IV when given 5 minutes before surgery end to reduce ED occurrence in children 2-6 years of age undergoing sevoflurane GETA for

adenotonsillectomy via the CHEOPS when compared to saline control. Although both treatments significantly reduced ED when compared to a control, dexmedetomidine was significantly superior to propofol.[118]

Furthermore, dexmedetomidine infusions may effectively prevent ED in pediatric surgical patients.[122-124] Shukry et al. studied the randomized effects of a dexmedetomidine infusion (0.2 mcg/kg/hr) without loading dose versus equal volume saline control solution begun after inhalational induction of general anesthesia with sevoflurane in children 1-10 years of age not receiving premedication. Dexmedetomidine significantly reduced the rate of ED when compared to the control treatment, 26% versus 60.8% respectively.[122] Comparatively, Kim et al. studied the effects of a 1 mcg/kg dexmedetomidine IV loading dose/bolus followed by 0.1 mcg/kg/hr IV infusion versus saline control when randomly assigned to children receiving sevoflurane general anesthesia and caudal block without premedication for ambulatory surgery. Dexmedetomidine significantly reduced ED occurrence when compared to control, 5% versus 55% respectively. Furthermore, HR and BP were significantly lower but within normal limits when compared to the saline group.[123]

Finally, the addition of dexmedetomidine to a caudal block may reduce ED incidence while providing additional analgesia, reduction in PONV, and a better quality of sleep. Anand et al. conducted a randomized, prospective, parallel group, double-blinded study, observing the effects of children receiving sevoflurane LMA general anesthesia and a caudal block with either 0.25% ropivicaine 1 ml/kg and 2 mcg/kg dexmedetomidine or ropivicaine 0.25% 1 ml/kg and equivalent volume of saline. There was significantly less pain (up to 15 hours post-operatively) and a noted prolonged duration of arousable sedation with significantly less ED in the

dexmedetomidine treated group, via Ramsay's sedation and FLACC pain scales, with stable hemodynamic and no significant post-operative complications.[125]

These results are further confirmed by the meta-analysis performed by Zhang et al.[126] After analyzing 12 pediatric ED RCTs including patients treated with dexmedetomidine versus placebo, 459 versus 353 patients respectively, under sevoflurane general anesthesia, they concluded that IV dexmedetomidine significantly reduces ED (RR=0.346, 95% CI 0.263-0.453, P<0.001) and post-operative pain (RR=0.405, 95% CI 0.253-0.649, P<0.001) but increases time to emergence (WMD=0.997, 95% CI 0.392-1.561, P=0.001) and extubation (WMD=0.617, 95% CI 0.253-0.649, P<0.001). They further note the need for additional research regarding the effects on PONV.

In addition, dexmedetomidine was found to be equally effective in ED prevention and analgesia promotion when compared to narcotics. The meta-analysis conducted by He et al.[127] reviewed 5 trials, including 482 pediatric patients receiving general anesthesia with volatile inhalational agents for adenotonsillectomy and concluded that IV dexmedetomidine was equivalent to IV morphine and/or fentanyl in ED prevention, analgesia promotion, incidence of PONV, and time to emergence/extubation. "The relative risks for dexmedetomidine versus morphine and dexmedetomidine versus fentanyl were 1.90 (95 % CI, 0.68 to 5.31: p=0.22) and 0.45 (95% CI, 0.24 to 0.83, p=0.01), respectively."

However, this is contradicted by the meta-analysis performed by Zhu et al.[128] After analyzing 20 prospective RCTs, including 1364 pediatric patients (696 in the IV dexmedetomidine group and 668 receiving IV placebo, fentanyl, or midazolam) receiving sevoflurane general anesthesia, they conclude that IV dexmedetomidine provides significant ED

prevention (RR=0.37 95% CI 0.30-0.46), reduced PONV (RR=0.57, 95% CI 0.38-0.85), and reduced PACU analgesic requirements (RR=0.43, 95% CI 0.31-0.59) when compared to placebo. Unfortunately, dexmedetomidine significantly delayed emergence (WMD=1.16, 95% CI 0.72-1.60), extubation (WMD=0.61, 95% CI 0.27-0.96), and discharge (WMD=2.67, 95% CI 0.95-4.39) times compared to placebo. Furthermore, there was no significantly greater effect on ED noted when compared to IV fentanyl (RR=1.39, 95% CI 0.78-2.47) or midazolam (RR=1.12, 95% CI 0.54-2.35), independent of dose or administration timing. However, the post-operative analgesic effects of dexmedetomidine may play an additionally important role in ED prevention as evidence by no statistically significant difference noted in PACU pain when compared to fentanyl (RR=1.12, 95% CI 0.66-1.91).

Contradicting this is the meta-analysis performed by Ni et al.[129] They analyzed 19 trials (1608 patients) comparing placebo, IV dexmedetomidine, midazolam, propofol, ketamine, and fentanyl for pediatric surgical patients. Dexmedetomidine significantly reduced ED incidence (RR=0.34, 95% CI 0.25-0.44, P<0.00001), severe post-operative pain (RR=0.41, 95% CI 0.27-0.62, P<0.0001), and rescue drug requirements (RR=0.31, 95% CI 0.18-0.53, P<0.0001) but increased time to eye opening by 0.98 min. (P=0.01) and time to discharge by 4.63 min. (P=0.02) when compared to placebo. With the exceptions of fentanyl and propofol, other treatments were insignificant in ED prevention.

Clonidine. Similar to dexmedetomidine in sedative and analgesic profile, clonidine represents an efficacious alternative in ED prevention.[130-138] Tazeroualti et al. performed a randomized, double-blinded study of the effects of PO midazolam 0.5 mg/kg, clonidine 2 mcg/kg, or clonidine 4 mcg/kg given 30 minutes before sevoflurane induction and maintenance of general anesthesia in preschool children undergoing circumcision with a penile block and

receiving rectal (PR) paracetamol (30 mg/kg). They noted the greatest reduction of ED incidence in the 4 mcg/kg PO clonidine group when compared to the midazolam group, 25% versus 60% respectively, without any increase in side-effects or delays in recovery or discharge.[130]

Other studies note similar yet slightly different effects when comparing clonidine and midazolam.[132,133] Under similar conditions but comparing 0.5 mg/kg midazolam PO with 5 mcg/kg clonidine PO, Sangetta et al. noted dissimilar results. Although both groups were efficacious in ED prevention, midazolam was superior for pre-operative sedation and anxiolysis ($P<0.001$) and cooperation during IV establishment and facemask application ($P<0.001$). Conversely, clonidine possessed better palatability ($P<0.001$), higher parental satisfaction ($P<0.001$), more stable perioperative hemodynamics ($P<0.001$), better analgesia post-operatively ($P<0.001$), and improved nighttime sleep patterns ($P<0.05$).[132]

This is contested by further research.[134,135] Fazi, et al. treated pediatric patients age 4-12 years pre-operatively with either placebo and clonidine 4 mcg/kg PO or placebo and midazolam 0.5 mg/kg PO 60-90 minutes and 30 minutes before anesthetic induction in their double-blinded, double-dummy study. They noted more intense anxiety at separation and at mask induction in the clonidine group via the modified Yale Preoperative Anxiety Scores scale, and significantly lower mean BP, decreased supplemental oxygen requirements post-operatively, and shorter surgery, anesthesia, and emergence times when compared to the midazolam group. However, the clonidine group also required additional analgesics/narcotics via the CHEOPS in the phase 1 PACU.[134]

By producing sedation, decreasing anesthetic requirements and providing greater analgesia, clonidine notably decreases ED incidence when administered by any route.[136-138] Kulka et al. reported that male children age 2-7 years undergoing sevoflurane general anesthesia

with a penile block for circumcision were randomized to receive IV clonidine 2 mcg/kg or placebo. The incidence of ED was significantly lower in the clonidine group, 10% versus 80% respectively, and produced significantly lower HR and BP in the PACU.[137] Furthermore, Bock et al. report a dose-dependent reduction in ED via the caudal route. They studied 80 children age 3-8 receiving sevoflurane induction and maintenance of general anesthesia with placement of a caudal block containing 0.175% bupivacaine (1 ml/kg) for minor surgery. Patients were then randomly assigned to one of four treatment groups: 1) 1 mcg/kg clonidine added to caudal block, 2) 3 mcg/kg clonidine added to caudal block, 3) 3 mcg/kg clonidine IV, or 4) no clonidine administered. Incidence of ED was 22%, 0%, 5%, and 39% in groups 1, 2, 3, and 4 respectively, with no significant difference in discharge times between all groups.[138]

N-Methyl D-Aspartate (NMDA) Receptor Antagonist. Although once thought to cause ED, new research establishes ketamine as a possibly effective preventative adjuvant to general anesthesia in pediatric patients. It promotes analgesia and sedation through noncompetitive NMDA receptor antagonism of thalamic, cerebral cortex, and spinal cord sites, and possible action as an agonist at opiate receptor sites.[74]

When given pre-operatively, PO ketamine may effectively prevent ED incidence post-operatively.[96,140-142] Kararmaz et al. studied the effects of ketamine 6 mg/kg PO given 30 minutes pre-operatively versus placebo in children undergoing adenotonsillectomy, with/without myringotomy and tube insertion, and general anesthesia with desflurane maintenance. Ketamine pre-treatment yielded significantly less ED when compared to control, 18% versus 56% respectively, without any statistically significant difference in emergence or recovery times between groups.[141]

Pediatric Emergence Delirium/Agitation

Furthermore, Khattab and El-Siefy compared the effects of midazolam 0.5 mg/kg PO or ketamine 2 mg/kg PO pre-operatively when given with ibuprofen 10 mg/kg PO in 92 children age 2-6 years of age undergoing sevoflurane general anesthesia for elective dental fillings and extractions. They found no significant differences between groups with relation to onset of premedication, time to eye opening/recovery, or PONV occurrence. However, the midazolam group required significantly more frequent rescue doses of fentanyl 1 mcg/kg IV for ED-like behavior, produced higher ED scores post-operatively, and had significantly longer times to discharge when compared to the ketamine group.[96]

The use of ketamine IV intra-operatively has further produced positive results in ED prevention.[16,20,101,143-146] Abu-Shahwan and Chowdary studied the effects of randomly administering a saline control or ketamine 0.25 mg/kg IV toward the end of surgery in pediatric patients undergoing dental repairs given sevoflurane general anesthesia, after premedication with midazolam and acetaminophen PO. There were no statistically significant differences between groups with regards to recovery characteristics, however the ketamine treated group had significantly less ED incidence compared to the control group, 16.6% versus 34.2% respectively, via the PAED scale.[143] Furthermore, Lee et al. produced similar results independent of dose. They randomized 93 children 2-14 years old undergoing sevoflurane general anesthesia for adenotonsillectomy to receive either saline control, ketamine 0.25 mg/kg IV, or ketamine 0.5 mg/kg IV 10 minutes prior to surgery end. They found no significant differences among groups with regards to recovery times (extubation, PACU arrival, or discharge) or incidence of PONV. Subsequently, both ketamine treatment groups produced significantly less ED when compared to the control group, via the CHEOPS tool, with no significant difference found between ketamine

doses. However, pain scores in PACU were significantly less in the 0.5 mg/kg treated group when compared to the 0.25 mg/kg treated group.[20]

Additionally, IV ketamine administration before surgery start may prevent ED incidence with supplementary benefits. Jeong et al. randomly assigned 60 children age 2-8 years old reporting for brief ophthalmic surgery to receive normal saline, ketamine 1 mg/kg IV before entering the OR, or ketamine 0.5 mg/kg IV 10 minutes before surgery conclusion. Both ketamine treatments significantly reduced ED incidence when compared to control, with no significant difference between the treatment groups via the CHEOPS. However, the 1 mg/kg IV pre-operative treatment further significantly reduced separation anxiety, post-operative pain, and ED without any delay in recovery or discharge.[145]

Moreover, when given as an IV bolus/loading dose followed by IV infusion, ketamine is equal to dexmedetomidine in ED prevention.[146] Chen et al. studied the effects of ketamine 1 mg/kg IV bolus followed by 1 mg/kg/hr IV infusion versus dexmedetomidine 1 mcg/kg IV bolus followed by 1 mcg/kg/hr IV infusion or IV normal saline control in children undergoing elective strabismus surgery under sevoflurane LMA general anesthesia. Researchers collected data via the PAED scale and assessed pain and PONV in PACU. Peak ED scores were lowest in the dexmedetomidine and ketamine groups, $P<0.001$ and $P=0.02$ respectively, when compared to placebo. Pain scores were also significantly lower when compared to placebo (dexmedetomidine $P<0.001$, ketamine $P=0.001$), however the ketamine treatment produced PONV similar to placebo, which was significantly more frequent than the dexmedetomidine treated group.

Finally, IV ketamine at the conclusion of surgery is as effective as other treatments in ED prevention.[16,101] Abdelhalim and Alarfaj found 0.5 mg/kg ketamine IV and 1 mcg/kg fentanyl IV given10 minutes before surgery end in children pre-treated with midazolam to be equally

effective in prevention/reduction of ED incidence when compared to saline control, via the CHEOPS.[16] Additionally, Dalens et al. studied children anesthetized for painless MRI procedures. Patients randomly received saline, ketamine 0.25 mg/kg, or nalbuphine 0.1 mg/kg IV at the end of the procedure, after undergoing sevoflurane LMA general anesthesia. Ketamine and nalbuphine produced no negative effects on awakening, recovery, or discharge times but both significantly reduced ED incidence when compared to the saline control group.[101]

Electrolytes/Magnesium. More recently, the use of magnesium, as magnesium sulphate or magnesium hydroxide, has been studied in ED prevention. Magnesium sulphate is an adjuvant to anesthesia primarily utilized as a tocolytic, venodilator, bronchodilator, or CNS depressant by altering calcium transport and bioavailability. It can also cause negative effects such as prolongation of depolarizing and non-depolarizing neuromuscular blockade. However, it also inhibits catecholamine release at adrenal medulla and peripheral adrenergic nerve terminals and decreases alpha-adrenergic receptor sensitivity.[74] These properties may modulate LC stimulation output and catecholamine secretion, thus promoting sedation while preventing ED.

Abdulatif et al. performed a randomized, double-blind, controlled study investigating the effects of magnesium sulphate on the incidence ED in children receiving sevoflurane general anesthesia for adenotonsillectomy. After induction, patients randomly received a 30 mg/kg IV magnesium sulphate bolus followed by 10 mg/kg/hr IV infusion or equal volume normal saline infusion. Results were assessed via the PAED and CHEOPS scales. ED occurred more frequently in the control group (72%) when compared to the study group (12%), (P=0.004, RR=0.51, 95% CI 0.31-0.84, and ARR=0.35, 95% CI 0.10-0.54, with NNT=3, 95% CI 2-9). Furthermore, they noted equivalent PACU pain scores, no increase in post-operative side effects, and no delay in recovery.[147] Similar results were obtained by Dahmani et al, however they noted

increased PONV and post-operative side effects, resulting in their recommendations for pain management therapies and alpha-2 agonists to more effectively prevent/treat ED.[44]

Melatonin. Melatonin, a hormone secreted by the pineal gland in the brain that is responsible for regulation of other hormones, has strong antioxidant properties, and maintains normal circadian rhythms of the body, may play a role in ED prevention. Melatonin levels are highest in young age at nighttime and naturally decline during aging. This may explain aberrant sleep patterns of older adults, namely earlier bed and wake times.[148] However, supplementation of melatonin aids in better sleep patterns and may also prevent ED in children.

Samarkandi et al. studied the effects of differing doses of PO melatonin or midazolam premedication given with PO acetaminophen PO versus placebo in their double-blind, placebo-controlled study. Patients were randomly assigned to receive midazolam 0.1, 0.25, or 0.5 mg/kg PO or melatonin 0.1, 0.25, or 0.5 mg/kg PO, each treatment with 15 mg/kg acetaminophen PO, or an acetaminophen only control group. Midazolam and melatonin, in doses of 0.25 or 0.5 mg/kg each, were equipotent in prevention of separation anxiety and anxiety during mask induction. Midazolam significantly increased recovery times, especially as the dose increased, when compared to melatonin. Furthermore, melatonin significantly reduced ED-like behavior ($P=0.049$) at 10 min. post-operatively, produced significantly lower incidence of sleep disturbances at 2 weeks post-operatively via the Post Hospitalization Behaviour Questionnaire ($P=0.046$), and no ED-like behavior was noted at 20, 30, and 45 min. post-operatively when compared to midazolam or placebo.[149]

Other studies have produced similar results. Ozcengiz et al. reported that melatonin is effective in ED prevention; however, they found it to be equipotent to midazolam and dexmedetomidine when given PO pre-operatively.[150] Similarly, Kain et al. noted that increasing

doses of PO melatonin pre-operatively prevented ED more effectively than midazolam 0.5 mg/kg PO (P=0.05). Melatonin dosed at 0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg PO produced ED incidences of 25%, 8.3%, and 5.4% respectively. However, midazolam was significantly more effective in pre-operative anxiolysis.[151]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Relative to the proposed theory of pain prevention on ED incidence, NSAIDs have been studied as adjuvants and independent agents in ED prevention and treatment. Pain is a notable risk factor in ED occurrence and analgesia is necessary for ED prevention.[3] However it is not the sole contributing factor. ED is a multi-modal phenomenon and the use of NSAIDs for ED prevention has presented mixed results.

Ketorolac. Ketorolac is a potent analgesic agent with anti-inflammatory properties that reduces narcotic requirements for adequate analgesia.[74] It is effective in pain control for pediatric patients, given by PO, IV or intramuscular (IM) routes, however its effects on ED prevention are debatable. Some studies suggest that ketorolac may be beneficial in ED prevention.[79,152] In the prospective, double-blinded study by Davis et al., the effects of IV ketorolac 1 mg/kg given intra-operatively versus saline control was studied in pediatric patients presenting for bilateral myringotomy with pressure equalization tube placement under randomly selected sevoflurane or halothane general anesthesia. 46-48% of patients in the control group presented to the PACU with ED-like behavior requiring rescue doses of analgesics, compared to 14-22% in the study group, independent of anesthetic agent utilized. They suggest that in ultra-short procedures, IV ketorolac is significantly more effective in pain management and ED prevention when compared to placebo. However, PO ketorolac may be less efficacious than other agents, as it is difficult to gauge administration timing in order to achieve plasma concentrations that coincide with recovery and provide optimal postoperative analgesia promotion.[79]

In contrast, Kim et al. suggest that IV ketorolac has no benefit in ED prevention. They performed a prospective, randomized, double-blind, control study of 85 children aged 3-7 presenting for elective surgical procedures performed under sevoflurane general anesthesia after thiopental induction. Patients were admitted the night before surgery, pre-operative anxiety was measured by the modified Yale Preoperative Anxiety Scale (m-YPAS), and IV access established. Before procedural completion, patients received ketorolac 1 mg/kg IV or placebo. Anxiety scores pre- and intra-operatively were similar between groups, as were the times to extubation and recovery. The found no significant difference in ED incidence between groups 41% in control group and 32% in the study group (P=0.526). They further noted no significant difference in median agitation scores via the PAEDS and a four-point agitation scale (FPAS) between groups, concluding that ketorolac is ineffective as an independent agent for ED prevention.[24]

Acetaminophen and Ibuprofen. Often given PO pre-operatively to promote post-operative analgesia and ED prevention, acetaminophen and ibuprofen are ineffective agents.[152-154] Bennie et al. randomly administered 15 mg/kg acetaminophen, 10 mg/kg ibuprofen , or placebo PO pre-operatively to children reporting for elective bilateral myringotomy and tube insertion in their prospective, double-blind, placebo-controlled study. Pain scores, via the CHEOPS, were not significantly different between all groups, nor was the frequency of rescue analgesia administration.[153] Furthermore, after myringotomy, Watcha et al. noted no analgesic difference between placebo and oral acetaminophen given preoperatively[152] and Tobias et al. noted a significant benefit in analgesia only when the pre-operative combination of acetaminophen 10 mg/kg PO and codeine 1 mg/kg PO were given when compared to acetaminophen 15 mg/kg PO

alone.[154] This reaffirms the requirement for narcotic administration to promote analgesia and prevent ED.

Gabapentin. The anticonvulsant gabapentin is a structural analogue of GABA. It possesses anxiolytic and analgesic properties. It is increasingly been utilized as an adjuvant to pain management in anesthesia and other settings. It may additionally prevent pediatric ED. Salman et al. randomly assigned children age 3-12 years undergoing sevoflurane general anesthesia for tonsillectomy and adenoidectomy to receive either gabapentin 15 mg dissolved in 10 ml saline or 10 ml of saline PO 30 minutes prior to induction of anesthesia. General anesthesia was maintained with sevoflurane and nitrous oxide. ED was assessed in PACU via a 5 point scale and parents were contacted 24 hours post-operatively to ascertain levels of pain, parents' satisfaction, side effects, and total analgesic administration. In the 20^{th} and 30^{th} minutes in PACU, agitation scores were significantly lower in the treatment groups when compared to placebo, $P<0.01$ and 0.05 respectively. Additionally, the treatment group required significantly less analgesics in the first 24 hours post-operatively ($P<0.01$) and parent satisfaction scores were significantly higher ($P<0.05$).[155] Although seldom studied, this suggests that gabapentin PO premedication may be useful in ED prevention and analgesia promotion.

Other Pharmacologic Interventions. Various other treatments have been studied in ED prevention. They include treatments for PONV prophylaxis and combination PONV prophylaxis/analgesics. Overwhelmingly, these treatments have failed to prevent ED occurrence.

Ondansetron. The serotonin-3 receptor antagonist, through its ability to prevent PONV, has been implicated as an adjuvant to ED prevention, however has yet to produce positive results. [156] Hosten et al. randomly administered IV ondansetron (0.1 mg/kg for children <40 kg and 4 mg for children >40 kg) or normal saline 2 ml IV after PO midazolam pre-medication,

induction of anesthesia with sevoflurane, and IV access establishment. Sevoflurane and nitrous oxide LMA general anesthetic maintenance ensued. ED was measured by the CHEOPS tool. No significant difference in ED incidence was noted at 10 min. post-operatively between placebo and ondansetron groups, 30.3% and 32.4% respectively. ED incidence, as expected, evenly resolved over the first 30 min. post-operatively in both groups.[156]

Granisetron. In the same drug class as ondansetron, granisetron has also failed at ED prevention. As previously noted, McKay et al. performed a blinded, randomized, controlled trial comparing morphine/meperidine, dexamethasone, granisetron, and a combination of all three treatments versus a saline control in ED prevention. The only independently efficacious agent to emerge was morphine. The control groups suffered the greatest incidence of ED (18/40; 45%[95% CI 29-61%]) compared to morphine (1/20;5%[95% CI 0.2-26%]), however incidence of PONV was unacceptably high in this group. Granisetron failed to provide any significant difference from placebo on ED incidence.[99]

Droperidol. This dopamine-2 receptor antagonist provides PONV prophylaxis but is ineffective in ED prevention. A case study by Wells and Rasch noted that droperidol, along with ketamine and scopolamine, are associated with ED-type behavior post-operatively along the spectrum of age and must be carefully administered or avoided.[26]

Decadron. The corticosteroid, decadron, is often utilized in anesthesia for its anti-inflammatory, analgesic, and PONV prophylaxis properties. However, similar to the NSAIDs, it is unable to independently reduce the incidence of ED.[44,99]

Tropisetron. The 5-HT_3 receptor antagonist, tropisetron, may be the exception to the trend. Although other PONV prophylaxes have been unable to prevent ED occurrence, through an unknown mechanism tropisetron has been shown to effectively prevent ED. Lankinen et al.

studied the effects of the random assignment of placebo, tropisetron 0.1 mg/kg IV, or clonidine 1.5 mcg/kg IV given after induction with sevoflurane in unpremedicated children age 1-7 years presenting for adenoidectomy under sevoflurane GETA. Patients additionally received alfentanil 20 mcg/kg IV and diclofenac 1 mg/kg IV intra-operatively, while post-operative pain was treated with 0.05 mg/kg oxycodone IV. The incidence of ED was significantly lowest in the tropesitron group (32%) when compared to the placebo and clonidine treated groups (62% and 54%, respectively, $P<0.05$). However, times to recovery and discharge were similar between all groups.[157] The efficacy of a 5-HT_3 serotonin receptor antagonist on ED incidence is suggestive of a serotoninergic role in ED.[158] This supports the LC hypothesis via the serotoninergic pathways governed by the LC via stimulation of the caudal raphe nuclei and dorsal raphe nuclei.[46]

Non-Pharmacologic

In addition to pharmacologic/homeopathic adjuvants for ED prevention and/or treatment the day of surgery/procedural undertaking, various non-pharmacologic therapies are available. These therapies primarily involve psychological relaxation, anxiety prevention, distraction, skill building, and parental presence.[9,44,159,162-172] Pre-treatment and pre-conditioning of the patient, including the family, prior to arrival at the procedural location aids in building and strengthening socialization skills, including coping and adaptability, that alleviate anxiety and provide for a better, more successful anesthetic/surgical experience.[160]

Home/Public Environment. The pre-operative/home environment of the pediatric patient plays a vital role in ED prevention. The social environment of the child can heavily influence personality, coping, and adaptability. Those with lower thresholds (i.e. those that are more sensitive) and possesses low adaptability (i.e. inability to cope with changes in

environment or situation) have low tolerance and present with more anxious/distressed behavior even during minor in-office procedures, including venipuncture or immunization. This inadaptability has been associated with failed sedations and ED, although it is not an independent risk factor for ED occurence.[8]

Additional traits related to the home environment have further influenced ED and the manifestation of maladaptive behaviors post-operatively. Kain et al. demonstrated that impulsive children with no siblings and who are not enrolled in daycare, or other environmentally social group activities, are at greatest risk of developing negative behavioral change post-operatively. These behaviors included night terrors, separation anxiety, and bedwetting, and were present two weeks or longer post-operatively.[161]

Hospital Environment.

Parental Involvement. The roles and attitudes of the family, especially parents/guardians, can greatly contribute to the success or failure of interventions to promote anxiolysis and prevent ED. Although not an independent risk factor for ED development, pre-operative anxiety displayed by the pediatric patient plays a role in its incidence.[23,43,44] However, parental presence during the surgical process may attenuate ED incidence. Arai et al., demonstrated that supportive parental presence during induction of general anesthesia decreased anxiety pre-operatively and during transport to the operating room (OR) while also improving mask acceptance for anesthetic induction.[162] In addition, ED incidence and severity is decreased by reuniting the child/patient with parents/guardians in the PACU, despite the presence[163] or lack of procedural pain.[164]

A randomized control trial by Kain et al. compared the effects of midazolam 0.5 mg/kg and acetaminophen 10 mg/kg PO premedication against parental presence to the OR until after

anesthetic induction versus a control group receiving no premedication or parental presence on the incidence of ED or presence of anxiety at any point during the surgical process. There was no difference noted in pre-operative anxiety among groups, however the midazolam group displayed significantly less anxiety upon parental separation/transport when compared to the control or parental presence groups (P=0.02). This was shown to be true at entrance to the OR (P=0.0171) and mask introduction (P=0.0176). Poor mask compliance was highest in the control group when compared to parental presence or midazolam treatments (25% vs. 17% vs. 0%, P=0.013). All groups were similar with regards to induction length, PONV, and recovery time. Interestingly, no significant difference was noted in post-operative excitement scores between groups nor the parent reported incidence of negative behavioral changes in the immediate post-operative period or at 2 weeks post-surgery.[165]

They further note that parental anxiety was significantly reduced in the midazolam treatment group when compared to control and parental presence groups (P=0.048). Therefore, midazolam premedication may be more efficacious in managing pediatric patient and parental anxiety peri-operatively when compared to parental presence or no treatment.[165]

Unfortunately, parental presence in the OR can be counterproductive in patient anxiolysis if parents are inadequately prepared. Parental behaviors such as criticism, excessive reassurance, and stern commands are associated with increasing distress in pediatric patients.[165] The preparation of the child for surgery is largely the responsibility of the parents/guardians, many of which are anxious and uncertain of their expectations of the hospital experience or their roles in managing the experience for their child(ren).[166] Parents/guardians that are overly anxious pre-operatively can transmit this anxiety to their children, adding to the anxiety already being

experienced[9,167] and reducing/eliminating any benefit.[168] Similar patterns of anxiety in response to surgical admission have been noted in parents and children.

Furthermore, Ellerton and Merriam note a relatively strong, positive correlation between total child and parent anxiety (Cramer's V=0.34, P<=0.004) throughout the surgical experience.[166] Kain et al. also noted increased patient anxiety in the pre-, intra-, and post-operative periods when increased parental anxiety was present pre-operatively. Parents reported that seeing an upset child prior to anesthetic induction, separation after induction, and the observation of the limp child after induction were the most upsetting/distressing factors. [165]

The RCT of Wright et al. slightly contradicts these findings. After randomly assigning pediatric patients to retain parental presence until the time of induction versus no parental presence in the OR, via m-YPAS scales, anxiety was significantly higher in the no parental presence group at the time of separation only. Otherwise, anxiety was similar between groups during mask introduction and anesthetic induction, suggesting no benefit to parental presence for induction.[169]

Additionally, the role of parental presence may further produce anxiolysis when in conjunction with standard pre-medication. Kazak et al. studied the effects of 0.5 mg/kg PO midazolam premedication against 0.25 mg/kg PO midazolam premedication with parental presence through induction versus no premedication and parental presence alone. They found no significant difference between either pre-medicated groups. However, parental presence alone produced significantly more anxiety and agitation when compared to both treatment groups. These findings suggest that although parental presence can be beneficial in anxiolysis, it is not a stand-alone treatment option.[170]

Pediatric Emergence Delirium/Agitation

Unfortunately, parental presence/involvement in the surgical/anesthetic process on the day of surgery may provide only minimal benefits, and possibly none at all. Parental presence alone is not an independent predictor of anxiety reduction or ED prevention.[171,172] This is evident in the systematic review performed by Yip et al. in 2009. They reviewed 17 RCTs, from developed countries, that included 1796 children, their parents, or a combination of the two. 8 studies concluded that no significant improvement was achieved in pediatric anxiety reduction or cooperation during induction when parents were present. Furthermore, one of these studies noted that parental presence was significantly less effective when compared to midazolam pre-medication.[172]

Although parental presence for surgery alleviates some anxiety and may prevent ED incidence, especially when coupled with midazolam premedication, the practice is not widely applied. In the United States in 1998, only 25% of children < 3 years of age were routinely pre-medicated. Also, most anesthesiologists (59%) never have parents present in the OR, 23% report that they utilized parental presence <25% or the time, and 10% report utilization in >75% of cases.[165]

Distraction. The role of distraction has been studied in the successful reduction of pre-operative anxiety in pediatric surgical patients. Patel et al. randomly assigned 112 children age 4-12 to the following treatments 20 min. before arrival in the OR for induction of general anesthesia for elective outpatient surgery: 1) parental presence only, 2) pre-medication with 0.5 mg/kg midazolam PO and parental presence, or 3) parental presence and a hand-held video game rated E ("everyone") of their choosing. Data were collected via the m-YPAS tool for anxiety measurement. Anxiety was significantly reduced in the pre-medication and video game groups, when compared to parental presence alone at all points. Anxiety was also lower in the video

game group when compared to the pre-medication group, but the difference was not significant. Finally, 63% of children in the video game treatment experienced decreased anxiety at anesthetic induction as compared to baseline scores in the pre-operative area.[173] This level of reduction was not experienced in the other treatments and is significant given that the anxiety is often highest during the time of parental separation to anesthetic induction.[171]

Additionally, Vagnoli et al. studied the effect of distraction by child-friendly models, clowns, accompanying children to the OR on anxiety levels. 75 healthy children age 5-12 reporting for elective outpatient surgery were randomly assigned to one of three groups: 1) presence of 2 clowns and one chosen parent to the OR, 2) pre-medication with 0.5 mg/kg PO midazolam at least 45 min. prior to OR entrance and one chosen parent to the OR, or 3) one chosen parent accompaniment to the OR. The clowns employed developmentally/age-appropriate methods of distraction, including puppets, magic tricks, games, and music. Anxiety scores were collected by m-YPAS tool pre-operatively and at face-mask introduction. The group including clowns combined with parental presence experienced significantly decreased anxiety at induction when compared to the other treatment groups.[174]

Relaxation Techniques. Various and differing techniques have been utilized to promote relaxation in order to reduce pediatric patient anxiety. Yip et al. note the benefits of 2 techniques aimed at pediatric relaxation directly and one indirectly. They note that hypnosis of the pediatric patient provides a non-significant reduction in anxiety at induction (m-YPAS <24, RR=0.59, 95% CI 0.33-1.04-39% vs. 68%: one trial). Providing a less stimulating/low sensory environment has been shown to ameliorate anxiety and improve cooperation during induction (RR=0.66, 95% CI 0.45-0.95: one trial) versus no benefit obtained from a music therapy intervention.[172]

They further noted the indirect reduction in pediatric anxiety from provisions of parental relaxation. More children were cooperative (RR=0.63, 95% CI 0.4-0.99) and displayed less anxiety at all points (m-YPAS MD 17, 95% CI 3.49-30.51) when parents received acupuncture versus sham-acupuncture leading up to the day of surgery. Parents were also noted to be significantly more relaxed. However, two trials involving a pre-operative videos failed to produce any effect on parental or child anxiety.[172]

Certified Child Life Specialist (CCLS). As a result of the need for effective pediatric patient and family preparation, education, and direction, with collaboration and preparation of healthcare practitioners/providers, to alleviate fear and anxiety while reducing the risks of ED, specialized practitioners have become involved in the process at all levels. The American Academy of Pediatrics states, "The children life specialist focuses on the strengths and sense of well-being of children while promoting their optimal development and minimizing the adverse effects of children's experiences in a hospital setting."[166] They help alleviate negative reactions resulting from separation anxiety, loss of control, foreign routines, medical equipment, and unfamiliar/intimidating environments.[175]

CCLSs are at least baccalaureate trained in child development, have successfully completed an internship in child life services (CLS), and have passed a national certification examination. Their actions aid other healthcare members to be more informed/prepared as to appropriate measures of patient care, be aware of any special needs/requirements, and allow for more efficient time utilization.[166]

The utilization of child life programs through has increased dramatically with the realization of the vulnerability of and possible harm caused to pediatric patients in healthcare settings, especially in surgery/procedures. Since 1965, the number of such programs has doubled

and continues to rise. The National Association of Children's Hospitals and Related Institutions regards the provisions of CLS as a quality benchmark for any health system providing child services. Although initially utilized primarily in inpatient pediatric services, the current trend is toward outpatient and ambulatory services.[166]

CCLSs facilitate pediatric patients, and their family members, in developing/enhancing coping and adjustment skills in three primary domains: 1) Play (making experiences of play available), 2) Psychological Preparation (producing information about procedures, circumstances, and timetables in a developmentally appropriate manner), and 3) Family Support (building rapport and therapeutic relationships with patient and family while aiding the family to be appropriately involved in care). [166]

Play. Play is the process of engaging pediatric patients in developmentally appropriate activities to moderate anxiety and reduce the risk of normal development disruption due to healthcare encounters. It is the primary modality utilized and aims to reduce environmental intimidation while increasing comfort through experiences of child-directed play and guided play, while allowing the patient to exert control and gain familiarity. Activities often involve medical play (exploration of medical equipment and environments through nondirective means) and dramatic play (using games, puzzles, art, or other activities depicting medical themes in situations that may be encountered).[166]

Psychological Preparation. Developmentally appropriate programs are utilized to prepare children and families with possible situations/procedures they may encounter in order to reduce emotional distress. Accurate descriptions are made available to families with developmentally appropriate interpretations for children. Coping strategies, including relaxation, visualization, and pain management strategies, are provided. The CCLS is present to support the

child, support the familial contributions to patient calm and cooperation, and, in the absence of familial support, to provide patient support and encouragement.[166]

Family Support. Familial involvement can provide positive effects on the pediatric patient's abilities to cope and adjust. The CCLS educates and supports parents/family members, primarily to reduce fear and anxiety, which may negatively influence pediatric patient anxiety and fear. CCLSs are agents of family-centered services that develop therapeutic alliances, remain vigilant in reactions to events, and provide information promptly. They may further be involved in grief counseling and provide support to siblings.[166]

Contributions. CCLSs provide healthcare members with better time utilization and the ability to communicate care issues related to age-specific competencies and individual needs. They are keenly aware of concerns and needs of families, and are consulted to build physical environments/settings to provide greater coping and adaptation. Furthermore, they contribute to a more smooth transition to home, school, and community after the healthcare experience.[166] Their utilization has also been shown to significantly decrease anxiety related to surgery when compared to other methods, including videos or books.[175]

CCLSs are aware of age and sex differences in pediatric coping abilities. Children that are younger and have previously undergone a surgical/procedural intervention manifest the greatest degree of pre-operative anxiety. Children age 3 to 6, in the preoperational stage of development, are less able to delineate reality from fantasy resulting in decreased logical thinking. They benefit mostly from play and distraction. However, the concrete operational stage begins after age 6, whereby logical progression of steps and increased abilities to cope are present. Children in the older group benefit from decreased anxiety when preparation begins at

least 5-7 days prior to surgery/procedure. In contrast, preparation 1 day in advance resulted in increased rates of anxiety.[175]

Additionally, child sex plays an important role in anxiety coping abilities. Girls tend to express anxiety verbally while boys manifest it physically, as a result of limitations placed upon physical abilities during hospitalization. Researchers speculate that girls may receive more support in hospitals as a result. [175]

The involvement of CCLSs and CLS in educational programs has benefitted ED reduction through increased anxiety prevention/relief while increasing cooperation[165,175,176] and retention of teachings with delivery of adequate information through open communication.[177] A double-blind, alternate assignment intervention study by Brewer et al. studied the effects of formal preparation for surgery by CCLSs versus no preparation in 142 children between age 5 and 11 reporting for elective otolaryngology surgery, an independent risk factor for ED. Anxiety was measured by the Child Drawing: Hospital instrument pre- and post-intervention. Statistically significant reductions in anxiety were noted in the intervention group when compared to no intervention ($P=0.04$).[175]

Additionally, Farrell et al. demonstrated that children involved in a comprehensive child life interventional program, that begins in the waiting area with a CCLS and continues through anesthetic induction, experience significantly less anxiety and exhibit more cooperative behaviors when compared to standard care. Via the m-YPAS instrument, they noted a significant anxiolytic effect of child life interventions [$x^2(1, N=63)=10.0, P=0.002$]. From the last five minutes in the pre-operative waiting area to arrival in the induction area, significantly less clinical anxiety was noted in the intervention group when compared to the control, 18% vs. 57% respectively. Induction compliance was significantly positively affected by the child life

intervention [$x^2(1, N=63)=8.2, P=0.004$]. Furthermore, a significant relationship is present between clinical non-compliance and clinical anxiety [$x^2(1, N=63)=8.2, P=0.004$], with non-compliance during induction occurring significantly more frequently in the control group when compared to the intervention group, 20% vs. 3%. Finally, 76% of participants in the intervention group scored a 0 (no anxiety, calm and cooperative) compared to 24% in the control group. They note 3 factors responsible for these results: 1) allowing the child-patient's choices in distraction methods, 2) respect for patient preferred coping strategies, and 3) parental presence during induction.[176]

Although previously shown to be of little to no benefit on ED and anxiety reduction, parental presence can positively affect the surgical process and outcomes when educated by a CCLS.[176,177] An estimated >80% of parents prefer to be present during anesthetic induction. However, projection of anxiety and fear can derail interventions to reduce patient anxiety. Educational programs and counseling for parents have been shown to significantly reduce anxiety and provide skills that allow parents to appropriately aid in the induction process in a supportive, hands-on manner. This has resulted in smoother inductions, less pediatric patient anxiety, and decreased incidence of ED,[176] along with parent reported decreases in distress during procedures, including induction, IV catheter insertion, or mask vs. IV inductions.[177]

Finally, Kain et al. illustrated the importance of CCLSs' parental education/direction on the augmentation of positive results from parental presence. They randomly assigned children (age 2-10 yr.) and their parents to one of four groups:1) Control-standard care, no premedication or parental presence, 2) Parental presence-standard care and presence of parents(s), without any prior teaching or coaching, during induction, 3) ADVANCE group-standard treatment plus a multicomponent behavioral preparation program, ADVANCE (anxiety-reduction, distraction,

video, modeling and educations),begun 2-7 days pre-operatively, or 4) Midazolam group-standard care plus midazolam 0.5 mg/kg PO >30 minutes before separation. Anxiety in the pre-operative holding area was significantly the lowest among parents/children in the ADVANCE group compared to the other interventions (P=0.007). The ADVANCE group also experienced significantly less ED (P=0.038), required significantly less analgesic administration in PACU (P=0.016), and were discharged significantly more quickly (P=0.04) when compared to other groups.[178]

One Voice. The guiding principles of CCLSs are defined by the ONE VOICE approach to pediatric procedural support, developed by Debbie Wagers. It is the result of expert interdisciplinary clinical experience and empirical literature. It includes 8 individual elements targeting best practices in pediatric, pre-procedural care. These include: 1) one single voice heard during a procedure, 2) the need for parental involvement, 3) educate patient before the procedure about what is going to happen, 4) validate the child with words, 5) offer the most non-threatening, comfortable position to the patient, 6) individualize the game plan, 7) choose appropriate distraction methods, and 8) eliminate unnecessary people not actively involved in care.[179] It continues to be family-centered and supports all previously mentioned contributions provided by CCLSs.

CONCLUSION

Discussion

The phenomenon of ED is still poorly understood and prevention/treatment is fraught with conflicting results. ED manifests as pain with crying and combativeness, and is often mistaken for other pathologies.[3,5] These behaviors, coupled with mis-recognition and

misdiagnosis by healthcare providers, permit increased risk of harm to patients and healthcare staff.[3,5,7] ED occurs most commonly after the administration of volatile inhalational anesthetic agents. These agents are independent risk factors for ED occurrence and part of the cause through various mechanisms.[6,8,35-42]

One proposed MOA is related to CNS damage, resulting from neurotoxicity and/or increased rates of CNS apoptosis from inhalational anesthetic exposure.[65-75,180] Unfortunately, there is little prospective human data available. Most research pertaining to neonatal and pediatric human subjects has been performed retrospectively, possibly allowing for unrecognized confounding variables. Regardless, current human data supports animal RCT data and suggests the possibility of harm. For example, human studies suggest the same cumulative exposure model of neurotoxicity as is noted in animal studies.[55,59] Clearly, the risk of neuronal injury during the sensitive time of synaptogenesis does exist, but a cause and effect relationship with inhalational anesthetic agents is currently only suggestive.

It is postulated that the stimulation of centrally located NMDA and/or GABA receptors causes CNS depression and neuronal cell damage/apoptosis, resulting in neurotoxicity. This leads to the development of neurocognitive impairments. Similar outcomes were obtained from research performed with regards to fetal alcohol syndrome.[55]

The Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) research group of Columbia University Medical Center Department of Anesthesiology presented their dialogue between pediatric anesthesiologists and four pediatric surgery specialties (general surgery, urology, plastic surgery, and ophthalmology) at their third symposium.[180] Topics included delaying operative corrections, the requirements for multiple procedures, and parental concerns.

Across specialties, consensus was reached that delaying certain procedures (i.e. emergency, trauma, etc.) was not feasible. However, risks must be balanced against potential outcomes.

Further discussion included the topic of potential neurotoxicity and neurodevelopmental impairments. Surgeons voiced their discomfort with the speculation of harm produced and their hesitation to discuss this topic with patients and their families. Risks and benefits of anesthetic care were agreed to be the responsibility of the anesthesia providers, even though the first, and sometimes only, mentions of anesthetic delivery are commonly discussed in the pre-surgical office visit. Surgeons noted their primary concerns for anesthetics as providing no patient movement, no delays in scheduling, and assuring the likelihood of procedural success. Furthermore, the topic of anesthetic toxicity yielded open discussion and the mutual agreement for future collaboration, but no practice consensus.[181]

Prospective research is currently underway to assess the impact of anesthetics on neurocognitive development, determine cause-and-effect relationships, and assess the possible degree/extent of harm. These initiative include the Strategies for Mitigating Anesthesia-Related neuro-Toxicity in Tots (Smart Tots), The Effects of Anesthesia on Neurodevelopmental Outcomes and Apnoea in Infants, and The General Anesthesia During Human Infancy and Brain Development Study.[180]

Another hypothesis is related to inhalational anesthetic agent direct neuro-stimulation of the locus coeruleus and the resulting effects.[45,47] If the LC stimulation hypothesis is correct, this could explain behavioral and psychiatric manifestations of pediatric patients post-operatively. Sevoflurane induced LC stimulation most likely results in restless anesthetic sleep states from increased cortical activity/arousal and GABAergic suppression. In addition, psychiatric manifestations may be related to amygdala, hippocampal neuron, and dorsal raphe nucleus

stimulation, resulting in increased fear, anxiety, emotional memory formation/retrieval, and declarative memory formation. Finally, numerous sites of LC stimulation outflow result in increased motor activity and sympathetic nervous system stimulation, while suppressing parasympathetic nervous stimulation outflow.[46]

This becomes increasingly interesting given studies producing the most effective/leading pharmacologic treatments. Dahamani et al. recommend the routine promotion of analgesia with IV anesthetic/sedative agents for ED prevention. Their meta-analysis focused on children anesthetized with the modern inhalational anesthetic agents, sevoflurane, desflurane, or a combination of the two. They included 37 articles composed of 1695 pediatric patients in the intervention groups versus 1477 in the control groups. They considered the treatments of midazolam (4 articles), propofol (13), fentanyl (5), ketamine (4), alpha-2 adrenoceptor agonists (10), pre-operative local anesthetics (3), and 5-HT_3 inhibitors (2). Midazolam given PO 30 minutes pre-operatively or IV after induction was found to be ineffective in ED prevention when given alone [OR=0.88 (0.44, 1.76); I^2=47%, P=0.11] and when given with PO analgesics pre-operatively [OR=1.88 (0.85, 4.13); I^2=0%, P=0.79]. The same was true of the 5-HT_3 inhibitors (OR=0.39, 95% CI 0.12-1.31; I^2=0%, P=0.56).[158]

In contrast, they noted significant benefit in a number of anesthetic adjuvants. IV propofol was overall preventative of ED [OR=0.21 (0.16, 0.28), I^2=52%, P=0.01]. When given as continuous infusion [OR=0.17 (0.11, 0.27), I^2=36%, P=0.13] or as a bolus at surgical completion [OR=0.21 (0.09, 0.50), I^2=0%, P=0.47], but not as a bolus immediately following anesthetic induction [OR=0.46 (0.20, 1.06), I^2=40%, P=0.19], propofol significantly prevents ED. This is also true of IV and PO ketamine [OR=0.28 (0.13, 0.60), I^2=0%, P=0.68], the alpha-2 adrenoceptor agonists, dexmedetomidine and clonidine, via IV and caudal routes [OR=0.23

(0.17, 0.33), I^2=24%, P=0.2], and pre-operative analgesia [OR=0.15 (0.07, 0.34), I^2=8%, P=0.36]. Fentanyl also had an overall positive effect on ED prevention [OR=0.31 (0.18, 0.56), I^2=47%, P=0.06]. Specifically, IN fentanyl significantly prevented ED [OR=0.23 (0.13, 0.43), I^2=28%, P=0.24], however IV did not [OR=0.35 (0.13, 0.43), I^2=20%, P=0.29].[158]

Alpha-2 adrenoceptor agonists receive the greatest support as effective ED preventative agents, when given at any time via any route.[44,74,104,115-127,130-138,158] The sedative and analgesic effects support almost all study suggestions for the perfect anesthetic adjuvant against ED. This also supports the LC hypothesis in terms of the physiologic response. Whereas LC simulation is responsible for the release of numerous adrenoceptor stimulating agents at numerous cerebral sites, namely alpha-1 adrenergic receptors,[46] the alpha-2 adrenoceptor agonists are responsible for initiating a negative feedback loop that indirectly prevents/inhibits the release of CNS catecholamines, specifically noradrenaline.[183] Direct stimulation of these sites in the CNS appears to be responsible for individual manifestations related to ED via the LC stimulation pathway. This represents the singular most definitive MOA and treatment pathway for ED currently available.

Vlajkokic and Sindjelic provide support for the LC stimulation hypothesis of ED incidence. "Considering that sevoflurane-induced electroencephalogram changes are similar to those observed during the administration of either desflurane or isoflurane, but different from changes recorded with halothane, EA/ED may be related to similar CNS effects of these anesthetics, which may affect brain activity by interfering with the balance between neuronal synaptic inhibition and excitation in the CNS.[6]" Therefore, clonidine and dexmedetomidine may be the ideal agents to maintain and /or restore CNS balance, thus preventing ED.

Additionally, non-pharmacologic agents have produced significant results in ED prevention. Unfortunately, due to parental stress, lack of knowledge, and lack of adequate resources/training, these have been poorly utilized. However, certified child life specialists through departments of child life services have seen increasing utilization. Their services help to guide parents and families through the surgical/procedural processes by educating them on what to expect and how best to be supportive/assistive to the child-patient.[176-178] This maintains the familial involvement and reduces familial stress/distress, which can further reduce the stress and stress response of the child-patient. Furthermore, through play, psychological preparation, and family support, the CCLS alleviates fear from the child-patient through developmentally appropriate methods and equips/reinforces coping and adjustment skills.[166] This has been shown to significantly reduced anxiety at all points of the surgical/procedural process, while further reducing the incidence of ED.[166,175-178]

Recommendations

Evaluation Tools. Although numerous reliable/valid tools are currently available, they fail in the clinical setting. Many of these tools are for diagnosis purposes only.[6,17,20,23] At the presentation of ED, most anesthesia providers or PACU RNs will arbitrarily medicate with narcotics first, most likely fentanyl. Outside of research settings, the use of a diagnosis tool becomes invalid and of little utility in treating the patient.

The need for high quality, valid, reliable instruments for ED prevention is paramount. Much like PONV or pain, ED is a multimodal, treatable, and preventable phenomenon. Instruments designed to identify patients most at risk are needed to aid anesthesia providers in medication selection, timing, and administration, while also allowing other providers to be prepared for the patient, especially those in the PACU. Such instruments should provide a scaled

figure based upon factors such as patient age, gender, number of previous anesthetic/procedural experiences, current procedure type, expected post-procedural pain level, family history of anxiety, familial support/presence, socialization/interactive experiences, temperament, and participation/availability of child life services programs. Patients most at risk should be more aggressively treated/prepared prophylactically via research-supported methods, while those at decreased risk are treated more conventionally and as directed by the experiences of the anesthesia provider(s).

Locus Coeruleus Research. The facts that sevoflurane directly stimulates the LC in rat subjects,[46] the modern inhalational anesthetic agents (i.e. sevoflurane, desflurane, and isoflurane) produce similar EEG patterns[6] while different from halothane which produces significantly lower rates of ED in comparison,[3,5,25,30,33,43,55,76-87] and that the presentation of symptoms related to LC stimulation of CNS sites mirrors the presentation of ED, make it difficult to ignore the LC as a future area of ED research. Future studies investigating the LC should focus on the correlation of the degree of LC stimulation to severity of ED manifested, subjects most susceptible to LC stimulation, and agents capable of blocking/altering LC stimulation from inhalational anesthetic agents.

Sequelae. Although most sequelae from an episode of ED are preventable/treatable and ED presentation is self-limited, there is little known about the effects on cognition and neurocognitive abilities in later life. Research has linked singular inhalational anesthetic exposure before the age of 5 to later life neurocognitive, behavioral, and developmental deficiencies, and increasing rates of these deficiencies are noted with increasing frequency of inhalational anesthetic agent exposure prior to age 5.[47,65-75]

Future research should include longitudinal, sibling-paired or twin studies investigating a link between ED occurrence and severity/development of neurocognitive, behavioral, and developmental deficiencies/aberrations . Furthermore, a comparison of inhalational versus IV anesthetic agent administration upon the same later life effects should be studied.

Inhalational vs. IV Anesthetic Agents. As a result of research supporting the use of IV anesthetic agents (i.e. TIVA) over inhalational agents in ED prevention,[32,37,38,40,76] and the facts that inhalational agents are more likely to accumulate within the body and can cause malignant hyperthermia,[74] future research should focus on IV agents as sole anesthetic agents and their abilities to prevent ED without causing delays in extubation, emergence, or discharge, along with cost effectiveness of such treatments.

Additionally, better methods of IV agent pharmacodynamic and pharmacokinetic monitoring must be made available. Inhalational anesthetic agents have been available for much of anesthesia history and are heavily studied. Furthermore, methods of agent monitoring have improved and become increasingly sensitive. Inhalational agents are now closely monitored by means of inspiratory and expiratory concentrations via spectrometry, and anesthesia providers titrate these to the desired effect.[74] This type of monitoring allows for recognition of anesthetic depth and agent metabolism (i.e. uptake and out-gassing). IV agents have prescribed/studied guidelines but no sensitive means of measurement, including the consideration of patient-to-patient metabolic/distributive differences. Research has been conducted and found to reliably measure expiratory concentrations of propofol.[183-185] With increasing safety, reliability, and utilization of IV anesthetic agents, greater methods of accurate measurement are required to guide anesthetic delivery and prevent delays in care, emergence, recovery, and discharge.

Child Life Services (CLS)/Certified Child Life Specialists (CCLSs). Further research into the benefits of CLS/CCLS utilization should be performed. Additionally, any center caring for pediatric/neonatal patients should investigate and implement plans to begin offering such services. Research supports the reduction in ED and anxiety of the child-patient and family-patient when CCLSs are included.[165,166,175-78] Patients and families benefit from education and the presence of a healthcare professional that they have established rapport and trust with, while other healthcare providers benefit from advice on individualized patient care and greater time management. CLS/CCLSs are invaluable resources for all with regards to pediatric/neonatal inpatient and outpatient services.

Comparative Effectiveness Research (CER). In addition to utilization of treatments that statistically and reliably prevent/treat ED, those that are the most effective must be prescribed. Researchers have trialed a myriad of treatments with even more complicated rates of results. Some studies have compared treatments to each other and a control, however future studies need to continue this trend and further study the effects of multiple treatments[158] on ED prevention and the ability to retain effectiveness, safety, and fiscally appropriate post-operative times (i.e. extubation, emergence, recovery, and discharge). Additionally, modern research seems most concerned with more modern/newer treatment modalities. However, some of the more classical treatments have been proven through the history of ED to be effective agents. For example, the long-acting, mild narcotic morphine has been utilized through decades of research and continues to be effective in ED prevention/treatment;[99] at least as effective as more modern agents such as fentanyl.[98]

Comparative effectiveness research (CER) aims to answer these types of questions. It aids in provider informed decision-making by answering questions regarding the best methods

and treatment to implement/utilize for specific situations and conditions presented.[186] Utilization of CER provides the final word on questions of treatment options. CER would directly benefit providers and patients regarding their choices and options in prevention of ED.

Authors Note. With all the ED treatment adjuvants studied, there is another one that deserves attention, hydromorphone. During anesthesia school, one certified registered nurse anesthetist (CRNA) trained me in the administration of morphine for all pediatric cases, predominantly ENT surgery. Her rationale was for the beneficial provisions of extended duration of analgesia and brief period of drowsy emergence in PACU that kept patients comfortable and calm. Morphine was given IV 80-100 mcg/kg, once IV access was established. I had not heard of ED yet but I was so impressed with this technique that I planned to implement it in my practice.

When finally on my own, I implemented her technique. It continued to work well and impressed the PACU RNs. However, I was unique in this practice, which meant my failures stood out. Even though most of my pediatric patients did extremely well (i.e. analgesia, quick emergence, no delay in extubation, no delay in discharge, and no occurrence of ED), there was the rare instance where things did not go well. This usually meant decreased tidal volumes and sometimes bronchospasm, preventing me from extubating the patient in a respectable time and sometimes requiring reintubation with a transfer to the pediatric intensive care (PICU) unit for observation.

Because of these failures, and pressure from my group, I sought answers to this occurrence. My best guess is the increased histamine release from morphine. So, ceased administering morphine and found a comparable alternative, hydromorphone. The semi-synthetic narcotic is similar to morphine in duration of action, but slightly more potent.[74] I researched hydromorphone for a few months and calculated an equipotent dose to the previously mentioned

morphine dose. This dose was 12-15 mcg/kg IV. I began this regimen but found it to be too much, as patients were slightly over-sedated in PACU and delayed in discharge. I reduced the dose 10-12 mcg/kg IV.

Since making the conversion, my pediatric patients again perform post-operatively like the morphine treated patients, however I have not witnessed any untoward events. For example, I cared for a 3 year-old patient presenting for an ENT procedure at the beginning of 2010. He received the morphine treatment and had a poor outcome. He was unable to produce sufficient tidal volumes for extubation, and required reintubation after being extubated at the request of the attending anesthesiologist. He was then transferred to the pediatric intensive care unit for observation and safely extubated the next morning. This was also one of my last morphine treated pediatric patients. 7 months later, he returned for another ENT procedure and I was fortunate enough to care for him. This time, he received hydromorphone, and there were no issues. His parents remembered me and thanked me for a much better outcome. I have continued to utilize hydromorphone in pediatric surgery. I have had no issues like I did with morphine. My patients present with no signs or symptoms of ED and the PACU staff is very appreciative to receive my patients.

Based upon my observations, I continue to see pediatric patients leaving the OR screaming, crying, and restlessly flailing in their beds. They may be treated with a small dose of IV fentanyl during transport, but this merely stuns them. Less than 5 minutes later, the same behavior continues in PACU. The PACU staff then scramble for more fentanyl or to reunite patient with parents/guardians promptly, with varying degrees of success. This is not the case with hydromorphone treated patients. It is a smooth transition to PACU. Typically, my patients are sedate upon transport and begin to open eyes and look around just after I have concluded my

report to the PACU RN. I remain in constant contact with the PACU RN each time, and after 7 years of this practice, and approximately 3,000 procedures, I have yet to hear a complaint.

Research has shown that the longer-acting narcotic regimen is appropriate and effective. Morphine has prevented ED over many other treatments[99] and is at least as effective as fentanyl.[98] Hydromorphone deserves equal attention. I recommend performing RCTs involving hydromorphone compared to and/or in combination with the leading ED preventative treatments; morphine, fentanyl, and alpha-2 adrenoceptor agonists.

Finally, although I often induce pediatric patients without established IV access pre-operatively with a combination of sevoflurane and N_2O, once IV access is established I convert to desflurane with no N_2O. Although the potential for ED appears shared amongst all inhalational agents, desflurane seems to be the best matched agent available. Desflurane possesses a blood/gas partition coefficient of 0.42 and oil/gas coefficient of 18.7, while isoflurane and sevoflurane are 1.4/99 and 0.6/50 respectively.[74] This means that isoflurane has relatively high blood/gas and oil/gas coefficients while desflurane has relatively low coefficients (see Appendix D). Unfortunately, sevoflurane has very low blood/gas coefficient, but relatively high oil/gas coefficient. This mismatch may more commonly lend itself to the manifestation of ED from sevoflurane. Sevoflurane exits the blood quickly, leading to faster emergence, but exits oil tissue (adipose, brain, etc.) much more slowly. This can continue to stimulate sites, including the LC, for an extended period of time. The same restlessness after sevoflurane is noted in adult patients, however is not frequently noted in adult patients after isoflurane or desflurane. I believe for these reasons that desflurane is the superior agent in ED prevention. It is quicker to emerge from and leaves the body more quickly while also being the least metabolized agent available, while sevoflurane is the most highly metabolized.[74]

APPENDICES

Appendix A. FLACC preverbal pediatric patient pain scale.[21]

Parameter	0	1	2
Face	No expression	Occasional grimace	Frequent to constant quivering chin
Legs	Normal position or relaxed	Uneasy restless, tense	Kicking or legs drawn up
Activity	Lying quiet	Squirming, shifting back and forth.tense	Arched, rigid or jerking
Cry	No cry	Moans or whimpers	Crying steadily
Consolability	Content, relaxed	Reassurance, hugging	Difficult to console

Score: 0, no pain; 1–3, mild pain; 4–7, moderate pain; 8–10, severe pain.
FLACC: Face, legs, activity, cry, consolability

Appendix B. CHEOPS.[22]

Item	Behavioral		Definition
Cry	No cry	1	Child is not crying
	Moaning	2	Child is moaning or quietly vocalizing silent cry
	Crying	2	Child is crying, but the cry is gentle or whimpering
	Scream	3	Child is in a full-lunged cry: sobbing; may be scored with complaint or without complaint
Facial	Composed	1	Neutral facial expression
	Grimace	2	Score only if definite negative facial expression
	Smiling	3	Score only if definite positive facial expression
Child Verbal	None	1	Child not talking.
	Other complaints	1	Child complains, but not about pain, e.g., I want to see mummy or I am thirsty
	Pain complaint	2	Child complaints about pain.
	Both complaints	2	Child complaints about pain and about other things, e.g., It hurts: I want my mummy
	Positive	0	Child makes any positive statement or talks about other things without complaint.0
Torso	Neutral	1	Body (not limbs) is at rest: torso is inactive.
	Shifting	2	Body is in motion in a shifting or serpentine fashion
	Tense	2	Body is arched or rigid.
	Shivering	2	Body is shuddering or shaking involuntarily
	Upright	2	Child is in a vertical or upright position
	Restrained	2	Body is restrained
Touch	Not touching	1	Child is not touching or grabbing at wound
	Reach	2	Child is reaching for but not touching wound.
	Touch	2	Child is gently touching wound or wound area
	Grab	2	Child is grabbing vigorously at wound.
	Restrained	2	Child's arms are restrained
Legs	Neutral	1	Legs may be e in any position but are relaxed: includes gently swimming or separate-like movements
	Squirm/kicking	2	Definitive uneasy or restless movements in the legs and /or striking out with foot or feet.
	Drawn up/tensed	2	Legs tensed and /or pulled up tightly to body and kept there
	Standing	2	Standing, crouching or kneeling
	Restrained	2	Child's legs are being held down

Appendix C. PAED scale.[17]

Behavior	Not at all	Just a little	Quite a bit	Very much	Extremely
Make eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surrounding	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

1 – Calm; 2 – Not calm but could be easily consoled; 3 – Moderately agitated or restless and not easily calmed; 4 – Combative, excited, thrashing around

Appendix D. Inhalational Anesthetic Agent Properties.[74]

Inhalational Agent	Blood/Gas Partition Coefficient (at 37 degrees Celsius.	Oil/Gas Partition Coefficient (at 37 degrees Celsius.)	Metabolism Route	% Metabolized	Excretion Route
Halothane (Flutonane)	2.54	224	Hepatic (CYP2E1)	15-20%	Renal, Respiratory
Nitrous Oxide (N2O)	0.47	1.4	Hepatic (CYP2E1)	0.004%	Respiratory
Isoflurane (Forane)	1.4	99	Hepatic (CYP2E1)	0.2%	Renal, Respiratory
Sevoflurane (Ultane)	0.6	50	Hepatic (CYP2E1)	2-5%	Renal, Respiratory
Desflurane (Suprane)	0.42	18.7	Hepatic (CYP2E1)	0.02-0.2%	Respiratory

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