Dexmedetomidine Prophylaxis for Patient with a History of Emergence Delirium

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Emergence delirium (ED) is a commonly encountered complication of general anesthesia (GA) in the pediatric patient. This complex syndrome of symptoms encompasses several terms which are used interchangeably, including post-anesthesia agitation, post-anesthesia confusion, post-anesthesia delirium, or emergence agitation. Upon emergence from GA, the child is excessively uncooperative, irritable, combative or inconsolable. A unique characteristic of the phenomenon is that people or objects that should be recognizable are not. While it is usually self-limiting and resolved within 30 minutes, it can have a significant impact on the anesthetic course. The effects and treatment of ED may result in delayed recovery which is especially relevant in ambulatory surgery, poor patient and parental satisfaction, and disruption of surgical closure.[1] While most research has involved a healthy population, the following case report demonstrates the use of dexmedetomidine in a patient with fetal alcohol syndrome (FAS) and seizures.

Case Report

A 16 year old, 40.5 kg, 153 cm female presented for dental restorations and extractions under GA. The patient's medical history was significant for prenatal alcohol exposure with FAS, microcephaly, asthma, and seizures. Symptoms of FAS included developmental delay, attention deficit disorder, and psychotic outbreaks that were managed with daily methylphenidate and quetiapine. The patient experienced weekly absence or partial seizures that were treated with daily lacosamide and topiramate. Asthma exacerbations occurred monthly and responded well to inhaled albuterol. The patient had undergone several prior radiographic studies under GA, but had no prior surgical history. She was noted to have progressively worsening ED after each of

these prior procedures per report from her caretaker. Because previous anesthetics were performed at another facility, anesthetic records were not available to the author. Her caretaker reported that she was intubated at the other facility, and she had removed the endotracheal tube prematurely during emergence from the last anesthetic because of such severe agitation.

The patient exhibited facial deformities consistent with FAS including a narrow palpebral fissure between the upper and lower eyelid, a smooth upper lip lacking the normal groove and a thin upper lip. Breath sounds were clear bilaterally and absent of wheezing. Preoperative vital signs were within normal limits: heart rate (HR) 100/min, respiratory rate (RR) 24/min, blood pressure (BP) 119/76 mm Hg, room air SpO_2 99% and oral temperature 36.4°C.

The patient was evaluated in the preoperative holding area where she was noted to be uncooperative and combative. Midazolam 10 mg PO was administered 20 minutes prior to transport to the operating room (OR). Upon entering the OR, standard monitors were placed and anesthesia was induced with mask inhalation of sevoflurane 8% in a mixture of nitrous oxide 4 L/min and oxygen 2 L/min. Patient refusal to accept the anesthesia mask during induction required the assistance of the OR staff to facilitate patient restraint for induction. Following inhalation induction, a 20 gauge intravenous catheter was inserted in the right hand and vecuronium 4 mg was administered to optimize intubating conditions. A dexmedetomidine infusion was initiated at 0.5mcg/kg/hr. After direct laryngoscopy, a 5.5-mm RAE nasotracheal tube was placed without trauma. The patient was mechanically ventilated with sevoflurane, maintained at 1% in a mixture of nitrous oxide 1 L/min and oxygen 1 L/min. Local anesthetic was injected to the surgical site by the dentist. Vital signs remained stable throughout the procedure. The procedure consisted of dental restorations and cleaning. Ondansetron 4mg was administered intravenously 30 minutes before the end of surgery for nausea and vomiting

prophylaxis. At the end of the procedure, sevoflurane was discontinued, muscle relaxation was reversed with glycopyrrolate 0.4 mg and neostigmine 2.5 mg, and effective spontaneous ventilation was resumed. After thorough oropharyngeal suctioning, spontaneous eye opening and purposeful movement, the trachea was extubated. The infusion of dexmedetomidine was discontinued immediately following extubation. Time from induction to extubation was less than 90 minutes.

The patient was transported to the recovery room with supplemental oxygen via face mask at 6L/min. Postoperative vital signs were as follows: HR 105/min, RR 18/min, BP 123/57 mm Hg, SpO_2 100% on 6L/min of oxygen and oral temperature 36.9°C. The patient was drowsy but would arouse to voice. Thirty minutes after arrival to the recovery room the patient was awake, cooperative and appeared in no distress.

Discussion

The etiology of ED has yet to be fully explained in the literature. One possible reason for ED is rapid awakening owing to the low solubility of sevoflurane. This quick transition in level of consciousness places the patient in an unfamiliar environment with limited time to comprehend his or her surroundings.[1] Sevoflurane is noted to be irritating to the central nervous system (CNS) producing epileptiform activity on electroencephalogram (EEG).[2] This effect may have been especially relevant in this patient with a history of seizures. Other risk factors that may contribute to ED are unmanaged surgical pain, young age, otolaryngeal surgery, and preexisting anxiety or behavioral disorders.[1] The latter two risk factors and a history of ED placed this patient at an increased risk for ED.

The decision to use sevoflurane in a patient with a history of epilepsy requires careful consideration. While sevoflurane has epileptogenic properties, its clinical relevance has not been

demonstrated. Provided that protective measures are taken, such as premedication with a benzodiazepine and augmenting GA with nitrous oxide, which seem to attenuate epileptogenic EEG changes, sevoflurane is a useful agent especially in the pediatric population who benefit from the agent's hemodynamic profile.[2] Noting the extreme difficulty in attempting the placement of an intravenous catheter in this non-cooperative patient before induction, it was decided that a sevoflurane was a reasonable choice in order to achieve rapid induction in this patient whose epilepsy was well controlled with antiepileptic pharmacotherapy. Moreover, the dose of sevoflurane was significantly reduced by the addition of nitrous oxide and the dexmedetomidine infusion.

There are many unanswered questions about the pathology of FAS. Prenatal exposure to alcohol is linked to cognitive, motor and behavioral dysfunction.[3] Fetal alcohol syndrome has been correlated with decreased overall brain size, particularly in the frontal lobe, deficient development of the cerebellum and basal ganglia, and increased cortical thickening. Hypofunction of the dopaminergic system has become another possible focus for the hyperactivity and defective inhibitory control in the FAS child.[4] To date, little is known about treatment options as they relate to these pathological findings, therefore anesthetic management options are not readily available in the literature.

It is unknown whether FAS was a factor in this patient's susceptibility for ED after anesthesia, but it may have been contributory as preexisting behavioral disorders are associated with the incidence of ED.[1] Surgical pain did not seem to be a significant contributing factor to this patient's prior episodes of ED as she had experienced ED following non-invasive radiologic procedures. Dexmedetomidine was selected for its potential to mitigate ED during this surgical

procedure as it offers an alternative to other pharmacologic methods of ED prophylaxis such as the combination of midazolam and fentanyl which may cause respiratory depression.[5]

The sedative and anxiolytic effects of dexmedetomidine result from the drug's binding to α_2-adrenergic receptors in the locus ceruleus within the pons. Binding of dexmedetomidine to α_2-adrenergic receptors activates guanine-nucleotide regulatory binding proteins (G proteins), which in turn modulate ion channel activity. Potassium channels open which alter membrane potentials, and cause hyperpolarization of the neuronal cell membranes. A hyperpolarized cell has an increased threshold for responding to subsequent excitatory stimuli, which explains the inhibitory effects of dexmedetomidine in the CNS.[6] A study by Votava et al on mice showed that dexmedetomidine suppresses aggressive behavior, thus providing evidence of its calming properties which may be key in its ability to prevent ED.[7]

Surgical pain is another risk factor for ED.[1] Dexmedetomidine's analgesic properties may provide an explanation for its ability to reduce ED with potentially greater efficacy than pure anxiolytics. The anti-nociceptive properties of this agent are due to activation of α_2-adrenoreceptors in the dorsal horn of the spinal cord and inhibition of the release of substance P.[5] Just as binding to the α_2-adrenoreceptors in the brain causes anxiolysis by hyperpolarization of neurons, dexmedetomidine produces analgesia by hyperpolarization of neurons in the spinal cord.[8] Studies that compared either morphine or fentanyl and dexmedetomidine found similar recovery profiles, suggesting that analgesia may be one pathway in the prevention of ED.[9-11] The only analgesic administered in this case was local anesthetic and when the patient awoke she appeared free of pain and was not agitated. This was a notable improvement from prior procedures with anesthesia in this patient that were non-invasive and presumably not painful. The analgesic properties of dexmedetomidine may have been a benefit in this case. Schmidt et al

reported lower postoperative pain scores in patients receiving an α_2-agonist, either dexmedetomidine or clonidine, than scores reported in patients who received midazolam as ED prophylaxis.[12]

Despite its usefulness in ED prophylaxis, dexmedetomidine is not without side effects. Agonism of α_2-adrenergic receptors not only produces anxiolysis, but also can cause bradycardia and hypotension, by decreasing sympathetic outflow and thus decreasing central norepinephrine release.[13] This effect is most notable after bolus injections and less likely with a continuous infusion which achieves a steady state in the blood.[5] Dexmedetomidine was administered as an infusion in this case and no significant changes in blood pressure or heart rate were noted during or after the procedure. Monitoring and anticipation of possible changes in hemodynamics is imperative, especially in the pediatric population where a relatively fixed stroke volume dictates cardiac output.[14] When using dexmedetomidine, one must be prepared for bradycardia, by monitoring heart rate continuously and having rescue medications, such as glycopyrrolate and atropine immediately available.

In this reported case, where a dexmedetomidine infusion was used as an adjunct to GA with the goal of ED prophylaxis, the patient emerged calmly from anesthesia while spontaneously ventilating and without manifesting significant hemodynamic changes. Furthermore, the patient appeared comfortable and did not require rescue medications for agitation in the recovery room; which could have delayed discharge. While an infusion of dexmedetomidine was used, a bolus dose may have been just as effective and more convenient to administer, especially in an ambulatory setting where efficiency is important. It must be considered that bolus doses of dexmedetomidine are associated with higher incidence of bradycardia, and may require more extensive monitoring.[5] More research utilizing this

medication in patients with varied comorbidities will inform anesthesia practice with regard to routine use of dexmedetomidine for ED prophylaxis.

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Administration timing	Study first author and year	Dexmedetomidine dose
Premedicant	Mountain (2011)[2]	4 mcg/kg orally 30 min before transport to OR
	Ozcengiz (2011)[13]	2.5 mcg/kg orally 45 min before induction
	Schmidt (2007)[14]	1 mcg/kg transmucosal 45 min before surgery
Bolus after induction	Ibacache (2004)[17]	0.15 mcg/kg or 0.3 mcg/kg IV after induction
	Sato (2010)[16]	0.3 mcg/kg IV after induction
	Erdil (2009)[10]	0.5 mcg/kg IV after intubation
	Olutoye (2011)[12]	0.75 mcg/kg or 1 mcg/kg IV after induction
	Isik (2006)[15]	1 mcg/kg IV after induction
Infusion after induction	Shukry (2005)[18]	0.2 mcg/kg/hr IV after induction
Bolus and infusion after induction	Patel (2010)[11]	2 mcg/kg bolus IV followed by 0.7 mcg/kg/hr after induction

Table 1.