6-20-2016

Management of the Pediatric Patient with Emergence Agitation

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MANAGEMENT OF THE PEDIATRIC PATIENT WITH EMERGENCE AGITATION

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Bachelor of Science in Nursing, College of Saint Scholastica, 2010

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

December

2016

PERMISSION

Title: Management of the Pediatric Patient with Emergence Agitation

Department: Nursing

Degree: Master of Science

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ABSTRACT

Title: Management of the Pediatric Patient with Emergence Agitation

Background: The incidence of emergence agitation (EA) in children after Sevoflurane anesthesia is reported to be as low as 10% and as high as 80%. A couple of the main risk factors for EA include younger age and use of volatile agents such as Sevoflurane and Desflurane due to their blood gas solubility and fast offset. The exact etiology of EA is unknown and research is ongoing. EA is a known post-operative occurrence in the pediatric population especially in ages 1-12 years old. It has detrimental effects on the patient by causing self-injury, disruption of the dressing, surgical incision, or indwelling catheters, and can further result in parental and staff dissatisfaction with the anesthetic.

Purpose: The purpose of this case study focuses on the anesthetic management of a 7-year-old female, with a preoperative diagnosis of dental caries. This patient underwent dental restorations under Sevoflurane general anesthesia. This case study will be compared with a current literature review of similar cases and identifying proper assessment and management for a pediatric patient with the aim of decreasing the incidence of EA during the postoperative period. The major anesthetic goals for this patient population are to recognize and anticipate the increased risk of emergence agitation (EA) due to the age and volatile anesthetics used for general anesthesia and possibly decreasing the incidence by utilizing various anesthetics that have been suggested and effective interventions.

Process: A comprehensive review of literature within the past 7 years was performed utilizing PubMed, Clinical Key and Google Scholar through the University of North Dakota Harley E. French Library of the Health Sciences. Additional resources within the literature was found by exploring the references cited in some of the articles. Each article was reviewed and evaluated to develop evidence based recommendations for pediatric patients at risk for EA.

Results: The use of propofol and decreasing the volatile agents during the emergence process has shown to be effective in decreasing or eliminating the incidence of EA. A number of factors increase the risk of EA and should be recognized and evaluated to form a plan of care specific to the pediatric patient.

Implications: Emergence agitation can have a high incidence in the pediatric population and recognition and intervention can improve patient safety and improve the postoperative outcome.

Keywords: *pediatrics; emergence; agitation; delirium; propofol; sevoflurane*

Management of the Pediatric Patient with Emergence Agitation

Background

Children ages 2 to 5 years are at the highest risk for emergence agitation (EA)/delirium (ED), which is a state of hyperexcitation that includes disorientation, inconsolable crying and/or screaming, and violent movements such as flailing kicking and rolling (Vacanti, 2011). While the exact causes of EA/ED are still unknown, they are thought to be the result of factors such as untreated pain, preoperative anxiety, volatile anesthetics, and the patients' temperament. EA usually appears immediately after emergence but can occur up to 30 minutes following discontinuation of the anesthetic. There are certain medications that can be given during the perioperative period that may help reduce the incidence of emergence agitation.

Sevoflurane is an inhalational anesthetic used widely with pediatric populations and also in outpatient anesthesia due to its excellent hemodynamic stability and low blood solubility. This allows for rapid induction and emergence from general anesthesia, as well as control of the depth of anesthesia. Sevoflurane has been suggested to be one of main causes of emergence agitation in the pediatric population due to its fast onset and rapid removal due to its low blood solubility. Other contributing factors and explanations for emergence agitation include the child's ability to adapt to sudden environmental changes upon awakening, immature neurological development, preoperative anxiety of being separated from their parents, and any residual pain sensations and sympathetic hyperactivation from surgery.

Case Report

A 7-year-old, 20kg female patient presented for dental restorations under general anesthesia. The patient's past medical history included anxiety and dental caries. The patient had no known allergies, no past surgical history, and no current home medications. The pre-

anesthetic evaluation revealed an anxious fearful school-aged child accompanied by her parents. No anxiolytic medications were given pre-operatively per anesthesiologist preference. Prior to taking the patient back to the operating room (OR), the anesthesia student and team members engaged in friendly and playful interaction with the patient while explaining what would happen next. The patient tolerated this well and she was wheeled back to the OR without the presence of her parents.

On arrival to the OR, the patient was initially hesitant and resistant to moving onto the OR table. With reassurance by the anesthesia team, the patient was assisted to the OR table. An inhalational mask induction was initiated utilizing oxygen 3 liters per minute and nitrous oxide 7 liters per minute until the patient was more relaxed. At the same time as standard monitors were being applied by members of the anesthesia team, Sevoflurane was incrementally added up to 8%. The patient tolerated the inhalational induction well.

The patient continued to breathe spontaneously with mask ventilation. A 22 gauge peripheral intravenous (IV) catheter was placed in the left hand and secured. Following placement of the IV, propofol 40 mg and fentanyl 20 mcg were administered. Phenylephrine 0.25% was administered in each nare during placement of IV catheter and administration of IV medications. Following induction, a 4.5 mm cuffed nasal RAE endotracheal tube (ETT) was passed through the right nare with no resistance. A grade I view was achieved with a MAC 2 blade and the ETT was guided atraumatically under direct visualization through the vocal cords. The ETT was secured and the patient was repositioned for the procedure. After some assisted breaths, the patient resumed spontaneous respirations. General anesthesia was maintained using a minimum alveolar concentration (MAC) of 1.5% Sevoflurane with fresh gas flows at 1.5 L/min oxygen and 1.5 L/min air. The induction, maintenance, and surgery were uneventful.

The surgeon placed a throat pack in the hypopharynx prior to starting the procedure. Additional intravenous medications given during the intraoperative period included: dexamethasone 4mg, ondansetron 4 mg, and fentanyl 30 mcg. Total IV fluids were 350 mL of lactated ringer's solution for the case.

At the conclusion of the procedure, the throat pack was removed, Sevoflurane was discontinued, and a total of 40 mg of propofol was administered with the goal of maintaining a deep level of anesthesia yet maintaining spontaneous breaths. The patient was deeply suctioned and was subsequently extubated with little to no expired end tidal Sevoflurane indicated on the monitor. An oral airway was placed and the mask was reapplied to ensure spontaneous breaths and adequate tidal volumes. A simple facemask was applied with oxygen at 6 L/min and the patient was then transferred to the post anesthesia care unit (PACU). Report was given with vital signs and oxygen saturation levels being adequate. The PACU nurses were informed of the anesthetic that was used and to assess for emergence agitation upon wake up.

A complete post-operative evaluation was not able to be performed by the student registered nurse anesthetist (SRNA) due to timing of patient being discharged home per the anesthesiologist. The PACU nurses informed the anesthetist of the outcome during the wakeup of the patient and reported it being very pleasant as if "she woke up from a nap".

Discussion

Emergence agitation (EA) is characterized by self-limiting aggressive agitation that develops in the early phase of awakening from anesthesia at the end of surgery. The term is used interchangeably with emergence delirium and postoperative agitation (Nagelhout, 2014). For the purposes of this review, the author refers to this complex as EA. During EA, altered behavior in the immediate postoperative period manifests as non-purposeful restlessness, crying, moaning,

incoherence, and disorientation, which can be very upsetting for both the parents and caregivers. EA can be self-limiting or even last for up to 45 minutes. The incidence ranges from 10-80% as stated earlier and typically occurs in the early stage of emergence during initial awakening.

EA Hypotheses

There has been no single factor identified to cause EA only suggested hypotheses. Some of the hypotheses suggested include biologic, pharmacologic, psychological, social components and most recent hypotheses have implicated that the low-solubility volatile anesthetic agents of Sevoflurane and Desflurane are one of the main culprits. Proposed causes also include rapid awakening in unfamiliar settings, pain, stress during induction, child's personality, premedication, and type of anesthesia (Nagelhout, 2014). In a network meta-analysis of RCT's conducted by Fang et al. (2015), propofol, ketamine, fentanyl, dexmedetomidine, and preoperative analgesia were found to prevent episodes of EA in children. Another meta-analysis of published studies conducted by Dahmani et al. (2010), also found beneficial effects of propofol, ketamine, and fentanyl for prophylactic use in preventing EA while, midazolam and $5HT_3$ inhibitors did not have any protective effects. However, the question remains as to which prophylactic treatment regimen should be used to decrease the incidence of EA is still unclear (Fang et al., 2015).

Preoperative Anxiety

As research and understanding of different factors that contribute to EA continue to suggest, preoperative anxiety, postoperative behavior, and parental participation in the child's health care experience have all become important considerations to include in anesthetic management (Banchs & Lerman, 2014). Preoperative anxiolysis and evidence has suggested children who are anxious in the holding area and during the induction period of anesthesia

experience an enhanced distress period immediately postoperatively (Banchs & Lerman, 2014). The preoperative anxiolysis in the holding room and prior to induction was not as extreme as some cases but was still present in this case report. Banchs & Lerman (2014) note the risk for postoperative negative behavior is 3.5-fold greater in children who experience preoperative anxiety and as suggested earlier administration of fentanyl, dexmedetomidine, propofol, or ketamine would help reduce the incidence of EA if given preoperative or during maintenance of anesthesia.

Preoperative anxiety measurement. A high level of preoperative anxiety has been associated with an increase in EA (Key et al., 2010). Measuring preoperative anxiety can be challenging as an anesthesia professional but is worth quantifying the degree through clinical parameters and observation during the patient interview to stratify an appropriate and therapeutic intervention to mitigate its effects (Banchs & Lerman, 2014). Preoperative interventions to reduce stress include attention to patient temperature, providing a quiet, calm enviornment with dim lighting, and encouraging the patient to bring comfort items from home (Key et al., 2010). There has been conflicting evidence in the literature regarding preoperative medications such as midazolam or clonidine and their benefit in preventing EA. Midazolam specifically has shown no reduction in the incidence of EA but has produced longer wake up times (Key et al., 2010). Dahmani et al. (2010) notes that new studies on EA prevention should be based upon the use of a standardized preoperative anxiety scales in order to accurately evaluate pediatric EA.

Risk factors for EA

Several risk factors contribute to preoperative anxiety and postoperative EA. Risk factors for EA include preschool age 2 to 5 years, difficult parental separation behavior, and postoperative pain. In a smaller randomized control study of 75 pediatric patients ages 4 months

to 7 years, Singh et al, (2012) found additional factors that have been presumed to be associated with high incidence of EA including no previous surgery, poor adaptability, adjuvant medications, short time to awakening, environmental factors such as noise, unfamiliarity, and temperament of the child.

A recent survey conducted by Rosen et al. (2015) was administered to 209 Canadian Pediatric Anesthesia Society (CPAS) members that yielded a 51% response rate examined the opinions and practices in the development of EA and if the responses were in agreement with the literature on risk factors. The responses for risk factors were preschool age (74%), previous history of ED (65%), undertreated postoperative pain (60%), high level of patient anxiety (57%), rapid emergence (55%), and ear, eye, or dental procedure (50%). The respondents in the same survey included 'inhalational agents' or 'sevoflurane' written in the free text space provided as a risk factor. Additionally, Rosen et al. (2015) asked about the effectiveness of premedication with midazolam. Twenty-seven percent of the providers responded by it having no effect, 17% said it contributed to ED, and 33% did not know its effect. Sixty-eight percent of the respondents reported that parental presence at induction of anesthesia has no effect on the development of ED.

The responses of the members coincide with findings in Banch & Lerman's (2014) review found parental presence has not been shown to be effective in decreasing the incidence or severity of EA. Additionally, Key and colleagues (2014) would also coincide with the responses of midazolam as they found it did not significantly reduce the incidence of EA in two of their RCT reviewed, but rather had a nine-fold higher risk of developing EA over children who were not premedicated.

The studies of the effects of age on anxiety during the induction of anesthesia have yielded inconsistent results. Banchs & Lerman's (2014) review discussed how infants are less likely to experience separation anxiety, pediatrics 1 to 3 years experience separation anxiety but respond positively to distraction and comforting measures, and children aged 4 to 6 years seek explanations and desire to maintain control of their environment. Children between the ages of 2 and 5 years are more likely to experience EA on recovery from general anesthesia.

It has been suggested that the psychological immaturity of a child's nervous system and the rapid awakening from general anesthesia in an unfamiliar environment may be responsible for the occurrence of EA (Martini, 2005). The immaturity of the cholinergic centers and the hippocampus and low levels of neurotransmitters may provide an explanation for the susceptibility of younger children to EA (Banchs & Lerman, 2014). The $GABA_A$ receptor could be *excitatory* rather than *inhibitory* in early infancy as a result of high intracellular concentration of chloride ions, explaining this paradoxic reaction to anesthesia in young children. As the child matures, the $GABA_A$ receptor transforms into an inhibitory neurotransmitter, and the reaction no longer occurs, as in the adult. One of the suggested physiologic explanations for the switch in excitatory rather than inhibitory in early infancy is because of the high to low chloride content in the neurons. Other evidence, however, provides conflicting views leaving the mechanism behind EA behavior unexplained (Ben-Ari, 2002).

A child's temperament can also contribute to perioperative anxiety and influence the reaction to surrounding stimuli and stressful environments. Children who are emotional, impulsive, or withdrawn are at increased risk for developing EA. Four temperament components have been identified as an observer-based measurement tool for parents to assess their child's temperament. The EASI scale is used to measure the temperaments of emotionality, activity,

sociability, and impulsivity score between 1 and 5 for a total score between 5 and 25 (Banchs & Lerman, 2014). Although the scale is good validity and reliability, it has not been studied in all age groups and is subject to parental bias. Future research studies could be aimed at correlating this scale with EA. Ideally there would be improvements made to the scale to minimize the potential for parental bias.

Previous hospital experience has also been found to be a contributing factor in perioperative anxiety and should be considered by anesthesia professionals. Children who have had previous negative health care encounters can experience increased anxiety both in the holding area and during separation from parents. By reducing a child's anxiety during the preoperative period, it may benefit the perioperative process and also decrease anxiety for future anesthesia encounters. Stressful life experiences that take place close to a hospital admission can also affect how a child reacts to anesthesia and the overall surgical experience (Banch & Lerman, 2014).

The type of surgical procedures and influencing the incidence of preoperative anxiety and postoperative EA is unclear. Banch & Lerman (2014) found several studies had concluded the type of surgery does not increase the risk of postoperative EA, whereas other studies reviewed they found surgery of the genitourinary system and inpatient surgery were associated with an increased risk of postoperative EA. In addition, Cho et al. (2014) conducted a RCT that included 90 children between the ages of 1 and 13 years old undergoing strabismus surgery had also suggested that children undergoing ophthalmic surgery may experience a high incidence of EA due to visual disturbances.

Conversely, Kanaya et al. (2014) found in their meta-analysis of RCT's that surgical procedures could be a contributing factor affecting the incidence of EA, specifically,

adenotonsillectomy procedures being at high risk. The study demonstrated a significantly lower incidence of EA following propofol anesthesia associated with these procedures compared to Sevoflurane anesthesia (Kanaya et al., 2014).

Scales used to measure EA/ED

More than 16 scales can be utilized by the anesthetic professional in order to evaluate EA/ED in the postoperative period. The Pediatric Emergence Anesthesia Delirium (PAED) scale and the Watcha scale are two common scales that will be discussed in this review.

The PAED scale ranges from a minimum score of 0 to a maximum score of 20. The degree of ED increases directly with the total score. There are five categories that consist of: child making eye contact with caregiver, child's actions are purposeful, child is aware of his/her surroundings, child is restless, and child is inconsolable. The five categories are scored from 0-4, 0= extremely to 4= not at all for the first three categories, and 0=not at all to 4= extremely for the last two categories (Pieters, B. J. et al, 2010). Cho and colleagues (2012) utilized the PAED scale in their RCT that will be discussed later but had showed an 84% reliability and 89% consistency with the results. The sensitivity and specificity analysis revealed a sensitivity of 64% and specificity of 86% which support reliability and validity of the PAED scale making it a more favorable evaluation tool for EA.

The other scale that is also used in the postoperative period is the Watcha four-point scale. This scale is a more simplified scale with scores ranging from 1-4. 1= calm, quiet, 2= crying, but can be consoled, 3= crying, cannot by consoled, and 4= agitated and thrashing (Costi, 2014). These scales are only a few that could possibly become a standardized method in evaluating EA in the postoperative period and help with future anesthetic management for pediatric patients.

Sevoflurane and Its Effects on EA

As compared to halothane, Sevoflurane is one of the most commonly used volatile anesthetic gases for children because of its low lipid solubility and therefore quick onset in pediatrics (Key et al., 2010). Halothane was the induction agent of choice for children for many years until Sevoflurane was introduced, which made it more favorable because of lack of significant cardiac depression and dysrhythmias compared to halothane (Kim, 2011). Sevoflurane is usually given continuously throughout the procedure and turned off at time of emergence.

EA is very common for children, especially preschool children which is one of the suggested causes of waking up restless, agitated, delirious or thrashing around after receiving this particular anesthetic. This can occur even when no pain is present and usually will resolve within 30 minutes of waking up. Fang et. al (2015) discusses the association between Sevoflurane and EA and how its been postulated to alter brain activity by interfering with the balance between neuronal synaptic inhibitions in the central nervous system. Cho et al. (2014) found a similar finding on how EA is related to a variation of neurologic recovery rate in different brain areas and to the immaturity of neurons. They reported the effects of inhalation agents known to exert a paradoxical excitatory effect in both animals and human patients, mainly in children.

Anesthetic Techniques and Management for EA

Of course no study would be performed without having to address the means of how the anesthesia professional can attempt to decrease the incidence of EA from occurring as an adverse effect of general anesthesia. Numerous studies that will be discussed have investigated and reported the effects of different anesthetic agents such as opioids and benzodiazepines on EA.

There are multiple techniques that can be utilized in the pediatric population to eliminate or decrease the incidence of EA. The current literature and studies reveal techniques that include preoperative doses of midazolam, intraoperative doses of ketamine, dexmedetomidine, propofol, and fentanyl all in efforts to prevent the incidence of Sevoflurane-related EA in children and the most recent evidence will be discussed.

Midazolam. The most commonly utilized agent for anxiolysis is orally administered midazolam. The major appeal of oral midazolam is due to its safety profile, effectiveness, and reliability in reducing preoperative anxiety in children. Most clinicians administer doses of 0.5 mg/kg without regard for the child's age (Banch & Lerman, 2014). Midazolam also has synergistic effects when used with propofol; thus the amount of propofol can typically be reduced during the induction of anesthesia.

As midazolam can be an appealing premedication to anesthesia professionals, there are also some unappealing characteristics related to EA. Dahmani and colleagues (2010) performed a study to provide a meta-analysis aimed towards the pharmacologic prevention effects of EA in children. Out of thirty-seven articles that included 1695 patients in the intervention group and 1477 in the control group, midazolam and $5HT_3$ inhibitors showed no protective effects on EA. One concern with midazolam administration is prolonged emergence time. In the RCT study by Cho and colleagues (2014), 90 children underwent strabismus surgery under general Sevoflurane anesthesia. Three groups being tested and randomized to receive either 0.03mg/kg of midazolam, 0.05mg/kg of midazolam, or saline just before the end of surgery. The results showed a significant lower incidence of EA in both midazolam groups at 16.7% and the saline group 43.3%. Emergence time was longer in patients receiving midazolam 0.05mg/kg compared

to midazolam 0.03mg/kg and the saline group making it the more favorable dosing option for the pediatric patient to reduce the incidence and severity of EA without prolonging emergence time.

Ketamine. While midazolam remains a commonly used sedative in children preoperatively and upon emergence, Ketamine has also proven to show beneficial effects to reduce the incidence of EA. It can be given orally as a premedication in doses of 6mg/kg or intraoperatively 1mg/kg intravenously (IV) followed by an infusion of 1/mg/kg/hr.

In a small RCT conducted by Kim et al. (2015), 68 patients age 1-6 years old underwent elective ophthalmic surgery under general Sevoflurane anesthesia and randomly assigned either midazolam 0.01mg/kg or ketamine 1.0mg/kg IV. The ketamine group showed a significant decrease in EA during the early emergence period between 10-20 minutes at 24% compared to the midazolam group which was 52.9%. The midazolam group also required more rescue medication which made ketamine the more preferable medication of choice in this study.

In a similar study by Lee and colleagues (2010), different doses of ketamine were compared to determine the most effective dose in reducing EA. In this study, 93 children ages 2-14 years old undergoing an adenotonsillectomy. They were randomly assigned to three groups receiving saline, ketamine 0.25mg/kg, or ketamine 0.5mg/kg. Each group was administered the study drug 10 minutes prior to the end of surgery and evaluated in the PACU on a four-point scale for EA: 1, asleep; 2, awake but calm; 3, agitated but consolable; 4, severely agitated and difficult to console. The results showed significant difference between the saline group (54%) compared to the ketamine groups (2%)for EA scores. There was also a significant difference between the two ketamine groups when comparing post-operative pain control using the modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). The group that received

0.25mg/kg had 75% median scores of 6/10 while the 0.5mg/kg ketamine group had a 75% median score of 2/10.

Dexmedetomidine. Dexmedetomidine (DEX) has also become a popular anesthesia adjunct to reduce EA in the pediatric population. Dexmedetomidine and other alpha-2 adrenoreceptor agonists has not been U.S. Food and Drug Administration (FDA) approved for the use as a sedative, anxiolytic, and analgesic in the pediatric population. However, dexmedetomidine has been reportedly used in pediatrics as a premedication sedation preoperatively, as an adjunct to inhaled anesthetics, and prophylactically on emergence to reduce EA (Hauber et al., 2015). A RCT study conducted by Hauber et al. (2015) examined the hemodynamic effects of a rapid IV bolus injection of DEX on emergence agitation on a large sample of 393 children ages 4-10 undergoing tonsillectomy with or without adenoidectomy. There were two randomized groups, one receiving a rapid IV bolus of DEX at 0.5 μg/kg over 2-3 seconds and the other receiving an equal volume of saline over 2-3 minutes. The incidence of EA was significantly lower in the DEX group at 36%, whereas the saline group was 66%. The concern for hemodynamic instability due to the administration of DEX are related to the rate and infusion dose (Hauber et al., 2015). In this study, there was a slight decrease in heart rate (HR) by 22% compared with 10% in the control group and was noted that coadministration of ketamine with DEX seems to prevent the decrease in HR (Hauber et al., 2015). There was no significant hemodynamic instability between the two groups in regards to blood pressure and HR and DEX did not delay PACU phase 1 length of stay at the main hospital but did lengthen the stay at the PACU surgery center by an average of 9.2 minutes. The DEX group also required less postoperative supplemental opioids (73% vs 48%) and had fewer postoperative adverse effects (9% vs 17%). Another concern with DEX that continues to be an issue is the cost of

DEX. In this study the use of DEX was collaborated by surgery pharmacy to reduce the cost and well as sterilely prepare 10-mL syringes of DEX in 4 μg/ml solutions (Hauber et al., 2015).

In a similar smaller RCT, the effects of DEX were observed and recorded in 40 children undergoing ambulatory hernioplasty or orchiopexy under general Sevoflurane anesthesia. There were two groups; DEX group received 1μg/ml while the second group received volume matched saline injection. There was a significant reduction in EA with the DEX group than in the saline group (5% vs 55%) without having any differences in post of pain or discharge times (Kim et al., 2014). The hemodynamic effects of DEX in this study showed a significantly lower mean arterial pressure and HR reduction by 22%-28% and 18-21% respectively in the DEX group than the saline group (Kim et al., 2014).

Fentanyl. Fentanyl has also been an anesthetic commonly utilized in conjunction with either midazolam or propofol upon emergence to eliminate post-operative pain which is one of the suggested factors thought in causing EA. Although, Mountain et al. (2011) reported how many studies have documented occurrence of EA after the use of Sevoflurance despite the absence of pain in children who had regional blocks. In a prospective, randomized, double-blind study, performed by Kim et al. (2012) 222 children 18 month- six-years old underwent ambulatory inguinal hernia repair under general Sevoflurane anesthesia and were randomly assigned to receive propofol 1 mg/kg, fentanyl 1μg/kg, or saline at the end of anesthesia. To evaluate the incidence in severity of EA the PAED score was evaluated in the PACU. Both fentanyl and propofol PAED scores were significantly lower than the saline group. The results showed a decrease in EA with both fentanyl and propfol being comparable therefore showing no difference in efficacy in one drug over the other in decreasing the incidence and severity of EA after sevoflurance anesthesia.

On the other hand, Kim et al. (2012) found that the incidence of nausea or vomiting in the fentanyl group was 26% higher than the propofol group. Another concern for fentanyl or propofol administration has been delayed awakening time which did occur in the study but only for 10 minutes. The propofol and fentanyl groups were discharged from PACU after a 10 min wake up whereas the saline group took more than 15 minutes for discharge due to the incidence of EA (Kim et al., 2012).

Propofol. One of the more commonly used techniques and relevant to this case report used for prevention or decreasing EA is the use of propofol. Propofol is a widely used intravenous anesthetic with desirable characteristics of a smooth and rapid recovery with few postoperative side effects (Kanaya et al., 2014). The speculation that propofol maintenance during a case might allow for a calm wake-up in pediatric populations was observed in this case report and has encouraged conduction of randomized control trial (RCT) in comparing propofol and Sevoflurane anesthesia. This research will be discussed in more detail later in this review.

The above propofol technique has also been utilized with pediatric patients undergoing dental procedures. Messieha (2013) describes the technique used in an ambulatory dentist office by conducting a Sevoflurane washout in the spontaneously breathing intubated child. The technique utilized by the anesthesia professional during the final 30 minutes of the procedure, encompassed discontinuation of the volatile anesthetic, Sevoflurane, and maintained the anesthetic state with a propofol infusion using an infusion pump. The infusion was guided by the both Bispectral Index System (BIS) number and the usual standard patient vital signs. It was concluded that the BIS-guided propofol washout technique in the final 30 minutes was significantly effective in reducing EA without compromising extubation and recovery times.

Messieha (2013) notably has conducted over 300 cases utilizing the technique described above and has noted a significant limitation of EA in over 90% of those cases.

Kanaya et al. (2014) also compared the incidence of EA in propofol and Sevoflurane anesthesia. A meta-analysis of RCTs included 14 studies in which 560 patients were anesthetized with Sevoflurane and 548 patients were anesthetized with propofol and evaluated for the incidence of EA. The results showed a significant decrease in EA with the propofol group being 10.9% who experienced EA compared to 30.2% in the Sevoflurane group. Another prospective RCT conducted by Costi et al. (2014), was aimed to determine whether transition to propofol over three minutes at the end of Sevoflurane anesthesia would reduce the incidence of EA in children. This RCT consisted of 230 children ages 1-12 years who underwent MRI scans under Sevoflurane and randomized to receive either 3mg/kg over three minutes (propofol group) or no propofol (control group), at the end of Sevoflurane. The PAED and the Watcha scale were used in this study to determine the level of EA until 30 min after emergence. Data was analyzed for 218 children and results of the study revealed the incidence of EA and severity was *lower* in the propofol group on both PAED (29% vs 7%) and Watcha scale (39% vs 15%). The emergence time and time in PACU were increased by a mean of 8 minutes, but there was no significant difference in time to discharge home (Costi et al., 2014).

In the case report presented, propofol was a successful anesthetic option in eliminating EA for a 7-year-old child who had preoperative anxiety and noted to be at high risk. With its high safety profile and low overall cost propofol was the anesthetic agent chosen and did not cause any side effects or delay emergence or discharge for an ambulatory procedure. This was one case performed by the writer and suggested as a primary adjunct for anesthesia that will

continue to need further research but could possible be a future solution and gold standard option for treatment and/or eliminating the risk of EA in the pediatric patient.

The inconsistent results among studies and whether propofol is the preferred method for anesthesia and the consistent results of lowering the incidence of EA in children still remains unclear and necessitates further research and studies.

Evidence Based Recommendations

The cause of EA is still unknown and needs further investigation to determine what anesthetic technique is most effective in eliminating or decreasing the incidence of occurrence in the pediatric patient. The current research does provide several hypotheses for EA development and methods that have clearly shown significant efficacy with general anesthesia delivery to pediatrics. However, there has been no development of a gold standard or best practice for EA prevention and the exact cause(s) remains unclear.

Future research in EA and anesthetic techniques such as effectiveness in preoperative medications, titration of medications upon emergence, and pediatric scales used to anticipate or guide anesthesia professionals to an approach most safe and suitable for the patient seems to be the most popular approach and where the research continues to grow. Research on EA has been conducted for over 5 decades and has been difficult to evaluate because of the unknown cause and the absence of having a standardize agitation rating system. The rating systems can vary so much because they are mainly observational in defining the stages of agitation and some systems are unable to be used due to the type of surgery that is being performed. This variation in agitation rating systems needs to be improved by narrowing down the evaluation scales and standardizing one particular scale such as the PAED or the Watcha Scale. By doing so, EA can be evaluated, recorded, and tracked in PACUs more accurately for ongoing research to clearly

identify the appropriate treatment for EA. These scales and standard scores can then be used in future studies to determine the best clinical anesthesia practice to decrease EA in pediatric patients and develop a standardardized treatment regimen to decrease or eliminate the incidence of EA.

With the many anesthetic options available for the prevention of EA, no single medication has shown significant positive or negative outcomes during the postoperative period. The literature suggests many different strategies to prevent EA and how anesthesia professionals utilize these strategies either before induction, change in maintenance technique, administering an anesthetic agent on emergence or even a combination of two. Among these strategies the use of an anesthetic agent upon emergence is thought to be the most convenient and most applicable method in most clinical situations. Some anesthetic agents are favored over others but the most important aspect is a patient specific plan and best anesthesia option by utilizing these different strategies and assessment tools in order to minimize the risk of EA in the high risk pediatric population.

Conclusion

The pediatric patient, specifically ages 2 to 5 years of age, remain at highest risk for developing emergence agitation. In addition, risk factors including general anesthesia, inhalational agents, preoperative anxiety, type of surgery, and pain can all contribute to emergence agitation in the perioperative setting. To mitigate emergence agitation for this at risk population, it is crucial for the anesthesia professional to conduct a preoperative evaluation on each patient and to subsequently develop patient specific treatment goals.

The benefits of reducing or eliminating emergence agitation include a smooth emergence process that can decrease the risk of injury to the child or surgical site. As mentioned earlier, EA

can be problematic in the PACU requiring extra nursing staff and leaving caregivers unsatisfied with anesthesia care. Furthermore, the supplemental sedatives and/or analgesic medications in the PACU used to control EA can lead to longer recovery times thus delaying patient discharge and therefore accruing higher costs to the patient and hospital.

Prevention and treatment goals should include limiting (or eliminating) the amount of volatile agents used during the case by incorporating intravenous anesthetic agents, such as propofol, during emergence. As we progress further with research and gain a deeper understanding of the precise mechanism of EA consequently we may be able to specifically identify and target the true cause of EA and eliminate this disturbing and potentially dangerous condition in the postoperative period.

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Appendix A: NDANA Presentation

Management of the Pediatric Patient with Emergence Agitation

Jessica McDonnell, SRNA

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Introduction

- Emergence Agitation/Emergence Delirium:
  - A state of hyperexcitation that includes disorientation, inconsolable crying and/or screaming, and violent movements such as flailing kicking and rolling (Macanti, 2011)
- Incidence: 10-80% with Sevoflurane
- Etiology: Children ages 1-12, ages 2 to 5 years are at the highest risk

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Introduction

- The exact causes of EA/ED are still unknown, possible factors include:
  - Untreated pain
  - Preoperative anxiety
  - Volatile anesthetics (sevoflurane specifically)
  - Patients' temperament

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Case Information

- Dental restorations
- 7-year-old
- 20kg
- Female
- ASA I

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Pre-operative Evaluation

- Past Medical History
  - Anxiety
  - Gingivitis
  - Dental caries
- Surgical History
  - No previous history
- Pre-op VS
  - HR: 117
  - BP: 113/67
  - RR: 16
  - Temp: 36.6
  - SaO2: 97%
- Allergies
  - NKA
- Medications
  - No home medications
- Airway evaluation
  - Mallampati: 2
  - Neck: Full ROM
  - Dentition: Intact
- Labs/Tests
  - None taken

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Preoperative Evaluation

- The pre-anesthetic evaluation:
  - Anxious, fearful school aged child with her parents
- No preoperative medication given (per MDA)

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Anesthetic Course

- Induction
  - Inhalation mask induction
    - 70/30 Nitrous & Oxygen mixture
  - Sevoflurane added to 8%
  - 22 gauge IV was placed
  - Propofol 40 mg IV
  - Fentanyl 20 mcg IV
  - Phenylephrine 0.25% in each nare
  - Intubation with grade I view
    - direct visualization with 4.5 mm cuffed nasal RAE ETT
- Post Induction
  - GA maintained with:
  - MAC of 1.5% Sevoflurane
  - Fresh gas flows:
    - 1.5 L/min oxygen
    - 1.5 L/min air
- Maintenance
  - Dexamethasone 4mg
  - Ondansetron 4 mg
  - Fentanyl 30 mcg
  - IV fluids: LR 350 mL
- Induction, maintenance, and surgery were uneventful

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Intraoperative Issues

- No intraoperative issues
  - Hemodynamically stable throughout the case
  - Spontaneously breathing
  - Case length: approximately 45 minutes
- Emergence
  - Sevoflurane was discontinued
  - A total of 40 mg of propofol was administered
  - Extubated with little to no MAC of Sevoflurane
  - Oral airway placed with simple facemask, oxygen at 6 L/min
  - Patient was then transferred to PACU

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PACU

- Report was given with vital signs stable
- PACU nurses were informed of the anesthetic
- Post-operative evaluation was unable to be performed
- PACU nurses reported wakeup being very pleasant as if "she woke up from a nap"

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Discussion

- Emergence agitation (EA):
  - Characterized by self-limiting aggressive agitation that develops in the early phase of awakening from anesthesia at the end of surgery
    - EA can be self-limiting or even last for up to 45 minutes
- Network meta-analysis study by Fang et al. (2015), found propofol, ketamine, fentanyl, dexmedetomidine, and preoperative analgesia good adjuncts to prevent episodes of EA in children
- Another meta-analysis study by Dahmani et al. (2010), found beneficial effects of propofol, ketamine, and fentanyl for prophylactic use in preventing EA, while midazolam and $5HT_3$ inhibitors did not have any protective effects

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Discussion

- Preoperative Anxiety Factors:
  - Preoperative anxiety
  - Postoperative behavior
  - Parental participation in the child's health care experience
- Administration of fentanyl, dexmedetomidine, propofol, or ketamine would help reduce the incidence of EA if given preoperative or during maintenance of anesthesia.
- Benefits of measuring preoperative anxiety
  - Evidence has suggests children who are anxious in the holding area and during the induction period of anesthesia experience an enhanced distress period immediately postoperatively.

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Discussion

- Risk Factors cont.
  - *Psychological Immaturity*
    - The psychological immaturity of a child's nervous system and the rapid awakening from general anesthesia in an unfamiliar environment may be responsible for the occurrence of EA.
      - $GABA_A$ receptor could be *excitatory* rather than *inhibitory* in early infancy as a result of high intracellular chloride ions, thus explaining this paradoxic reaction to anesthesia in young children
      - As child matures, the $GABA_A$ receptor transforms into an inhibitory neurotransmitter, and the reaction no longer occurs, as in the adult.

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Discussion

- Risk Factors cont.
  - *Previous Hospital Experience*
    - Children who have had previous negative health care encounters can experience increased anxiety both in the holding area and during separation from parents.
    - By reducing a child's anxiety during the preoperative period, it may benefit the perioperative process and also decrease anxiety for future anesthesia encounters.
    - Stressful life experiences that take place close to a hospital admission can also affect how a child reacts to anesthesia and the overall surgical experience. (Banch & Lerman, 2014)

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Discussion

- Risk Factors cont.
  - *Type of Surgical Procedures*
    - Banch & Lerman (2014) found several studies had concluded the type of surgery *does not* increase the risk of postoperative EA
      - Also found studies with surgical procedures of the genitourinary system and inpatient surgery were associated with an increased risk of postoperative EA.
    - Cho et al. (2014) conducted a RCT that included 90 children between the ages of 1 and 13 years old undergoing strabismus surgery
      - Suggested that children undergoing ophthalmic surgery may experience a high incidence of EA due to visual disturbances.
    - Conversely, Kanaya et al. (2014) conducted a meta-analysis of RCT and found surgical procedures, *specifically*, adenotonsillectomy at highest risk for EA
      - Lower incidence of EA following propofol anesthesia associated with these procedures compared to Sevoflurane anesthesia (Kanaya et al., 2014).

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Discussion

Scales used to measure EA/ED

- More than 16 scales can be utilized by the anesthetic professional in order to evaluate EA/ED in the postoperative period.
  - The Pediatric Emergence Anesthesia Delirium (PAED) scale
  - Watcha four-point scale
- *Watcha four-point scale*
  - More simplified scale
  - Scores ranging from 1-4
    - 1= calm, quiet
    - 2= crying, but can be consoled
    - 3= crying, cannot by consoled
    - 4= agitated and thrashing (Costi, 2014)

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Discussion

- *Pediatric Emergence Anesthesia Delirium (PAED) scale*

Ranges from a minimum score of 0 to a maximum score of 20.
- The degree of ED increases directly with the total score
- There are *five* categories that consist of:

Table 1: Paediatric anaesthesia delirium scale

Score	0	1	2	3	4
The child makes an eye contact with the caregiver	Extremely	Very much	Quite a bit	Just a little	Not at all
The child's actions are purposeful	Extremely	Very much	Quite a bit	Just a little	Not at all
The child is aware of his/her surroundings	Extremely	Very much	Quite a bit	Just a little	Not at all
The child is restless	Not at all	Just a little	Quite a bit	Very much	Extremely
The child is inconsolable	Not at all	Just a little	Quite a bit	Very much	Extremely

Minimum score is 0 and maximum score is 20. The degree of emergence delirium increases directly with the total score

(Pices, B. J. et al, 2010)

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- Cho and colleagues (2012) utilized the PAED scale in their RCT
  - 84% reliability and 89% consistency with the results
  - Sensitivity of 64% and specificity of 86% which support reliability and validity of the PAED scale making it a more favorable evaluation tool for EA.
- These scales are only a few that could possibly become a standardized method in evaluating EA in the postoperative period and help with future anesthetic management for pediatric patients.

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Discussion

- Anesthetic Techniques and Management for EA
  - There are multiple techniques that can be utilized in the pediatric population to eliminate or decrease the incidence of EA.
  - The current literature and studies reveal techniques that include preoperative doses of midazolam, intraoperative doses of ketamine, dexmedetomidine, propofol, and fentanyl all in efforts to prevent the incidence of Sevoflurane-related EA in children.

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Discussion

- Anesthetic Techniques and Management for EA
  - *Midazolam*
    - The most commonly used and agent for anxiolysis
    - *Major appeal*: safety profile, effectiveness, synergistic effects when used with propofol
- Dahmani and colleagues (2010) performed a study to provide a meta-analysis aimed towards the pharmacologic prevention effects of EA in children.
  - Out of thirty-seven articles that included 1695 patients in the intervention group and 1477 in the control group midazolam and 5HT3 inhibitors showed no protective effects on EA
- Concern with midazolam is prolonged emergence time
  - In the RCT study by Cho and colleagues (2014), 90 children underwent strabismus surgery under general Sevoflurane anesthesia.
  - Results: Significant lower incidence of EA in both midazolam groups 16.7% vs 43.3% in saline group Emergence time: > midazolam 0.05mg/kg compared to midazolam 0.03mg/kg and the saline

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Discussion

- *Ketamine*
  - Also proven beneficial effects to reduce the incidence of EA
  - Small RCT by Kim et al. (2015), 68 patients age 1-6 years old
    - Ophthalmic surgery under general Sevoflurane anesthesia
    - Results: Significant decrease in EA Ketamine 24% vs midazolam 52.9%
    - Midazolam required more rescue medication
  - Lee and colleagues (2010), different doses of ketamine compared to determine most effective dose
    - 93 children ages 2-14 years old undergoing an adenotonsillectomy.
    - Results: Saline group (54%) vs both ketamine groups (2%) for EA scores
    - Post-op pain control Ketamine 0.25mg/kg (75% median scores of 6/10) vs Ketamine 0.5mg/kg (75% median score of 2/10)

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Discussion

- *Dexmedetomidine*
  - Dexmedetomidine (alpha-2 adrenoreceptor agonists) has not been FDA approved for the use as a sedative, anxiolytic, and analgesic in the pediatric population
  - A RCT by Hauber et al. (2015) examined the hemodynamic effects of a rapid IV bolus injection of DEX on EA
    - Large sample of 393 children ages 4-10 undergoing tonsillectomy with or without adenoidectomy
    - Results: DEX group at 36% EA vs Saline 66%
    - DEX group < postoperative opioids (73% vs 48%)
    - Slight decrease in heart rate 22% vs 10% in control group
  - A smaller RCT- the effects of dexmedetomidine in 40 children undergoing ambulatory hernioplasty or orchiopexy under general Sevoflurane anesthesia.
    - Significant reduction in EA → DEX vs Saline (5% vs 55%)
    - No differences in post of pain or discharge times (Kim et al., 2014).

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Discussion

- *Fentanyl*
  - Fentanyl commonly utilized in conjunction with either midazolam or propofol upon emergence to eliminate post-operative pain (suggested factors thought in causing EA).
  - In a prospective, randomized, double-blind study, performed by Kim et al. (2012)
    - 222 children 18 month- six-years old underwent ambulatory inguinal hernia repair under general Sevoflurane anesthesia
    - Results: Both fentanyl and propofol PAED scores were significantly lower than the saline group
    - Incidence of nausea/vomiting in fentanyl group was 26% higher than the propofol group
    - Propofol and fentanyl groups discharged from PACU after a 10 min wake up vs saline group took >15 minutes for discharge d/t incidence of EA (Kim et al., 2012).

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Discussion

- Anesthetic Techniques and Management for EA
  - *Propofol*
    - Desirable anesthetic due to smooth and rapid recovery with few postoperative side effects (Kanaya et al., 2014)
    - The "propofol technique" has been utilized in cases of the pediatric patient undergoing dental procedures
      - Messieha, Z. (2013) describes the technique by conducting a Sevoflurane washout in the spontaneously breathing intubated child
      - Conducted over 300 cases utilizing the technique and noted a significant limitation of EA in over 90% of those cases

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Discussion

- *Propofol cont.*
  - A prospective RCT conducted by Costi et al. (2014), was to determine whether transition to propofol over three minutes at the end of Sevoflurane anesthesia would reduce the incidence of EA in children.
    - Trial consisted of 230 children ages 1-12 years who underwent MRI scans
    - Result: Incidence of EA and severity was *lower* in the propofol group on both PAED (29% vs 7%) and Watcha scale (39% vs 15%).
  - Inconsistent results among studies and whether propofol is the preferred method and lowers the incidence of EA thus necessitates further research and studies

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Recommendations

1. ***Standardized Rating System***:
   - Standardizing one particular scale: i.e. PAED, Watcha Scale
   - Scales and standard scores for future studies
2. ***Anesthetic Technique***:
   - Many anesthetic options available with no single medication showing significant positive or negative outcomes in EA
   - Utilize strategies: induction, maintenance, emergence (combo)
   - Limit (or eliminate) the amount of volatile agents used during the case
   - Agent on emergence is thought to be most convenient and applicable
   - *Most important* →Patient specific plan

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Conclusion

- Pediatric patient ages 2 to 5 years of age remain at highest risk for developing emergence agitation
- Reducing or eliminating EA can decrease the risk of injury to the child or surgical site such as removal of dressings or IV catheters
- EA in the PACU requires extra nursing staff and unsatisfied caregivers
- Supplemental sedatives and/or analgesic medications lead to longer recovery times, delay patient discharge, and increased costs

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Thank You
Are There Any Questions?

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