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Dexmedetomidine Use in the Pediatric Postoperative Patient with Emergence Agitation: A Systemic Review

Elizabeth Kittredge

DEXMEDETOMIDINE USE IN THE PEDIATRIC POSTOPERATIVE PATIENT WITH EMERGENCE AGITATION: A SYSTEMATIC REVIEW

by

Elizabeth Kittredge

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Abstract

Emergence Agitation is a frequent complication in the pediatric postoperative population; with up to 80% incidence (Stamper, Hawks, Taicher, Bonta & Brandon, 2014). These patients will present with crying, overexcitement, thrashing, agitation and is seen within the first 30 minutes of emergence of general anesthesia (Mohkamkar, Farhoudie, Alam-Sahebpour, Mousavi, Khani & Shamomhammadi, 2014). Dexmedetomidine, a selective alpha 2 agonist, reduces norepinephrine output, initiates firing of inhibitory neurons such as the gama aminobutric acid system and reduces release of substance P and other catecholamines. These actions provide the patient with sedation, analgesia, and anesthesia (Nagelhout & Elisha, 2018). Due to the mechanism of action of dexmedetomidine, bradycardia and hypotension have been seen in pediatric patients. This has put a limit on the use of dexmedetomidine in this population. The purpose of this systematic review was to examine efficacy and side effects of various doses of dexmedetomidine to prevent emergence agitation in the pediatric postoperative patient. A comprehensive literature review was completed with the use of CINAHL Plus with full text, PubMed and Google Scholar. Preferred Reporting Items for Systematic Meta-Analysis (PRISMA), was used as guidelines to assist in proper identification of articles. The quality and critical appraisal of each randomized control trial was determined by the Critical Appraisal for Summaries of Evidence (CASE) worksheet. A cross study analysis table was created and used to analyze results of all studies. The findings of this systematic review determined dexmedetomidine was beneficial in emergence agitation prevention. Dexmedetomidine dosed at 0.5 mcg/kg-1mcg IV boluses and 1 mcg/kg – 2 mcg/kg intranasal sprays provided good relief with limited adverse effects.

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Background/Statement of the Problem

Emergence agitation, also known as emergence delirium, is a common phenomenon in postoperative pediatric patients after receiving anesthesia, specifically sevoflurane or desflurane anesthesia (Garg et al., 2018). Emergence agitation can happen in any patient at any age but has been found to occur three to eight times more commonly in pediatric patients (Stamper et al., 2014). The incidence of emergence agitation is the highest in children who are younger than six years old, have a history of anxiety, specifically preoperative anxiety, and experience a fast emergence from general anesthesia (Stamper et al., 2014). Emergence agitation is defined as "a mental disturbance during the recovery from general anesthesia consisting of hallucinations, delusions, and confusion manifested by moaning, restlessness, involuntary physical activity, and thrashing about in bed" (Stamper et al., p. 480). Sevoflurane, an anesthetic commonly used in general surgery, is found to have the highest incidence of emergence agitation in pediatrics (Peng & Zhang, 2015).

The child with emergence agitation presents with restlessness, combative movements, thrashing, confusion, and may be inconsolable (Zhu, Wang, Zhu, Niu, & Wang, 2015). All of these factors may cause discomfort to the patient, parents, post-operative registered nurses (RNs) and anesthesia providers. Emergence agitation also puts the patient at risk for self-injury including wound dehiscence and dangerous removal of various medical catheters that may be in place in the post-operative phase (Stamper et al., 2014).

The etiology of emergence agitation is uncertain; it may be related to pain, behavioral issues, anxiety, surgical type, character of patient, and the anesthesia used (Kim, Kim, Yoon, & Kil, 2015). One such sedative is dexmedetomidine, which is a highly specific alpha 2 agonist that produces a calming effect. It relieves anxiety without effecting the respiratory drive, which makes this medicine very beneficial for pediatric patients (Garg et al., 2018). The effectiveness of dexmedetomidine may be based on its unique pharmacological characteristics. It has been found to be useful in emergence agitation in adults as well (Garg et al., 2018). There is lack of labeling on the use of dexmedetomidine in pediatrics, but some literature suggests that it may be favorable for the pediatric population.

According to Mahmoud and Mason (2015), dexmedetomidine is found to be advantageous in decreasing emergence agitation in pediatric patients in the perioperative phase due to many factors such as neuro-protection, anxiolysis, analgesia, sympatholytic, and lack of respiratory depression. The intraoperative administration of dexmedetomidine has been shown to reduce emergence agitation in pediatric patients. Not only does it provide analgesia and anxiolysis but the use of dexmedetomidine intraoperatively can decrease the amount of anesthetics used, which in itself may be a triggering agent for emergence agitation. (Kim et al., 2015). According to Qiao, Xie, and Jia (2017), dexmedetomidine has beneficial effects preoperatively, intraoperatively, and postoperatively in pediatric patients.

There seems to be no common protocol for preventative measures or even diagnosis of emergence agitation (Stamper et al., 2014). Dexmedetomidine has been identified as a useful preventative measure (Kim et al., 2015). Other preventive measures

include comfort measures and small doses of fentanyl (Nagelhout & Elisha, 2018). The purpose of this paper was to conduct a systematic review to examine the efficacy and side effects of various doses of dexmedetomidine to prevent emergence agitation in the pediatric postoperative patient.

Next, the review of the literature will be presented.

Literature Review

The principal databases used to perform this systematic review included CINAHL Plus with full text, PubMed, and Google Scholar. The keywords used included emergence agitation, sevoflurane, dexmedetomidine, intraoperative, and pediatrics. The time period of the search was limited to ten years.

Emergence Agitation/Delirium

Emergence agitation, also known as emergence delirium and post anesthetic excitation, can occur in patients of any age. It was first described in the 1960s in a retrospective research study performed on patients who received general anesthesia. This study reviewed 14,436 cases and discovered the incidence of emergence agitation was highest in childhood, decreased in middle aged patients, and had a slight increase in the elderly (Eckenhoff, Kneale & Dripps, 1961). This highest incidence of emergence agitation in children remains true to this day. It is a frequent problem in the pediatric post anesthetic care unit. The incidence of pediatric emergence agitation can range from 10 to 80% (Mohkamkar et al., 2014). The large range of pediatric emergence agitation, which some studies report from 2% to 80%, is most likely due to the differing anesthetic techniques used on children (Stamper et al., 2014). The large range can also be related to the varying scoring systems used to determine emergence agitation (Dahmani et al., 2010). About four million children undergo general anesthesia each year and emergence agitation remains a significant problem (Mohkamkar et al., 2014).

Pediatric emergence agitation is a postoperative occurrence associated with digressive cognitive and psychomotor ways of acting (Stamper et al., 2014). Examples of these characteristics include crying, overexcitement, thrashing, and agitation. Emergence

agitation occurs within the first 30 minutes of emergence from general anesthesia, but it can last up to two days (Mohkamkar et. al., 2014). Post hospitalization behavioral changes (PHBC) are also associated with emergence agitation and 73% of children have been found to have these changes which include sleep disturbance, night terrors, separation anxiety, and aggression towards providers or caregivers (Pickard, Davies, Birnie & Beringer, 2014).

Emergence agitation is noted to be one of the major causes of frustration among parents and medical workers in the postoperative phase (Makkar, Bhatia, Bala, Dwivedi & Singh, 2016). These characteristics associated with this syndrome can put the patient, family, and medical staff at risk of injury and can interfere with the child's recovery time. The child may be at risk of removing certain medical catheters, dressings, and monitoring devices needed in the postoperative period and can cause self-harm (Mohkamkar et. al., 2014). Adverse effects of emergence agitation may be transient but can defer discharge from the post anesthetic care unit due to the risk of self-injury and injury to family or caregivers. The extra care required from the nursing team to care for a patient presenting with emergence agitation may strain nursing resources and cause dissatisfied post anesthetic care (Costi et al., 2014).

A key way to manage pediatric emergence agitation is to identify the phenomenon quickly (Stamper et al., 2014). Over the years, there has been a paucity of dependable and validated scales to measure emergence agitation in pediatrics. The lack of a standardized, accepted measurement tool contributes to the wide range of incidence of emergence agitation that is reported in the literature (Stamper et al.). Also, the lack of standardized measurement tools makes it difficult for providers to find a definite treatment for

emergence agitation (Stamper et al.). There remains an absence of prophylactic treatment for emergence agitation. (Costi et al., 2014). Treatment for emergence agitation has been suggested but no study has found one approach to be superior to the others (Mohkamkar et al, 2014). The treatment of emergence agitation is still up for debate based on the value of the interventions. (Stamper et al., 2014).

To determine emergence delirium in adults, medical providers use the Level of Consciousness-Richmond Agitation and Sedation Scale (LOC-RASS), but it has not been validated for pediatrics (Stamper et al., 2014). In 2004, the Pediatric Anesthesia Emergence Delirium (PAED) scale (Table 1) was developed due to the lack of standard of care regarding emergence agitation.

Table 1

Pediatric Anesthesia Emergence. Delirium Scale

Point	Description of Items	Scoring				
		not at all	just a little	quite a bit	very much	extremely
1	The child makes eye contact with the caregiver	4	3	2	1	0
2	The child's actions are purposeful	4	3	2	1	0
3	The child is aware of his/her surroundings	4	3	2	1	0
4	The child is restless	0	1	2	3	4
5	The child is inconsolable	0	1	2	3	4

Mohkamkar, M., Farhoudi, F., Alam-Sahebpour, A., Mousavi, S., Khani, S., & Shamomhammadi, S. (2014). Postanesthetic emergence agitation in pediatric patients under general anesthesia. *Iranian Journal of Pediatrics,24*(2), 186.

The PAED scale was created in an attempt to increase knowledge and communication to prevent unwanted side effects from emergence agitation (Costi et al., 2014). The PAED scale is more frequently used in studies after 2004 but its use is inconsistent in clinical practice and in research. It was developed based on a theoretical

framework of agitation, which focuses on changes in consciousness and cognition; this aids in distinguishing emergence agitation from pain. The PAED scale consists of five characteristics that are each scored by using a five-point scale. The five characteristics consist of the child's state of consciousness, ability to focus attention, ability to thoughtfully organize external stimuli, psychomotor behavior, and emotional behavior. A PAED score higher than or equal to 10 determines the presence of emergence agitation (Costi et al., 2014).

The PAED scale has been reported to be a more reliable and valid measurement for pediatric emergence agitation than the LOC-RASS scale (Costi et al., 2014). Stamper et al. (2014) performed a quality improvement project to evaluate the identification of pediatric emergence agitation by implementing the use of the PAED scale in the pediatric PACU. Four hundred patients were assessed using the PAED scale and the LOC-RASS scale in two different periods, 200 patients in the retrospective audit and 200 patients in the implementation period. A retrospective chart review was completed using LOC-RASS from perioperative electronic health records one year before the implementation period. A one-year time period was chosen to lessen the influence of education needed for perioperative staff members. Then data was collected during the implementation of the PAED scale using LOC-RASS and PAED scale. The incidence of pediatric emergence agitation in the implementation period with the LOC-RASS scale was 7.5% (n = 200) and the PAED scale was 11.5% (n = 198), whereas the incidence of emergence agitation only occurred in about 3% of the retrospective period population. But there was little difference in acknowledging emergence agitation in the implementation period;

emergence agitation was assessed in 12 patients with the LOC RASS and the PAED scale during the implementation period.

Effect sizes (ES) were calculated to establish the clinical significance of the differences in pediatric emergence agitation of each tool. The incidence between PAED scale during the implementation period and LOC-RASS during the retrospective was an ES of 0.79 or 95%. This suggests that the PAED scale was more likely to identify patients with emergence agitation than the use of LOC-RASS in the retrospective period. After analysis of all findings, this study suggested that PAED scale is more sensitive in identifying patients with emergence agitation after emergence of general anesthesia. The tool allows medical practitioners to better identify patients who are demonstrating a decrease level of consciousness, restless behavior, or both. The use of LOC-RASS may lead to false negatives (Stamper et al., 2014).

Emergence Agitation Risk Factors

Although emergence agitation was discovered in the 1960s, the etiology of emergence agitation is still unknown but various factors can be associated with it (Makkar et al., 2016). It is important for the anesthesia providers and postoperative nursing team to identify the risk factors for emergence agitation to manage them appropriately. The risk factors associated with emergence agitation is highest among children who are younger than six years of age, have preoperative anxiety, pain, general anesthesia, rapid emergence from general anesthesia, and head and neck surgery (Stamper et al., 2014).

Age. Children who are preschool age, younger than six years old, have been associated with emergence agitation more frequently (Stamper et al., 2014). Overall, the

pediatric brain is a mirror image of normal age-related regressive processes which cause a continuous decline in norepinephrine, acetylcholine, dopamine, and gama-aminobutyric acid (GABA). This puts young children at risk of developing emergence agitation (Kanaya, 2015). Mokhmakar et al. (2016) stated that children in the age range of 4-6 years old are most sensitive to emergence agitation based on their inability to cope related to rapid awakening in an unknown environment and psychological immaturity.

Preoperative Anxiety. Children with high anxiety levels at baseline and preoperative anxiety upon entering the operating room have been linked to emergence agitation (Stamper et al., 2014). Up to 65% of pediatric patients receiving anesthesia for surgical procedures will develop extreme fear and anxiety in the pre-operative unit and during induction of anesthesia (Kain et al., 2004). It also has been noted that children with anxiety during inhalation induction have a higher incidence of emergence agitation (Kanaya, 2015). The anxiety can be linked to separation anxiety, fear of anesthesia, surgery, the setting, and outcome of procedure (Kain et al.). Also, children with emotional, behavioral, and impulsive personality disorders will have a higher incidence of emergence agitation (Kanaya, 2015).

Pain. Inadequate pain relief can cause extreme agitation in children if no interventions are provided. Pain can actually mimic the emergence agitation phenomenon. It is very important to determine if pain is the cause of agitation or if emergence agitation is actually present. This is further complicated by the fact that assessing pain in the pediatric patient can be very challenging as is. The PAED scale includes a section regarding pain to help determine the presence of emergence agitation versus pain (Costi et al., 2014). Although pain can be associated with agitation in

children, many studies have found that in procedures not associated with pain, the child may still present with emergence agitation, especially if the patient has received sevoflurane anesthesia (Kanaya, 2015). For example, in many ophthalmologic cases where no postoperative pain is present and the child received sevoflurane, emergence agitation presented (Kanaya). Therefore, with lack of pain, emergence agitation still presents (Mokmahkar et al., 2014).

General Anesthesia. Inhalation of anesthetics are used to provide general anesthesia. This is considered an "altered physiological state characterized by reversible loss of consciousness, analgesia, amnesia, and some degree of muscle relaxation" (Butterworth, Mackey, & Wasnick, 2018). The first anesthetics originated in the 1800's; with advanced technology and pharmacokinetics new anesthetics have been derivated from the original anesthetics with more ideal properties and side effects. The two most commonly used anesthetics include desflurane and sevoflurane. Desflurane is an inhalation anesthetic first introduced in 1993 and sevoflurane was introduced in 1995 in the United States (Nagelhout & Elisha, 2014). The increased use of sevoflurane and desflurane in medically advanced countries are associated with emergence agitation (Dahmani et al., 2010)

Desflurane is halogenated with fluorine and has a low solubility in blood and body tissues. This ensures that a very rapid induction and emergence of anesthesia may occur (Butterworth, Mackey, & Wasnick, 2018). Multiple studies suggest that desflurane is associated with emergence agitation due to the rapid induction and recovery time (Bedaway, 2018). But there is very little data on what drugs to use to prevent emergence agitation related to desflurane use (Makkar et al, 2016). Although desflurane has been

linked to emergence agitation, sevoflurane has gained more popularity and is used more routinely in the pediatric population.

Sevoflurane is halogenated with fluorine but has a slightly higher blood solubility. One benefit of sevoflurane is the non-pungency, less irritation rapid induction and emergence. These factors make it a great choice for smooth and fast induction and emergence of pediatric patients (Butterworth, Mackey, & Wasnick, 2018). The child can easily breathe this anesthetic in by face mask and works very quickly. It will be given continuously during the surgical procedure to keep the child under general anesthesia. It is turned off when it is time for the child to wake up. But since sevoflurane's launch, it has been associated with emergence agitation, predominately in pediatric patients (Costi et al., 2014). It has been suggested that sevoflurane anesthesia may cause triggering events or even a neurotoxic effect in the central nervous system (Costi et al). Sevoflurane has an epileptogenicity that may be the triggering cause of emergence agitation. (Kanaya et al., 2013). Although rapid awakening from sevoflurane and painful procedures are linked to emergence agitation, some studies have found even with a slow awakening from sevoflurane anesthesia and nonpainful procedures, pediatric patients present with emergence agitation (Na, Song, Hwang, Do, & Oh, 2012).

Rapid Emergence. Emergence agitation is precipitated by rapid emergence from anesthesia and short acting volatile anesthetics, specifically sevoflurane. Rapid emergence may cause a dissociative state, so when children awaken from anesthesia in this state they will present with altered cognitive perception (Dahmani, et al., 2010). Kim et al. (2015) performed a meta-analysis of randomized controlled trails (RCTs) to investigate the incidence and severity of emergence agitation related to the use of

desflurane and sevoflurane anesthetics. They reviewed 12 RCTs with a total of 1127 patients. Five hundred and eighty-eight patients received desflurane anesthesia and 608 received sevoflurane anesthesia. Eight studies include patients in the age range of one year to eight years old, while the four studies include children over the age of ten. Overall, they found that sevoflurane and desflurane both had equivalent incidences of emergence agitation at 1.21 and with low heterogeneity, even with desflurane having a more rapid awakening time than sevoflurane.

Surgery Type. Otorhinolaryngological, ophthalmological, abdominal, and orthopedic surgical procedures have been closely linked to emergence agitation. (Mohkamkar et al., 2014). In fact, any surgery involving the head and neck are associated with increased risk of developing emergence agitation (Stamper et al, 2018). The specific physiological compromise during these surgeries increase the risk (Zhu et al., 2015). Otorhinolaryngological and ophthalmological surgeries were discovered to be risk factors of emergence agitation in the 1960s. It was described as a "sense of suffocation" while the patient awakened from anesthesia; there is no randomized controlled trials to backing this hypothesis (Kanaya, 2015).

A study performed by Mohkamkar et al. (2014) compared the prevalence of emergence agitation in 134 children aged three to seven years. Each child underwent an elective surgical procedure, either an otorhinolaryngological surgical procedure, abdominal surgery, orthopedic surgery, urology surgery, or ophthalmic surgery. Out of all five surgeries, otorhinolaryngological surgical procedures had the highest incidence of emergence agitation. A significant relationship between the site of operation, specifically the head and neck, and occurrence of emergence agitation ($P<0.05$) was found.

Otorhinolaryngological surgeries were linked to higher pain and increased anxiety with induction (Mohkamkar et al).

Prevention of Pediatric Emergence Agitation

Emergence agitation puts the pediatric patient at risk of harm to self and delay of recovery time. It also requires extra care and monitoring from the medical and nursing staff and can put them at risk of injury as well. The patient's family or caregivers may be dissatisfied and upset regarding the emergence agitation and blame the symptoms on the anesthetic management (Costi et al., 2014). Preventative measures will be required, which include pharmacological, physical restraint, or comfort measures. The most frequent preventative measure is pharmacological (Costi et al). The patient cannot be discharged until the emergence agitation has subsided and the patient is safe.

Pharmacologic Management. Frequently used medications for emergence agitation treatment are mainly opioids and sedatives. Some of these drugs may have adverse effects on the patient and may delay recovery and discharge time for the patient. (Costi et al., 2014). Frequently used drugs to help prevent or stop the incidence of emergence agitation include midazolam, ketamine, dexmedetomidine, fentanyl, remifentanil, NSAIDs, and propofol boluses (Costi et al.). Each pharmacological intervention has different molecular mechanisms that can influence the patients' outcomes. For example, a bolus of fentanyl during induction of anesthesia has been shown to reduce the incidence of emergence agitation, but it has negative side effects such as respiratory depression and retching (Kanaya, 2015).

Mohkmakar et al. (2014) performed a cross sectional descriptive and analytic study on 747 pediatric patients aged 3-7 who underwent general anesthesia to determine

the associated risk factors and prevalence of emergence agitation in pediatric patients undergoing general anesthesia. Mohkmakar et al. (2014) found that midazolam, a benzodiazepine that provides amnesia and anxiolysis, was used as a premedication for some patients in this study and no increased incidence of EA was found with this use of this sedative medication. Propofol and ketamine was used intraoperative with the anesthetic sevoflurane and there was lack of incidence related to the use of both of these as well.

The choice of the anesthetic can prevent emergence agitation as well. Another anesthetic option for children is the use of propofol. Propofol is a 2, 6-diisopropyl phenol. It has rapid distribution after intravenous bolus dose to brain and high perfused organs. This leads to rapid induction and rapid reawakening after sedative and anesthetic doses (Nagelhout & Elisha, 2018). The use of propofol for induction has not been proven to reduce emergence agitation, but the use of it after induction has been shown to reduce emergence agitation (Kanaya, 2015). A meta-analysis compared the use of sevoflurane in 560 patients and the use of propofol in 548 patients. This study found that 95% of the patients had lower incidence of emergence agitation with the use of propofol (Kanaya et al., 2013).

Dexmedetomidine has been linked to a large reduction in risk of EA (Costi et al., 2014). In one study it was found to be the most appropriate intervention in preventing sevoflurane- related emergence agitation (Kanaya, 2015). Costi et al. (2014) performed a systematic review regarding involved 137 studies and 14,045 children. Participants included children under the age of 18 years old who were to receive general anesthesia. The children were separated into two groups based on alternative general anesthesia

versus use of sevoflurane and use of sevoflurane versus sevoflurane with an adjunct. This systematic review found that propofol, halothane, dexmedetomidine, opioids, and ketamine all reduce the risk of EA. Thirty-four studies compared sevoflurane and halothane for risk of emergence agitation; all studies found the use of halothane has a lower risk of emergence agitation compared to sevoflurane. Propofol at the end of anesthesia was used in five studies; 1mg/kg boluses were administered at the end of anesthesia and showed a decrease in emergence agitation. One study used 3 mg/kg bolus of propofol for induction and showed no effect on the risk of emergence agitation, along with another study who used 2-2.5 mg/kg bolus and found no reduction of emergence agitation as well. Ketamine as oral premedication was found to reduce overall risk of emergence agitation in two studies, where as one study found no reduction of emergence agitation with the use of ketamine after induction of anesthesia. Three other studies did find that ketamine as a 0.25mg/kg bolus at the end of anesthesia reduces the risk of anesthesia. Twelve studies showed an overall decrease in risk of emergence agitation with the use of IV fentanyl. Twelve studies investigating this intervention found a significant reduction in the risk of EA (RR 0.37, 95%). Another added four studies found that after dexmedetomidine was used there was a lower risk of emergence agitation as well (Costi et al.)

Use of Dexmedetomidine to Prevent Pediatric Emergence Agitation

Background. Dexmedetomidine, also known as precedex, is part of the imidazole class and is an alpha 2 agonist with a short half-life. It is a freely soluble in water with a ph of 4.5-7.0 and is preservative free (Nagelhout & Elisha, 2018) and it is administered via intravenous infusion. Alpha 2 receptors are G-protein-coupled receptors, when

activated by dexmedetomidine, inhibit calcium channels, activate potassium channels, and provide direct modulation of the exocytic release of proteins, which produces hyperpolarization of cells and inhibit cells (Nagelhout & Elisha, 2018). Dexmedetomidine's alpha 2 receptor mediated side effects are generated by its effect in the locus ceruleus and spinal cord. The main site of action of this medication is at the pontine noradrenergic nucleus in the locus ceruleus. Dexmedetomidine provides a sedative effect by binding to the alpha 2 receptors in the locus ceruleus, reducing norepinephrine output and initiating the firing of inhibitory neurons such as the gama aminobutric acid system. Dexmedetomidine also binds to the alpha 2 receptors found in the dorsal horn and supra-spinal sites, which reduces the release of substance P and reduces the release of other catecholamines (Pickard et al., 2014).

Dexmedetomidine has sedative, analgesic, and cardiovascular sympatholytic actions, is an anxiolytic, and reduces post-operative shivering (Nagelhout & Elisha, 2018). It is used commonly in anesthesia and intensive care (Bedirli et al., 2017). Dexmedetomidine can be used intraoperatively and is known to reduce intravenous and inhaled anesthetic use in the operating room. It also can be used outside of the operating room to help with anxiety and analgesia. The use of dexmedetomidine is approved for up to 24 hours for sedation in a critical care unit, as well as sedation for short term surgical procedures (Nagelhout & Elisha, 2018). Dexmedetomdiine has been found useful in the pediatric perioperative period to help control emergence agitation. It enhances the tolerance, weaning of narcotics and lessens the amount of sedation needed for mechanically ventilated patients (Nagelhout & Elisha, 2018).

Dexmedetomidine produces a stage 2 non rapid eye movement sleep through initiation of the endogenous sleep-promoting pathway. It will induce a conscious sedation; the patient can be drowsy yet arousable (Zhu et al., 2015). A unique characteristic of dexmedetomidine is that it has little to no respiratory depression. This is beneficial because dexmedetomidine will provide analgesia with lack of respiratory depression (Pickard et al., 2014). The brain respiratory center is able to remain responsive to carbon dioxide levels and airway patency and the airway reflexes are present as well. It produces a sedation that is similar to patients' natural sleep while they remain easily arousable. The medication does not change cerebral metabolism but decreases cerebral blood flow because of cerebral vasoconstriction. A neuroprotective effect has also been noted. The dose of dexmedetomidine can be given via bolus 1 mcg/kg over 1- minute followed by an infusion at 0.2-0.7 mcg/kg/hr (Butterworth, Mackey, & Wasnick, 2018).

Although dexmedetomidine has unique benefits, it does have some unwanted side effects. It may cause bradycardia and decrease blood pressure due to its sympatholytic effects. It has been reported to cause sinus arrest after a bolus dose of dexmedetomidine in some pediatric patients. It also may cause transient hypertension with rapid initial loading doses or high maintenance doses due to vasoconstriction. Dose dependent hypotension is considered normal in this drug (Nagelhout & Elisha, 2018). These cardiovascular effects are from the stimulation of CNS alpha receptors and systemic vasodilation that ensues. There is a reduction in myocardial oxygen demand which provides an antianginal effect (Nagelhout & Elisha). These hemodynamic side effects cause providers to limit the use of it in anesthesia pediatric practice (Bedirli et al., 2017).

Prevention of Emergence Agitation. There is a lack of recommendations regarding what medications to use to prevent emergence agitation. Some studies suggest the use of fentanyl, midazolam, ketamine, NSAIDs, alpha 2 agonists, and/or propofol. As discussed above, dexmedetomidine has many pharmacological benefits that other pharmacological agents do not, such as a conscious sedation, analgesia, anxiolysis, and it also does not cause respiratory depression. The literature related to dexmedetomidine for the use of prevention of emergence agitation is abundant. Many RCTs do expose the fact the dexmedetomidine can be beneficial, but some studies found side effects of dexmedetomidine may outweigh the preventative emergence agitation benefits.

Kim et al. (2015) conducted a randomized control trail to study the appropriate dose of dexmedetomidine, given the reported side effects of prolonged sedation and cardiovascular complications associated with administration. Twenty-one children participated in the study, all between the ages of 2 and 12 years old, all undergoing either a tonsillectomy, adenoidectomy, or both procedures. All patients received general anesthesia for the procedure, were maintained with desflurane, and dexmedetomidine was given intravenously before the start of surgery. A scale called the Emergence Agitation Scale, developed by Cole et al. (2002), was used to detect emergence agitation. Kim et al. (2015) chose this scale based on its previous use in identifying emergence agitation with the use of dexmedetomidine. A score of greater than 4 or 5 was considered positive for emergence agitation. In the event that a patient experienced emergence agitation, a 0.1 mcg/kg dose of dexmedetomidine greater than the one before would be administered. If no emergence agitation was experienced, the dose of dexmedetomidine would be decreased by 0.1 mcg/kg. They used the Dixon's up and down sequential method to

determine threshold of amount of increase or decrease of medication administered. If a patient had a pain score > 8 or needed rescue medication for emergence agitation they would give nalbuphine 0.1 mcg/kg.

Nine patients developed emergence agitation. They all received nalbuphine 0.1 mcg/kg, the 50% effective dose (0.25mcg/kg) of dexmedetomidine, and the 95% effective dose (0.38mcg/kg) of dexmedetomidine. Cardiovascular symptoms, such as bradycardia or hypotension, did not occur in any of the children upon administration of dexmedetomidine. This may be due to the fact that intubation and a bolus dose of 0.2 mg/kg of atropine occurred after the administration of dexmedetomidine, so stimulation prevented the cardiovascular complications. Prolonged sedation was not observed with participants who received dexmedetomidine. This could be contributed to the fact that the doses were smaller compared to other studies (Kim et al., 2015).

Makkar et al. (2016) performed a study comparing 100 patients who randomly received either 0.3 mcg.kg of dexmedetomidine, 1 mg/kg propofol, or 0.9% saline 15 minutes before the end of surgery. The patients were between the ages two and eight years, American Society of Anesthesiologist (ASA) physical status of 1 or 2 and scheduled for general anesthesia with a single-shot caudal block for elective infra-umbilical surgery. No premedication was given to the children, the parents were present for induction, and sevoflurane was used for inhalation induction. The PAED scale was used and a score of 10 or more was consistent with diagnosis of emergence agitation. Emergence agitation was found in 9.4% (n = 32) of children who received dexmedetomidine intraoperatively, 13.9% (n = 36) of children who received propofol, and 40.6% (n = 32) of children who received saline. Although dexmedetomidine was

found to be most effective in preventing emergence agitation, it was associated with longer sedation times and longer extubation times.

A study performed by Bedirliet et al. (2017) compared the use of dexmedetomidine and tramadol. Seventy- Seven patients were enrolled in this study and received either dexmedetomidine or tramadol intraoperatively for an adenotonsillectomy under sevoflurane anesthesia. Each drug was compared based on its hemodynamic stability, postoperative pain management, control of emergence agitation, and post-operative sedation levels. The authors found that both dexmedetomidine and tramadol were effective in reducing emergence agitation. Patients received either 1 mcg/kg IV bolus of dexmedetomidine (Group D; n = 38) or 2 mg/kg IV dose of tramadol (Group T; n = 39). Tramadol was associated with a lower incidence of nausea and vomiting, and extubation times were shorter with the use of a tramadol. Dexmedetomidine had higher incidence of intraoperative bradycardia, hypotension, longer stays in PACU, and extended sedation times. There was a lack of a placebo group, so the ability to determine the effectiveness of both drugs was limited. In conclusion, both tramadol and dexmedetomidine were effective in analgesia control and decreased incidence of emergence agitation.

In summary, conflicting results related to the use of dexmedetomidine for prevention of emergence agitation exists and side effects of dexmedetomidine in the pediatric population exist. The purpose of this review is to conduct a systematic review to examine the efficacy and side effects of various doses of dexmedetomidine to prevent emergence agitation in the pediatric postoperative patient.

Next, the theoretical framework will be presented.

Theoretical Framework

The theoretical framework used to guide this study was Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Preferred Reporting Items for Systematic Meta-Analysis provides an evidence-based checklist with 27 items and a four-phase flow diagram. The use of a checklist and flow diagram provide an unequivocal and complete report of a systematic review (Liberati et al., 2009). This framework helps spotlight common topics, results, and relationships of variables found throughout RCTs. The 27-item checklist (Table 1) provides recommendations on what should be reported regarding the title, abstract, introduction, methods, results, discussions, and findings. (Liberati et al). After each section of the checklist, obligatory guidelines are found that help develop a more concise and accurate systematic review.

Table 1
27 Item Checklist for Preferred Reporting Items for Systematic Reviews and Meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 - 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 - 7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 - 11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	(Table e-1)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7 -11
Synthesis of results	21	Present main results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	(Table e-1)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13 - 16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

The four-phase flow diagram (Figure 1) is used to report the total number of records found and then the articles excluded along with the reasons for the exclusion. The

process of trial and selection is shown through this diagram, as well as the eligibility criteria (Liberati et al., 2009). The flow diagram provides a graphical representation of the entire process including article identification, screening, eligibility, and what studies were included in the final study

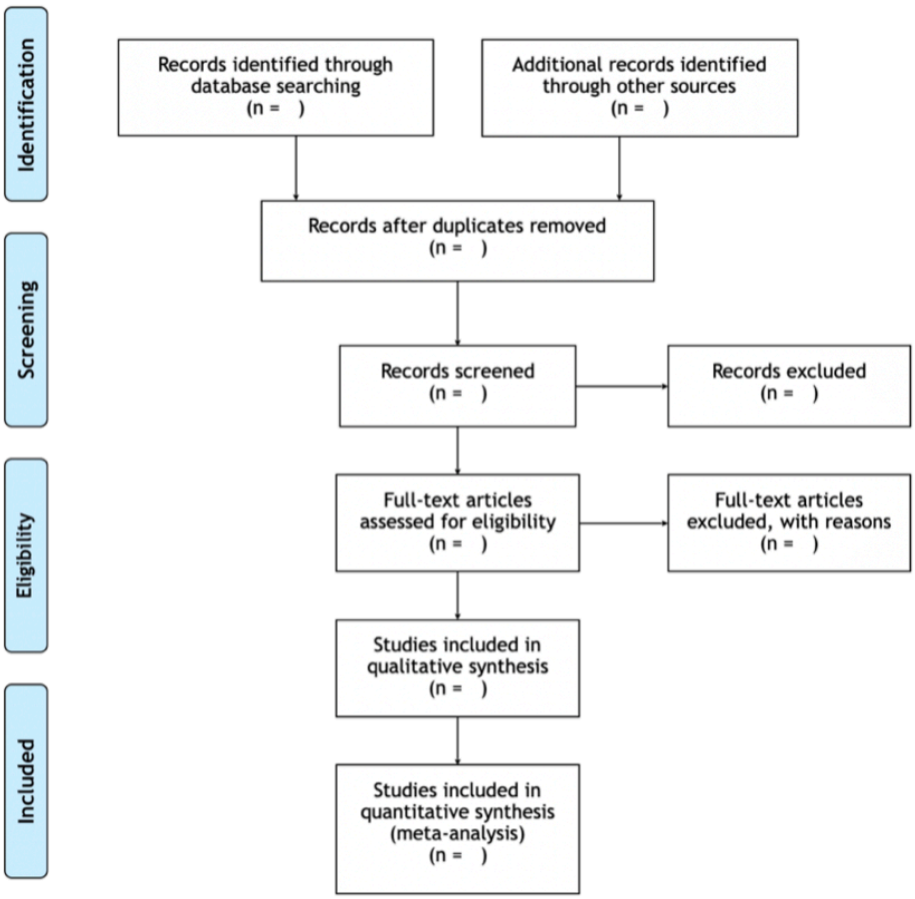

Figure 1. Four phase flow diagram for preferred reporting items for systematic reviews and meta-analysis (Liberati et al., 2009)

Overall, PRISMA is very helpful but lacks detail related to the quality assessment of a randomized control trial. The Critical Appraisal for Summaries of

Evidence (CASE) worksheet was used to critically appraise the included studies (Foster & Shurtz, 2013).

Next, the methods will be presented.

Method

Purpose

The purpose of this paper was to conduct a systematic review to examine the efficacy and side effects of various doses of dexmedetomidine administration in prevention of emergence agitation in the pediatric postoperative population.

Outcomes

Outcomes included incidence of emergence agitation and side effects in the postoperative phase in pediatric patients.

Inclusion/Exclusion Criteria

Inclusion criteria included studies specific to emergence agitation in the pediatric population; subjects less than eight years old; ASA one or two; the use of an emergence agitation scale; use of sevoflurane; and the use of only dexmedetomidine for sedation. Only randomized control trials or systematic reviews from 2009 to 2018 and in English were utilized.

Exclusion criteria included any studies before 2009; studies that examine adult subjects; studies that do not use an emergence agitation assessment tool; studies that use alternative drugs as a placebo; and those not meeting the inclusion criteria.

Search Strategy

Research articles were found via CINAHL Plus with full text, PubMed, and Google Scholar. A detailed search was conducted using the search terms dexmedetomidine, sevoflurane, pediatrics, emergence agitation, and intraoperative. The PRISMA flowchart was utilized to document the process used to select studies for the systematic review.

Data Collection

A separate table was formed to summarize selected outcomes of the individual studies (Table 2).

Table 2

Data Collection Table: Outcomes of the Study

Emergence Agitation	Emergence Agitation Scale	Dexmedetomidine Dose	Adverse Side Effects	Limitations

A data collection table was created to summarize each study, including the design, sample, surgical procedure, and method. (Table 3).

Table 3

Data Collection Table: Study Demographics

Purpose	Design	Sample	Surgical Procedure	Method

Critical Appraisal

The Critical Appraisal for Summaries of Evidence (CASE) worksheet was used for quality assessment of the evidence provided. The quality of the data gathered from the studies was determined via the Critical Appraisal for Summaries of Evidence (CASE) worksheet (Table 4). This tool is used to evaluate quality of evidence and provides a

standard for evidence-based medicine point of care summaries. It has 10 questions that explore the specificity, authorship, reviewers, methods, grading, clarity, citations, currency, bias, and relevancy for each study (Foster & Shurtz, 2013). The answers must be either "yes", "no", or "not completely". Each study was reviewed, and the ten questions were answered.

Table 4

Critical Appraisal for Summaries of Evidence (CASE) Worksheet

Critical Appraisal for Summaries of Evidence (CASE) Worksheet **Numbers in evaluation correspond with those assigned to articles in data extrapolation chart**	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	Yes- Not completely- No-
Summary Methods	
2. Is the authorship of the summary transparent?	Yes- Not completely- No-
3. Are the reviewer(s)/editor(s) of the summary transparent?	Yes- Not completely- No-
4. Are the research methods transparent and comprehensive?	Yes- Not completely- No-
5. Is the evidence grading system transparent and translatable?	Yes- Not completely- No-
Summary Content	
6. Are the recommendations clear?	Yes- Not completely- No-
7. Are the recommendations appropriately cited?	Yes- Not completely- No-
8. Are the recommendations current?	Yes- Not completely- No-
9. Is the summary unbiased?	Yes- Not completely- No-
Summary Application	
10. Can this summary be applied to your patient(s)?	Yes- Not completely- No-

Data Synthesis & Cross Study Analysis

The cross-study analysis tool (Table 5) was designed to collect and organize information from each study. Each column presents a topic to allow for descriptive information to be placed. This table was used to compare each study based on their outcomes.

Table 5

Cross Study Analysis Tool

Study Number	Emergence Agitation Incidence	ASA classification/Patient Characteristics	Anesthetic Used	Bradycardia	Hypotension	Length of Stay in Hospital
1						
2						
3						
4						
5						

Next, the results will be presented.

Results

Figure 2 on the next page provides a visual analysis of the search strategy used to perform this systematic review. The initial search began with "dexmedetomidine" and "pediatrics". This search yielded 203 results among selected databases. The search term "sevoflurane" was added and generated 26 results. Lastly "emergence agitation" was added to search term and the years were adjusted to 2009-2018; this yielded 17 results. After the article search was performed, 12 studies were excluded for not meeting the inclusion criteria listed above. Lastly, the remaining five studies were appraised and selected to complete this systematic review.

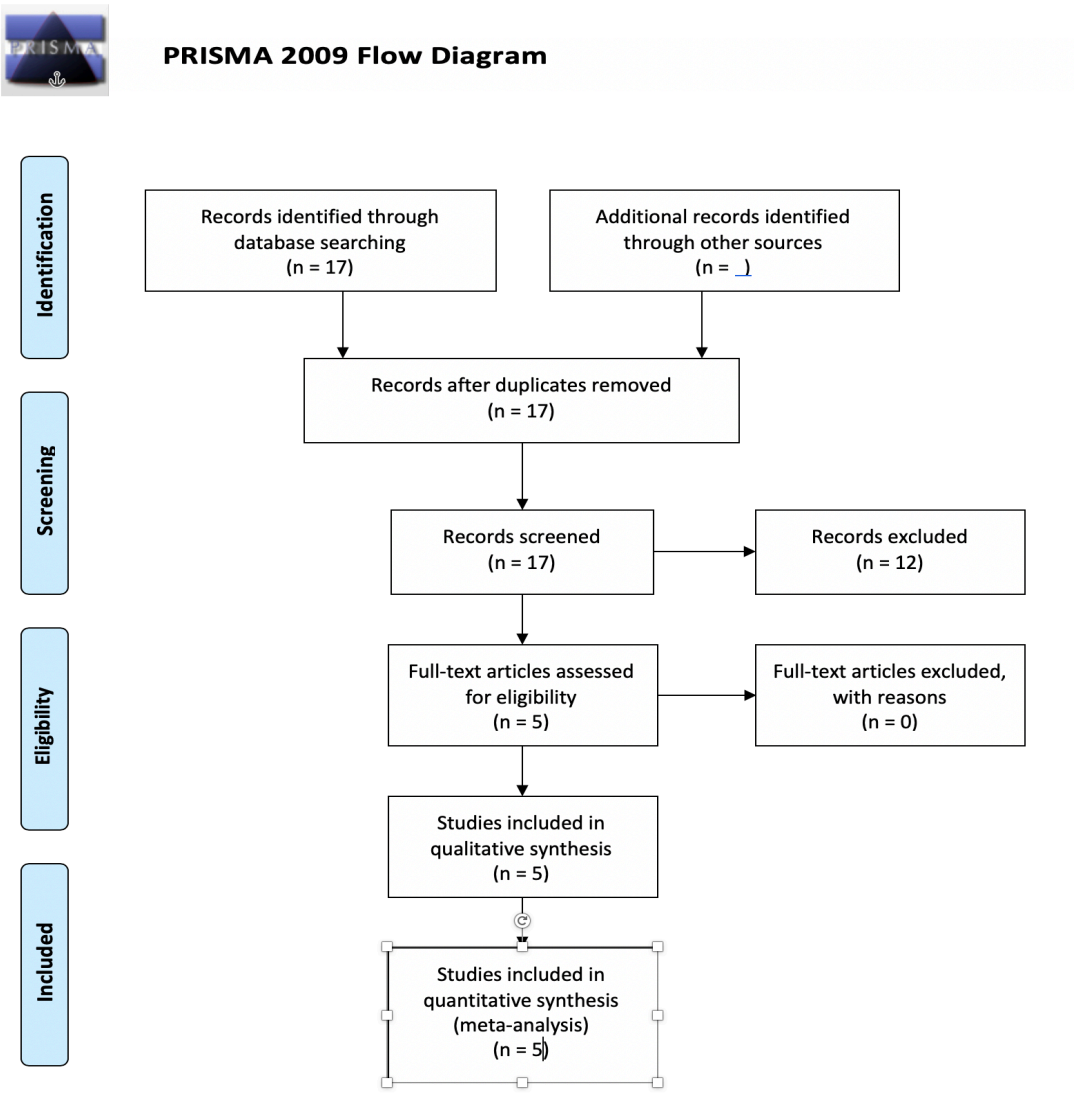

Figure 2. Completed PRISMA flow diagram demonstrating article identification, screening, eligibility, and inclusion (Moher et al., 2009).

Each of the five studies included in this systematic review were reviewed individually in this section and illustrated in Appendix A and Appendix B. Appendix A (Tables A1-A6) presents each studie's demographics and methods used. The main information in these study tables include purpose, design, sample, surgical procedure, and

method used. Next, Appendix B (Tables B1-B6) presents study outcomes. The main information found in these study tables include dexmedetomidine dose, efficacy, adverse side effects, and limitations. Appendix C presents Critical Appraisal for Summaries of Evidence (CASE) worksheet. This will aid in assessing for reliability, validity, and applicability of each study in this systematic review. Appendix D presents the cross-study analysis tool. Each study is numbered and examined based on emergence agitation incidence, ASA classification/Patient characteristics, anesthetic used, bradycardia events, hypotension events, and length of hospital stay.

Individual Studies

A prospective double-blind randomized study performed by Kim et al. (2014) (Appendix A, Table A1) assessed the effects of dexmedetomidine infusions with sevoflurane requirements, recovery profiles, and emergence agitation in children undergoing ambulatory surgery. The surgical procedure consisted of either a hernioplasty or orchiopexy. A total of 40 children with ASA 1 between the ages 1-5 years old were included in this study. Children with mental retardation, developmental delay, neurological or psychiatric illnesses that may be associated with agitation, coagulation disorder, spinal anomalies or bilateral procedures were excluded. The patients were selected at random into two groups, Group D and Group S. The parents of the patients selected remained with the children in the operating room until the child lost consciousness to decrease preoperative anxiety. Inhalation induction was performed on each child and an intravenous line was placed. After placement of intravenous line, Group D received dexmedetomidine and Group S received saline; both received 1 mcg/kg IV bolus over 10 minutes followed by a 0.1 mcg/kg/hr maintenance infusion until

the end of surgery. Each child also received a caudal block to help with postoperative pain. ET sevoflurane, mean arterial pressure and heart rate were recorded prior to the administration of dexmedetomidine or saline, just after loading doses, ten minutes after loading dose, start of operation and every ten minutes until operation was done.

The patients were then brought to post anesthetic care unit and EA was assessed at arrival and every 5 minutes for up to 30 minutes in PACU. Emergence Agitation was assessed with a four-point scale created by Watcha (Kim et al., 2015). Points were given based on 0= asleep, 1 = calm, 2= crying but can be consoled, 3- crying and unconsolable, 4 = agitated and thrashing. Children with a score of 3 or 4 were determined to have emergence agitation. Pain and sedation were assessed only with first oral intake, discharge time, and adverse effects.

Outcomes for this study by Kim et al. (Appendix B, Table B-1) found that intraoperative dexmedetomidine bolus dose and infusion reduced both anesthetic requirements and emergence agitation without delaying discharge in pediatric ambulatory surgery. Emergence agitation was noted to be lower in group D than group S (5% vs 55%, p=0.001). Mean arterial pressure and heart rated were decreased by 22-28% and 18-21% in group D compared to group S. Six patients received atropine for bradycardia with or without hypotension with the dexmedetomidine bolus dose (P=0.020). The discharge time did not differ between either group (Group D, 201 minutes vs Group S, 207 minutes). There were no adverse effects such as nausea, vomiting, and urinary retention.

Evaluation of the integrity of this study by Kim et al., applied from the CASE worksheet (Appendix C, Table C-1), suggested that this trial brings an individualized topic specific to practice. It also found that there wqas transparency related to the authors,

methods, and observers. The study was approved by IRB and informed consent was done with each parent. Appropriate exclusion criteria were present. Groups were randomly assigned by a computer generated system, but they did not name the system. This study did present with some limitations. First, the authors suggested that uncertainty existed related to the proper scoring tool for use with EA. Kim et al. (2014) chose the Watcha et al. EA scale because it included a consolability component. They had concerns that the approved PAED scale did not apply to children who are asleep in PACU. Second, the researchers did not assess pain, which has been suggested to interfere with diagnosis of EA. Each patient did receive a caudal block, so Kim et al. believed pain was not a factor in this scenario. Last, the sample size calculation for each groups' dexmedetomidine dose was based on ET-sevo. ET–sevo, also known as end tidal sevoflurane concentration, tells the anesthesia provider how much MAC of sevoflurane the patient has. Based on other studies, Kim et al. (2014), monitored the ET-sevo, to help determine effects of dexmedetomidine. This suggested that the sample size of 40 patients may have been too small.

The randomized double-blind study by Di et al. (2017) (Appendix A Table A-2) evaluated the use of dexmedetomidine with low concentration sevoflurane vs high concentration sevoflurane and its effect on smooth deep extubation, emergence characteristics, recovery time, and incidence of airway complications. A total of seventy-five patients, who were either an ASA I or II, and between the ages 3-7 years old, who underwent an adenotonsillectomy were randomly divided into three groups by a computer-generated table of numbers. Group D0 consisted of 25 patients who received intravenous saline 4mcg/ml IV bolus. Group D1 consisted of 25 patients who received

dexmedetomidine 1 mcg/kg IV bolus over 10 minutes. Group D2 consisted of 25 patients who received dexmedetomidine 2 mcg/kg IV bolus over 10 minutes. Each group was maintained on sevoflurane for at least 10 minutes before deep extubation. Following extubation each patient was placed in a lateral position after adequate spontaneous ventilation and a patent airway was determined. Patient was then transferred to the PACU. The PAED scale was used to diagnose EA in the PACU. Emergence Agitation was defined with a score greater than 10.

Outcomes of this study by Di et al (2017) (Appendix B, Table B-2), demonstrated that the overall occurrence of emergence agitation was lower with the use of dexmedetomidine. After extubation no breath holding, laryngospasm, bronchospasm, and hypoxemia were observed. In the PACU, Group D0 (24%) presented with emergence agitation and were treated with fentanyl. In Group D1(0%) and Group D2 (0%), incidence of emergence agitation was significantly less than Group D0 (p=0.05). The times of discharge from PACU to home were longer in group D0 (33.7) and Group D2 (32.8) compared to Group D1 (25.5). No respiratory complications or nausea/vomiting were noted in the PACU in all groups.

When evaluating the integrity of this study utilizing CASE questionnaire (Appendix C, Table C-2), it was noted that the trial presented an individualized topic specific to practice, transparency related to the authors, methods, reviewers and editors. Each parent was presented with information and informed consent was obtained. Patients were randomly assigned into groups with a computer generated table of random numbers. A research observer was assigned to each patient to evaluate the quality of extubation and respiratory status. The observer was blinded to drug and groups. The results of this study

can be applicable to pediatric population undergoing ENT surgery. This study did have some limitations. The first limitation mentioned by the authors was the lack of plasma drug levels of dexmedetomidine. Therefore, there was no link between sedation and hemodynamic changes of dexmedetomidine in blood. Second, each patient was deep extubated, based on the absence of airway responsiveness and continuation of regular and spontaneous respiration after laryngopharyngeal suction. Per the Di et al (2017) a benefit of deep extubation is improved recovery and increase overall comfort. However, the authors did not take this into consideration when determining emergence agitation, so it is unclear if this benefitted emergence agitation or make it worse.

The double-blind randomized control trial by Chen, Wang, Huang, and Fu (2018) (Appendix A, Table A-3) evaluated the efficacy of different doses of DEX as a rapid bolus to aid in the prevention and treatment of EA in pediatric population. One hundred children ranked as ASA I or II, between the ages of 3-7 years old were randomly enrolled into five groups (Random number method was used). The control group was group D1 which received saline IV bolus, group D2 received 0.25 mcg/kg dexmedetomidine IV bolus, group D3 received 0.50 mcg/kg of dexmedetomidine IV bolus, group D4 received 0.75 mcg/kg of dexmedetomidine IV bolus and group D 5 received 1 mcg/kg of dexmedetomidine IV bolus. Inclusion criteria was normal intelligence, liver, and kidney function, scheduled for elective inguinal hernia repair surgery, no allergies to anesthesia, and entered the operating room without parents. The patients were brought into the operating room, inhalation induction with sevoflurane was performed and LMAs were placed once anesthetized. Once stable vital signs were achieved patients received medications based on what group assignment to. Heart rate, mean blood pressure, and

oxygen saturation were recorded before study drug was administered and every 5 minutes after. When surgery was complete, patients were extubated, and each patient was brought to the PACU. Emergence agitation, pain, and adverse effects were assessed in PACU. The PAED scale was used to assess emergence agitation, a score > 12 was a diagnosis of EA. Propofol 1 mg/kg was given for treatment of EA, if the patient was considered free of pain and if the parents or caregiver could not console the patient.

Outcomes of this study by Chen et al. (2018) (Appendix B, Table B-3), demonstrated that the incidence of EA was extremely lower in groups D4 (0%, $P < 0.001$) and D5 (0%, $P < 0.001$), and fewer incidences of EA was observed in group D2 (5%, $P= 0.096$) and D3 (5%, $P = 0.096$). Emergence agitation was found most commonly in group D1 (30%). It was noted as the dose of dexmedetomidine increased, the recovery time increased, but it was not considered a large difference in total adverse events. There were no large differences in adverse events and bradycardia in all the groups. Bradycardia was defined as a heart rate decrease by greater than 30% of baseline. Eight patients had a 30% decrease in heart rate from baseline but did not require treatment. No patient needed treatment for pain, cough, headache, or vomiting. All patients were able to breathe spontaneously and maintain their oxygen saturation greater than 98%.

When evaluating the integrity of this study by utilizing the CASE questionnaire (Appendix C, Table C-3), it suggested that the study presented a focused and clear issue. Informed consent was done with each patient's parent and the children were randomly assigned into groups using the random number method. Patients were excluded if they had an allergy to dexmedetomidine, G-6-PD deficiency, a history of arrhythmia, bronchial and cardiovascular disease, abnormal liver function, or a history of use of alpha

2 receptor agonist or antagonist. No patient received premedication. A BIS monitor was used to determine adequate anesthesia and then dexmedetomidine doses were administered at a rate of less than 5 seconds. The results of this study can be applicable to the pediatric population receiving inguinal hernia repairs. There were some limitations to this study. First, the study used the PAED scale; the authors noted that the subjective aspects of this scale may yield differing subjective evaluations by users, though this scale has been widely used for the use of emergence agitation. Second, the authors failed to mention if the study staff were blinded to the study drugs or if any personally received education on the PAED scale. Third, the rate of dexmedetomidine bolus was less than five seconds; various studies suggested bolus doses be administered over 10 minutes due to hemodynamic issues. It is unclear if the five second bolus skewed the adverse events results. Lastly, the sample size was 100 patients from one hospital which rather small and involving just one hospital. These findings suggest that the grading system was not completely transparent and translatable and that the summary was not completely unbiased.

The randomized double-blind clinical trial by He et al. (2013) evaluated the effects of two different doses of dexmedetomidine infusion on the end tidal concentration of sevoflurane required for smooth LMA removal and on postoperative recovery measures such as emergence agitation in pediatric patients. This trial studied eighty-seven patients with ASA scores of I or II, between the ages of 3-7 years old, who underwent elective minor surface surgery for less than an hour under general anesthesia. The patients were randomly assigned to one of three groups. Group C received saline. Group D1 received dexmedetomidine 0.5 mcg/kg and group D2 received dexmedetomidine 1

mcg/kg. Each study drug was labeled as study drugs and were prepared by an anesthesia nurse independent of the study. Patients were brought into the O.R., connected to appropriate monitoring and preoxygenation and inhalation induction with 8% sevoflurane was started. Once patient was anesthetized, LMA was placed. The study drug was placed on an infusion pump and administered as an IV bolus after LMA insertion. After surgery was complete, LMA removal occurred when the sevoflurane concentration reached 2.2%.

Patients were then transferred to the PACU and kept in the unit until they met an Aldrete score of 9 or more and were free from nausea and vomiting. The Aldrete score evaluates a patient's activity, respirations, circulation, consciousness, and oxygen saturation. The anesthetist would monitor respiratory complications and emergence agitation until arrival in PACU. The emergence time and recovery time were recorded in PACU. Behavior in PACU was recorded by a blinded observer with a 5 point scale; 1 for sleeping, 2 for awake and calm, 3 for irritable and crying, 4 for inconsolable crying, 5 for severe restlessness, disorientation and thrashing around. Scores greater than 3 indicated agitation and the patient received propofol 1 mg/kg if unconsolable. If pain was noted by complaints or if patient was trying to remove the surgical dressing they received 1 mcg/kg IV.

Outcomes of this study by He et al. (2013) demonstrated that emergence agitation was lowered with the use of dexmedetomidine. The incidence of emergence agitation was significantly lower in group D1 (17%) and in group D2 (6%) compared to group C (42%, P=0.003). But groups D1 and D 2 were comparable (P=0.179). Pain was found to be similar within all three groups (P=0.719). Hemodynamic issues were noted with a higher dose of dexmedetomidine (1 mcg/kg, Group D2). The issues did not overstep 20% of the

values prior to dexmedetomidine infusion. No patients suffered from severe respiratory complications such as laryngospasm, bronchospasm, or hypoxemia. Breath holding was found to be lower in group D2 (3%) than in Group C (27%, *P*=0.009) but comparable between groups D1 and C (*P*=0.385). Severe coughing was lowest in Group D1 (14%) and D2 (6%) as compared to Group C (39%, *P*=0.005). Groups D1 and D2 were comparable (*P*=0.323). Emergence times were prolonged in group D2 and Group C compared to Group D1 (*P*=0.014). Lastly, the recovery time was prolonged in Group D2 and Group C compared to Group D1 (*P*=0.010).

When evaluating the integrity of this study with the CASE questionnaire (Appendix C, Table C-4), it suggested the study addressed a clear and focused issue specific to practice and transparency related to the authors and observers. The study was approved by an ethics committee and each child's parents received informed consent. The study used a computer generated numbers system to assign groups. This study was not completely transparent regarding the research methods transparency and the grading system transparency. Some limitations were presented in the study. First, all of the procedures in the study were less than an hour and each patient received either a regional or local anesthetic block and no opioids were given. If the patient did not receive a type of block, or if the procedure was long, the outcomes might have been different. Second, each patient was accepted into the study if they were going to receive minor surface surgery, but the authors did not elaborate on what specific surgeries were examined. This may provide some bias. Third, patients that received 2 mcg/kg of dexmedetomidine in the pilot study were noted to be unarousable and sleepy for a long time after surgery, so the authors lowered doses in the study. Last, the researchers used an infusion pump to

administer the dexmedetomidine per the hospital protocol. The period of infusion was 10 minutes and it was unsure if this provided an advantage or not.

The randomized single blinded control study conducted by Lin et al. (2016) (Appendix A, Table A-5) evaluated the hypothesis that a single premedication dose of dexmedetomidine could reduce preoperative anxiety and also minimize emergence agitation in children undergoing cataract surgery, specifically with sevoflurane anesthesia. Ninety children from the ages 1 to 8 years old, ASA I or II undergoing cataract surgeries were enrolled in this study. Patients were randomly selected into 3 groups using a computer generated randomization program. Patients in group C received intranasal saline, Group D1 received 1 mcg/kg of dexmedetomidine, and Group D2 received 2 mcg/kg of dexmedetomidine. A masked research assistant administered intranasal study drugs 45 minutes before induction of anesthesia and the patient laid supine for 2 minutes to help with intranasal dexmedetomidine absorption. Anesthesia was induced via inhalational induction and an LMA was placed. All patients received topical proparacaine eye drops. After the procedure ended LMA was removed and patient was transferred to PACU.

On arrival to PACU, the patients were monitored for heart rate, blood pressure, and oxygen saturations by the PACU nurses. Every 5 minutes the patients were assessed with the PAED scale and the CHEOPS scale. PAED scores > 10 were considered emergence agitation. If the PAED score was above 15 the patients were treated with 1 mg/kg of propofol intravenously.

Outcomes of the study by Lin et al. (2016) (Appendix B, Table B-5) suggest that intranasal dexmedetomidine reduced the incidence of postoperative emergence agitation

with no delay in emergence time or lack of adverse event. Intranasal dexmedetomidine greatly reduced emergence agitation in group D 1 23.3% ($P<0.001$) and group D2 10% ($P<0.001$). Emergence agitation was found most commonly in group C 80%. This suggests a high amount of emergence agitation with just sevoflurane anesthesia. The emergence time and PACU stay time were comparable among all three groups. Clinically significant bradycardia, were not observed in any of the patients after the dexmedetomidine administration. The reductions in heart rate and blood pressure were found to not be statistically different in Group D1 and Group D2 ($P >0.05$).

When evaluating the integrity of this study utilizing the CASE questionnaire (Appendix C, Table C-5) it suggested the study addressed a clear and focused issue. There was no transparency related to authorship, design, or methods. Set protocols were used for intranasal dexmedetomidine administration, inhalation and maintenance of anesthesia, and PACU stay. The authors expressed there was a masked research assistant who administered the intranasal dexmedetomidine, but failed to say if anesthesia providers or PACU nurses knew which patients received study drugs. The authors failed to mention if informed consent was obtained from parents of the patients. Some other limitations the authors presented included the fact that the influence of resistance of mask inhalation induction may influence emergence agitation. Finally, the authors failed to find dose dependent effects of dexmedetomidine related to hemodynamic changes. This suggests that intranasal routes may affect the bioavailability of dexmedetomidine and provide some uncertainty.

Cross-Study Analysis

The cross-study analysis table (Appendix D) illustrates each study by number, the percentage of emergence agitation found in each study, the characteristics of each patient population, the type of anesthetic used, and adverse outcomes including; bradycardia, hypotension, and length of hospital stay. All five studies included patients between the ages 1-8 years old and ASA I or II. Surgeries varied throughout the studies, including hernioplasty/orchiopexy (Kim et al., study 1), adentonsillectomy (Di et al., study 2), inguinal hernia repair (Chen et al., study 3), minor surface surgeries (He et al., study 4), and cataract surgery (Li et al., study 5). All studies used sevoflurane anesthesia but some studies included regional anesthesia as well. Study 1 used sevoflurane but also included a caudal block to disregard postoperative pain and focus on results of emergence agitation. Study 3 used sevoflurane and ilioinguinal/iliohypogastric nerve blocks in an attempt to disregard postoperative pain as well. The studies 2 and 4 used sevoflurane anesthesia with no regional anesthesia. Study 5 used sevoflurane but the authors stated they gave 0.5% proparacaine hydrochloride drops to help with pain postoperatively.

All studies compared various doses of dexmedetomidine to a placebo of saline. Emergence agitation was assessed in the PACU in all studies. The scale to assess emergence agitation varied throughout the studies. The PAED was used in study 2, 3, and 5. Study 1 used the Watcha EA scale and Study 4 did not state the scale used.

Overall, the incidence of emergence agitation was decreased with the use of dexmedetomidine compared to saline. But based on dexmedetomidine dosing, the presence of emergence agitation varied. *In study 1* (Kim et al., 2017), group D received a 1 mcg/kg bolus of dexmedetomidine followed by an infusion of dexmedetomidine of 0.1

mcg/kg/hr until end of surgery. Only had 5% of emergence agitation was found in Group D compared to group S with 55% emergence agitation. Group S received saline. *In study 2* (Di et al., 2017), Group D1 received 1 mcg/kg bolus and Group D2 received 2 mcg/kg bolus; both had 0% of emergence agitation. Group D0 received saline which presented with 6% incidence of emergence agitation.

In study 3 (Chen et al., 2018), group D1 received saline and presented with the most emergence agitation. Group D 2 received 0.25 mcg/kg bolus of dexmedetomidine and 5% of patients presented with emergence agitation. Group D3 received 0.5 mcg/kg IV bolus of dexmedetomidine and 5% presented with emergence agitation. Group D4 received 0.75 mcg/kg IV bolus of dexmedetomidine and no emergence agitation was experienced. Group D5 received 1 mcg/kg IV bolus of dexmedetomidine and just like Group D4 0% of emergence agitation was noted. These findings demonstrate that the groups D4-D5, with doses of dexmedetomidine 0.75mcg/kg-1mcg/kg boluses, were most effective.

In study 4 (He et al., 2013), group D1 received 0.5 mcg/kg IV bolus of dexmedetomidine and 17% presented with emergence agitation. Group D2 received 1 mcg/kg IV bolus of dexmedetomidine and 6% experienced emergence agitation. Group C received saline and there were 42% emergence agitation cases. These findings suggest the dosing of dexmedetomidine of 1 mcg/kg IV bolus worked the best.

In study 5 (Lin et al., 2016), group C was given saline and had an 80% occurrence of emergence agitation. In group D1, which received 1 mcg/kg intranasal dexmedetomidine, 23.3% presented with emergence agitation. Group D2 received 2 mcg/kg of intranasal dexmedetomidine and had a 10% occurrence of emergence

agitation. These findings suggest that intranasal doses and bioavailability may work better with higher doses, like group D2, 2 mcg/kg intranasal.

Adverse effects such as hypotension and bradycardia were noted throughout all five studies. Studies 2 (Di et al., 2017), 3 (Chen et al., 2018), 4 (He et al., 2013), and 5 (Lin et al., 2016) did report hypotension and bradycardia all fell within a 20% decrease of patients' baseline. No patient had to be treated in these studies. In study 1, six patients were noted to have bradycardia with hypotension and without, all of whom received atropine.

All studies included same day surgeries and no patients had an extended stay due to dexmedetomidine. Study 1 (Kim et al., 2017), 3 (Chen et al., 2018), and 5 (Lin et al., 2016) did not note any delays in recovery time. Study 2, group D0 and group D2, had the longest recovery time in PACU. The authors believed this was due to the higher doses of dexmedetomidine in group D2 and the use of additional fentanyl for treatment of emergence agitation in group D0. Study 4 Group D 2 and group C presented with the longest recovery time in PACU. Group D2 received the highest dose of dexmedetomidine but group C received saline. Group C was noted to wake up in pain and patients more commonly received fentanyl, but all went home on the same day.

Next, the summary and conclusions will be presented.

Summary and Conclusions

Pediatric emergence agitation is a postoperative complication with cognitive and psychomotor affects (Stamper et al., 2014). The untoward effects of emergence agitation include crying, overexcitement, thrashing, and agitation (Mohkamkar et al., 2014). The pediatric patient with emergence agitation is at risk of causing self-harm and harm to medical staff and family or caregiver. The patient is also at risk of removal of medical catheters, dressings, and monitoring devices that may be needed postoperatively (Mohkamkar et al. 2014)). A pivotal way to manage pediatric emergence agitation is to diagnose it quickly (Stamper et al., 2014).

Dexmedetomidine, an alpha 2 agonist, binds to alpha 2 receptors in the locus ceruleus, decreases norepinephrine output, and produces analgesia. It also has an analgesic action by binding to alpha 2 receptors in dorsal spine and super-spinal sites and decreasing the release of substance P (Pickard et al., 2014). Dexmedetomidine also has an anxiolytic and reduces post-operative shivering (Nagelhout & Elisha, 2018). Benefits of dexmedetomidine include conscious sedation, similar to endogenous sleep patterns, and little to no respiratory depression (Zhu et al., 2015). Dexmedetomidine has been linked to a large reduction in pediatric emergence agitation. Although it has unique benefits, it does come with unwanted side effects. It produces sympatholytic effects that may cause bradycardia, and hypotension. It also may cause transient hypertension with rapid initial loading doses or high maintenance doses due to vasoconstriction.

The purpose of this systematic review was to examine the efficacy and side effects of various doses of dexmedetomidine to prevent emergence agitation in the pediatric postoperative patient. A comprehensive literature review was performed with

the use of CINHAL Plus with full text, Pub med, and Google Scholar. Keywords used to perform the search included emergence agitation, sevoflurane, dexmedetomidine, intraoperative, and pediatrics. The preferred reporting items for systematic reviews and meta-analyses was used as the theoretical framework and the PRISMA flow diagram was used to aid in the identification of eligible studies based on inclusion and exclusion criteria. (Liberati et al, 2009)

A total of five studies met the inclusion criteria. Data tables were created to illustrate key design components of each study. Then, a table was created to illustrate outcomes for each study, focusing on dose and efficacy of dexmedetomidine and incidence of emergence agitation. The Critical Appraisal for Summaries of Evidence (CASE) worksheet was used to perform a critical appraisal of each study. Last, study analysis was performed on each individual study that met inclusion criteria. A table was created to compare emergence agitation incidence, patient characteristics, anesthetic used, dexmedetomidine dose, hypotension/bradycardia event, and length of stay across the five studies.

The findings of this systematic review suggest that overall, the use of dexmedetomidine decreases the incidence of emergence agitation in the pediatric population. The dose of dexmedetomidine does provide more coverage and efficacy with rare adverse side effects. The range of bolus doses was from 0.25 mcg/kg to 2 mcg/kg boluses. In the Kim et al. (2014) study, the researchers started a dexmedetomidine infusion after the bolus dose. Lin et al. (2016) chose to use the intranasal route instead of intravenous. Kim et al. (2014) found the dose of 1 mcg/kg IV bolus followed by a 0.1 mcg/kg/min dexmedetomidine infusion reduced the incidence of emergence agitation

without delaying discharge. Chen et al. (2018) found that 0.75 mcg/kg and 1 mcg/kg IV bolus dose prevented emergence agitation with transient decrease in heart rate and blood pressure, but was well tolerated in the pediatric population. He et al. (2018) found the doses of 0.5 mcg/kg and 1 mcg/kg IV boluses of dexmedetomidine provided the best relief of emergence agitation with few side effects. Di et al. (2017) administered doses of 1 mcg/kg to reduce emergence agitation with no side effects. This study also found the efficacy of 2 mcg/kg IV bolus to be useful in emergence agitation reduction, but the patients presented with prolonged postoperative recovery. Lin et al. (2016) documented the best efficacy of intranasal doses 1 mcg/kg and 2 mcg/kg of dexmedetomidine in reduction of emergence agitation with only slight decreases in heart rate and blood pressure.

Overall, the studies revealed that bradycardia and/or hypotension can occur but most were within 20-30% of baseline vitals, which was determined to be tolerable in the pediatric population. The mean length of recovery was noted to be longest in the groups with the highest dose of dexmedetomidine compared to lower doses or groups who received saline.

Several limitations were found in this systematic review. First there were only five studies that fit into the inclusion criteria with a limited number of selectivity. Second, pediatrics is a specialty population but not all studies were performed in a specialized children's hospital. Both of these limitations could affect the generalizability. There were also several limitation throughout the studies in this review. All of the studies used sevoflurane for a volatile anesthetic. Two studies, Kim et al. (2014) and Chen et al. (2018), used nerve blocks and the study by Lin et al.(2016) used proparacaine eye drops.

Di et al. (2017) and He et al. (2013) used only sevoflurane and not other anesthetics. The use of these blocks suggests a limitation on the use of dexmedetomidine, potentially affecting this study results. Lack of blinding was found in some studies. Three studies included in this systematic review were double blinded (Chen et al., 2018; He et al., 2013; Kim et al., 2013), one was single blinded (Lin, 2016), and the last study was not blinded (Di, 2017). For induction of anesthesia, all studies used inhalation mask induction, but only one study listed it as a limitation. The resistance and anxiety of mask induction can increase emergence agitation.

Another limitation noted was the length of time of surgeries; in one particular study, He et al. (2013), all surgeries were less than one hour. All studies diagnosed emergence agitation, but not all used the same scale. The PAED is the standard tool for diagnosis of emergence agitation in pediatrics, but some studies did not use this measure. Only three studies, Di et al, (2014), Chen et al. (2018), and Lin et al. (2016), used the PAED scale, which suggests a lack of standardized care. Last, four out of five studies used intravenous dexmedetomidine and one study, Lin et al. (2016), used intranasal dexmedetomidine. This presented a limitation due to the lack of knowledge of dose dependent sides effects and the precise bioavailability of the intranasal route.

In conclusion, this systematic review found that dexmedetomidine was beneficial in emergence agitation prevention. Specific doses of dexmedetomidine provided better relief of emergence agitation: 0.5 mcg/kg – 1 mcg/kg IV boluses and 1 mcg/kg – 2 mcg/kg intranasal sprays provided the best relieve with limited adverse effects.

Next, the recommendations and implications for advanced nursing practice will be presented.

Recommendations and Implications for Advanced Nursing Practice

When pediatric patients undergo general anesthesia, it is a stressful time for the patient, parents, and even the provider. Upon awakening from general anesthesia, the pediatric patient can present with emergence agitation, which is yet another stressful situation for the patient and those directly involved in care. Emergence agitation can be found in up to 80% of pediatric patients (Makkar et al., 2015). In fact, emergence agitation is one of the most significant causes of dissatisfaction in parents and healthcare providers and can even result in physical harm to the child (Makkar et al.). The patient can present with restlessness, inconsolability, disorientation, delusion, hallucination, self-injurious behaviors, and memory impairment (Ali & Abdellatif, 2013). Upon transfer to PACU, the pediatric patient should be comfortable and resemble what they are like in a natural sleep due to dexmedetomidine. The patients', parents', and medical teams' satisfaction are noted to be higher with the use of dexmedetomidine to prevent emergence agitation. The CRNA must be able to recognize the importance of this. This systematic review was able to provide a guide for CRNAs on how to make educated decisions regarding the use, dose, and efficacy of dexmedetomidine in the pediatric population.

The CRNA should be expected to identify a patient who is at risk for emergence agitation. The CRNA is an essential member of a pediatric patients care inside and outside of the operating room. The CRNA must know the factors that play a role in emergence agitation: age; sevoflurane anesthetic; postoperative pain; separation anxiety; patients' personal character; and type of surgery (Fang et al., 2016). The incidence of emergence agitation is highest in pediatric patients who are less than six years old, have

preoperative anxiety, and have a rapid emergence from general anesthesia (Stamper et al., 2014).

The CRNA must realize the importance of preventing and/or diminishing emergence agitation to help with the patient's overall outcomes. Prevention and quick accurate diagnosis are key (Stamper et al., 2014).The use of the standardized tool, the PAED, is recommended. A PAED score higher than or equal to 10 determines the presence of emergence agitation (Stamper et al.). The CRNA should ensure proper education has been given to PACU nursing staff and various other medical staff who care for pediatric postoperative patients, regarding the use of PAED scale and emergence agitation itself.

Certified Registered Nurse Anesthetists are held up to a certain expectation on excellent patient care. Certified Registered Nurse Anesthetists follow policies and procedures strictly to ensure proper care is given and can play a leadership role in the development of policy and clinical guidelines. They have the expertise and training to design and support a policy related to the use of the PAED scale, in order to better ensure quick diagnosis and a treatment plan for emergence agitation. The information from this systematic review can be used to improve the care CRNAs provide and how the CRNA can educate and support other team members centered in perioperative and postoperative care. In order to support nursing education, the CRNA can design, implement, and evaluate additional educational tools and programs regarding emergence agitation itself, interventions, and diagnosis. Collaboration with the surgeon, anesthesia team, and nursing teams regarding emergence agitation is key with an emphasis on continuity of care.

The CRNA must know pharmacological interventions for emergence agitation. All studies in this systematic review support the use of dexmedetomidine in prevention of emergence agitation. Dexmedetomidine is a great choice for pharmacological intervention. It is an alpha 2 agonist that provide sedative, analgesic, and anxiolytic effects and also lacks respiratory depression. The CRNA can administer dexmedetomidine in the perioperative period. Intravenous bolus doses range are recommended from 0.5-1mcg/kg, based on how patient tolerates it. If the patient does not have an IV, the anesthesia provider can use 1– 2 mcg/kg intranasal dose to prevent emergence agitation as well.

The CRNA must also recognize the mechanism of action of dexmedetomidine and the proper treatment of any potential side effects. The CRNA must be mindful of each patients' individual characteristics when administering dexmedetomidine. All studies in this systematic review have validated that adverse effects from dexmedetomidine are minimal in pediatrics. But the CRNA must be aware of appropriate treatment if patient were to become bradycardic or hypotensive; studies have shown that atropine should be given if vital signs remain below more than 20% of baseline and remain there. Recognition of a patients' characteristics and swift action related to adverse effects based on evidence based knowledge is part of the critical thinking that CRNAs must be held too.

Although all five studies in this systematic review suggest minimal adverse effects in pediatrics, no study examined patients with any comorbidities or ASA scores greater than two. Studies chose the dose of dexmedetomidine based on previous studies and if a regional anesthetic was used. But no study had great rationale for choice of rapid

bolus dosing, slow bolus dosing, no bolus, bolus and infusion, and intranasal administration of dexmedetomidine. This suggests the need for more research to evaluate the most effective administration route for all pediatric patients. The PAED scale was not used in all five studies; this suggest the need for more research on the use of the PAED as a standardized tool. Research on the use of dexmedetomidine and pediatric emergence agitation has the potential to improve patient care, patient quality, patient safety, and patient and family satisfaction. Although more research is needed, this systematic review can provide information to help prevent, treat, and diagnose the patient with emergence agitation.

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Appendix A

Table A-1

Data Collection Table: Study Demographics and Methods
Kim, N. Y., Kim, S. Y., Yoon, H. J., & Kil, H. K. (2014). Effect of dexmedetomidine on sevoflurane requirements and emergence agitation in children undergoing ambulatory surgery. *Yonsei Medical Journal*, *55*(1), 209. doi: 10.3349/ymj.2014.55.1.209

Purpose	Design	Sample	Surgical Procedure	Method
Assess the effect of dexmedetomidine infusion on sevoflurane requirements, recovery profiles, and emergence agitation in children undergoing ambulatory surgery.	Randomized double blind study Group D = 1mcg/kg IV bolus of dexmedetomidine followed by 0.1 mcg/kg/h infusion Group S = saline. 1 mcg/kg IV bolus followed by 0.1 mcg/kg/h infusion	Forty children undergoing ambulatory surgery ASA 1 Aged 1-5 years	Hernioplasty or orchiopexy	EA assessed at arrival to PACU and every 5 minutes for up to 30 minutes. Watcha EA four-point scale

Table A-2

Di, M., Han, Y., Yang, Z., Liu, H., Ye, X., Lai, H., … Lian, Q. (2017). Tracheal extubation in deeply anesthetized pediatric patients after tonsillectomy: a comparison of high-concentration sevoflurane alone and low-concentration sevoflurane in combination with dexmedetomidine pre-medication. *BMC Anesthesiology*, *17*(1). doi: 10.1186/s12871-017-0317-3

Purpose	Design	Sample	Surgical Procedure	Method
Assess the recovery characteristics and extubation time with the use of sevoflurane and dexmedetomidine as a premedication.	No blinding Group D0 = IV saline Group D1 = dexmedetomidine 1 mcg/kg Group D 2 = dexmedetomidine 2 mcg/kg	Seventy-five patients ASA 1 or 2 Aged 3-7 years old	Adenotonsillectomy	Randomized control trial PAED scale used in PACU. Results of deep extubation were recorded.

Table A-3

Chen, F., Wang, C., Lu, Y., Huang, M., & Fu, Z. (2018). Efficacy of different doses of dexmedetomidine as a rapid bolus for children: a double-blind, prospective, randomized study. *BMC Anesthesiology*, *18*(1). doi: 10.1186/s12871-018-0562-0

Purpose	Design	Sample	Surgical Procedure	Method
To determine efficacy of different doses of dexmedetomidine as a rapid bolus for children to prevent and treat EA.	Double blind prospective study Group D1 = received saline Group D2 = 0.25 mcg/kg of dexmedetomidine Group D3 = 0.5 mcg/kg of dexmedetomidine Group D4 = 0.75 mcg/kg of dexmedetomidine Group D5 = 1 mcg/kg of dexmedetomidine	100 patients ASA 1 or 2 Aged 3-7 years old Normal intelligence, liver, kidney function No history of allergy to anesthesia	Elective inguinal hernia repair	Heart rate, blood pressure, SaO2 assessed immediately after dose, and every five minutes after. EA and pain assessed in PACU. PAED scale used.

Table A-4

He, L., Wang, X., Zheng, S., & Shi, Y. (2013). Effects of dexmedetomidine infusion on laryngeal mask airway removal and postoperative recovery in children anaesthetized with sevoflurane. *Anaesthesia and Intensive Care*, *41*(3), 328–333. doi: 10.1177/0310057x1304100309

Purpose	Design	Sample	Surgical Procedure	Method
To determine the effects of two different doses of dexmedetomidine infusion on the end tidal concentration of sevoflurane required for smooth LMA removal and on postoperative recovery measures such as emergence agitation in pediatric patients.	Randomized double blind study Group C = IV saline Group D1= 0.5 mcg/kg dexmedetomidine Group D 2 = 1 mcg/kg dexmedetomidine	Eighty-seven patients ASA 1 or 2 3-7 years old	Elective minor surface surgery < than an hour long	No premedication Study drug was given after LMA insertion via infusion pump and continued for 10 minutes. Lack of scale

Table A-5

Lin, Y., Chen, Y., Huang, J., Chen, H., Shen, W., Guo, W., & Gan, X. (2016). Efficacy of premedication with intranasal dexmedetomidine on inhalational induction and postoperative emergence agitation in pediatric undergoing cataract surgery with sevoflurane. *Journal of Clinical Anesthesia*, *33*, 289–295. doi: 10.1016/j.jclinane.2016.04.027

Purpose	Design	Sample	Surgical Procedure	Method
To test the hypothesis that dexmedetomidine as a premedication intranasal could reduce preoperative anxiety and minimize emergence agitation in children undergoing sevoflurane anesthesia	Single-blinded, randomized, placebo-controlled clinical comparison study Group C = saline Group D1=1 mcg/kg diluted dexmedetomidine Group D2 = 2 mcg/kg of undiluted dexmedetomidine Each group received half volume of study drug in nostrils 45 minutes before induction.	Ninety ASA 1 and 2 Cataract surgery	Cataract surgery	PAED scale used to assess emergence agitation. Emergence time PACU stay time, and adverse events were recorded.

Appendix B

Table B-1

Data Collection Table: Outcome of the Study
Kim, N. Y., Kim, S. Y., Yoon, H. J., & Kil, H. K. (2014). Effect of dexmedetomidine on sevoflurane requirements and emergence agitation in children undergoing ambulatory surgery. *Yonsei Medical Journal*, *55*(1), 209. Doi: 10.3349/ymj.2014.55.1.209

Dexmedetomidine Dose	Efficacy	Adverse Side Effects	Limitations
1 mcg/kg over 10 minutes followed by a 0.1 mcg/kg/hr infusion until end of surgery	EA was lower in group D than in group S (5% vs 55%). *P*=0.001 First oral intake and discharge time were the same in both groups.	Map and HR decreased by 22-28% and 18-21% in group D as compared to group S. Six subjects received atropine for bradycardia. *P*=0.020	Uncertainty of proper scoring tool for EA due to possible subjective views. Sample size may be too small because it was based on ET-Sevo.

Table B-2

Data Collection Table: Outcome of the Study

Di, M., Han, Y., Yang, Z., Liu, H., Ye, X., Lai, H., … Lian, Q. (2017). Tracheal extubation in deeply anesthetized pediatric patients after tonsillectomy: a comparison of high-concentration sevoflurane alone and low-concentration sevoflurane in combination with dexmedetomidine pre-medication. *BMC Anesthesiology*, *17*(1). doi: 10.1186/s12871-017-0317-3

Dexmedetomidine Dose	Efficacy	Adverse Side Effects	Limitations
Group D0 received IV saline. Group D1 received dexmedetomidine 1 mcg/kg. Group D 2 received dexmedetomidine 2 mcg/kg 10 minutes before anesthesia.	Group D0 6% had EA Group D1 0% had EA Group D2 0% had EA *P*= 0.05	Group D0 and D2 had longest time to discharge Group D0 33.7% and Group D2 32.8% Group D1 only at 25.5%	Plasma concentration of dexmedetomidine was not monitored. This means the correlation between length and how deep the sedation was and hemodynamic changes of dexmedetomidine in blood could not be determined.

Table B-3

Data Collection Table: Outcome of the Study

Chen, F., Wang, C., Lu, Y., Huang, M., & Fu, Z. (2018). Efficacy of different doses of dexmedetomidine as a rapid bolus for children: a double-blind, prospective, randomized study. *BMC Anesthesiology*, *18*(1). doi: 10.1186/s12871-018-0562-0

Dexmedetomidine Dose	Efficacy	Adverse Side Effects	Limitations
Group D1 saline solution Group D2 0.25mcg/kg dexmedetomidine IV bolus Group D3 0.5 mcg/kg dexmedetomidine IV bolus Group D 4 0.75 mcg/kg dexmedetomidine IV bolus Group D5 1 mcg/kg dexmedetomidine IV bolus	Group D4 (0.75mcg/kg) 0% incidence of EA Group D 5 (1 mcg/kg) 0% incidence of EA Both groups demonstrated significantly reduced incidence of EA, fewer trends noted in D2 and D3. Group D5 (0%, $P <$ 0.001) Group D4 (0%, $P <$ 0.001) Group D3 (5%, P= 0.096) Group D2 (5%, P=0.096).	Group D1 0% Group D2 5% bradycardia Group D3 15% bradycardia Group D4 10% bradycardia Group D5 10% bradycardia	Small sample size.

Table B-4

Data Collection Table: Outcome of the Study

He, L., Wang, X., Zheng, S., & Shi, Y. (2013). Effects of dexmedetomidine infusion on laryngeal mask airway removal and postoperative recovery in children anaesthetized with sevoflurane. *Anaesthesia and Intensive Care*, *41*(3), 328–333. Doi: 10.1177/0310057x1304100309

Dexmedetomidine Dose	Efficacy	Adverse Side Effects	
Group C received saline, Group D1 received 0.5 mcg/kg dexmedetomidine, Group D 2 received 1 mcg/kg dexmedetomidine after LMA insertion.	The MAC of sevoflurane was lower in Group D2 compared to Group D1, which both were compared to Group C. Group D1 had lower emergence agitation (17%, *P*=0.179), Group D 2 (6%, *P*=0.179), Group C (42%, *P=0.003*).	Emergence time prolonged in Group D2(8+3 minutes) and in Group C (8+3 minutes) Recovery time prolonged in Group D2 and Group C (15+6 minutes). Hemodynamic effects seen with higher doses 1 mcg/kg, but did not exceed 20% of the values before dexmedetomidine infusion.	Surgeries were less than one hour. General anesthesia was combined with either local anesthesia or an anesthetic block. Unclear if smaller doses of dexmedetomidine on an infusion pump would have been more beneficial

Table B-5

Lin, Y., Chen, Y., Huang, J., Chen, H., Shen, W., Guo, W., … Gan, X. (2016). Efficacy of premedication with intranasal dexmedetomidine on inhalational induction and postoperative emergence agitation in pediatric undergoing cataract surgery with sevoflurane. *Journal of Clinical Anesthesia*, *33*, 289–295. doi: 10.1016/j.jclinane.2016.04.027

Dexmedetomidine Dose	Efficacy	Adverse Side Effects	Limitations
Group C received saline. Group D1 received 1 mcg/kg and diluted with equal volume of saline. Group D2 received 2 mcg/kg of dexmedetomidine and was not diluted.	Intranasal dex greatly reduced emergence agitation. Group D1 23.3%, $P < 0.001$ Group D2 10% $P < 0.001$ Group C 80% Emergence and PACU time all remained the same between the 3 groups. Intranasal dex improved mask induction.	Reduction in heart rates, but did not require interventions.	Influence of the resistance of mask induction on emergence agitation. No dose-dependent effects of dex, unsure of intranasal route due to lack of knowledge of bioavailability .

Appendix C

Table C-1

Critical Appraisal for Summaries of Evidence (CASE) Worksheet

Kim, N. Y., Kim, S. Y., Yoon, H. J., & Kil, H. K. (2014). Effect of dexmedetomidine on sevoflurane requirements and emergence agitation in children undergoing ambulatory surgery. *Yonsei Medical Journal*, *55*(1), 209. doi: 10.3349/ymj.2014.55.1.209

Questions	Evaluations
Summary Topic	
1.) Is the summary specific in scope and application	Yes: X Not Completely: No:
Summary Methods	
2.) Is the authorship of the summary transparent?	Yes: X Not Completely: No:
3.) Are the reviewers/editors of the summary transparent	Yes: X Not Completely: No:
4.) Are the research methods transparent and comprehensive?	Yes: X Not Completely: No:
5.) Is the evidence grading system transparent and translatable?	Yes: Not Completely: X No:
Summary Content	
6.) Are the recommendations clear?	Yes: X Not Completely: No:
7.) Are the recommendations appropriately cited?	Yes: X Not Completely: No:
8.) Are the recommendations current?	Yes: X Not Completely: No:
9.) Is the summary unbiased?	Yes: X Not Completely: No:
Summary Application	
10.) Can this summary be applied to your patients ?	Yes: X Not Completely: No:

Table C-2

Critical Appraisal for Summaries of Evidence (CASE) Worksheet

Di, M., Han, Y., Yang, Z., Liu, H., Ye, X., Lai, H., … Lian, Q. (2017). Tracheal extubation in deeply anesthetized pediatric patients after tonsillectomy: a comparison of high-concentration sevoflurane alone and low-concentration sevoflurane in combination with dexmedetomidine pre-medication. *BMC Anesthesiology*, *17*(1). doi: 10.1186/s12871-017-0317-3

Questions	Evaluations
Summary Topic	
1.) Is the summary specific in scope and application	Yes: X Not Completely: No:
Summary Methods	
2.) Is the authorship of the summary transparent?	Yes: X Not Completely: No:
3.) Are the reviewers/editors of the summary transparent	Yes: X Not Completely: No:
4.) Are the research methods transparent and comprehensive?	Yes: X Not Completely: No:
5.) Is the evidence grading system transparent and translatable?	Yes: X Not Completely: No:
Summary Content	
6.) Are the recommendations clear?	Yes: X Not Completely: No:
7.) Are the recommendations appropriately cited?	Yes: X Not Completely: No:
8.) Are the recommendations current?	Yes: X Not Completely: No:
9.) Is the summary unbiased?	Yes: X Not Completely: No:
Summary Application	
10.) Can this summary be applied to your patients ?	Yes: X Not Completely: No:

Table C-3

Critical Appraisal for Summaries of Evidence (CASE) Worksheet

Chen, F., Wang, C., Lu, Y., Huang, M., & Fu, Z. (2018). Efficacy of different doses of dexmedetomidine as a rapid bolus for children: a double-blind, prospective, randomized study. *BMC Anesthesiology*, *18*(1). doi: 10.1186/s12871-018-0562-0

Questions	Evaluations
Summary Topic	
1.) Is the summary specific in scope and application	Yes: X Not Completely: No:
Summary Methods	
2.) Is the authorship of the summary transparent?	Yes: X Not Completely: No:
3.) Are the reviewers/editors of the summary transparent	Yes: X Not Completely: No:
4.) Are the research methods transparent and comprehensive?	Yes: X Not Completely: No:
5.) Is the evidence grading system transparent and translatable?	Yes: Not Completely: X No:
Summary Content	
6.) Are the recommendations clear?	Yes: X Not Completely: No:
7.) Are the recommendations appropriately cited?	Yes: X Not Completely: No:
8.) Are the recommendations current?	Yes: X Not Completely: No:
9.) Is the summary unbiased?	Yes: Not Completely: X No:
Summary Application	
10.) Can this summary be applied to your patients ?	Yes: X Not Completely: No:

Table C-4

Critical Appraisal for Summaries of Evidence (CASE) Worksheet

He, L., Wang, X., Zheng, S., & Shi, Y. (2013). Effects of Dexmedetomidine Infusion on Laryngeal Mask Airway Removal and Postoperative Recovery in Children Anaesthetized with Sevoflurane. *Anaesthesia and Intensive Care*, *41*(3), 328–333. doi: 10.1177/0310057x1304100309

Questions	Evaluations
Summary Topic	
1.) Is the summary specific in scope and application	Yes: X Not Completely: No:
Summary Methods	
2.) Is the authorship of the summary transparent?	Yes: X Not Completely: No:
3.) Are the reviewers/editors of the summary transparent	Yes: X Not Completely: No:
4.) Are the research methods transparent and comprehensive?	Yes: Not Completely: X No:
5.) Is the evidence grading system transparent and translatable?	Yes: Not Completely: X No:
Summary Content	
6.) Are the recommendations clear?	Yes: X Not Completely: No:
7.) Are the recommendations appropriately cited?	Yes: X Not Completely: No:
8.) Are the recommendations current?	Yes: X Not Completely: No:
9.) Is the summary unbiased?	Yes: X Not Completely: No:
Summary Application	
10.) Can this summary be applied to your patients ?	Yes: X Not Completely: No:

Table C-5

Critical Appraisal for Summaries of Evidence (CASE) Worksheet

Lin, Y., Chen, Y., Huang, J., Chen, H., Shen, W., Guo, W., … Gan, X. (2016). Efficacy of premedication with intranasal dexmedetomidine on inhalational induction and postoperative emergence agitation in pediatric undergoing cataract surgery with sevoflurane. *Journal of Clinical Anesthesia*, *33*, 289–295. doi: 10.1016/j.jclinane.2016.04.027

Questions	Evaluations
Summary Topic	
1.) Is the summary specific in scope and application	Yes: X Not Completely: No:
Summary Methods	
2.) Is the authorship of the summary transparent?	Yes: X Not Completely: No:
3.) Are the reviewers/editors of the summary transparent	Yes: X Not Completely: No:
4.) Are the research methods transparent and comprehensive?	Yes: Not Completely: X No:
5.) Is the evidence grading system transparent and translatable?	Yes: X Not Completely: No:
Summary Content	
6.) Are the recommendations clear?	Yes: X Not Completely: No:
7.) Are the recommendations appropriately cited?	Yes: X Not Completely: No:
8.) Are the recommendations current?	Yes: X Not Completely: No:
9.) Is the summary unbiased?	Yes: X Not Completely: No:
Summary Application	
10.) Can this summary be applied to your patients ?	Yes: X Not Completely: No:

Appendix D

Table 5						
Cross Study Analysis Tool						
Study #	EA	ASA / Patient Characteristics	Anesthetic	Dexmedetomidine dose	Hypotension/ Bradycardia	LOS
1 Kim et al.	Group D 5% vs Group S 55%	ASA 1 Ages 1-5 Hernioplasty or Orchiopexy surgery	Sevoflurane Caudal Block	D= 1mcg/kg bolus followed infusion of 0.1mcg/kg/hr S= saline	+ 22-26% + 18-21%	No delays in same day discharge noted.
2 Di et al.	Group D0 6% had EA Group D1 0% had EA Group D2 0% had EA *P*= 0.05	Seventy-five patients. ASA 1 or 2. Aged 3-7 years old. Tonsillectomy	Sevoflurane	D0= NS D1 = 1mcg/kg bolus of dex D2 = 2mcg/kg bolus	No interventions needed	Recovery time was longest in Group D2. Group D1 had shortest recovery time.
3 Chen et al.	Dex infused at 0.75 (Group D4) and 1.0 mcg/kg (group D5) prevents EA. Group D5 (0%, *P* < 0.001) Group D4 (0%, *P* <	100 patients. ASA 1 or 2, aged 3-7 years old, normal intelligence, liver, kidney function. No history of allergy to anesthesia. Elective	Sevoflurane Ilioinuguinal/iliohypogastric nerve block	D1 = saline D2 = 0.25mcg/kg dexmedetomidine IV bolus D3 = 0.5 mcg/kg dexmedetomidine IV bolus D 4 =	No interventions for hypotension. Group D1 0% Group D2 5% bradycardia Group D3 15% bradycardia Group D4 10% bradycardia Group D5 10%	N/A

	0.001) Group D3 (5%, *P*= 0.096) Group D2 (5%, *P*=0.096).	Inguinal hernia repair surgery.		0.75 mcg/kg dexmedetomidine IV bolus D5 = 1 mcg/kg dexmedetomidine IV bolus		
4 He et al.	Group D1 had lower emergence agitation (17%), Group D 2 (6%), Group C (42%).	Eighty-Seven patients. ASA 1 or 2. Aged 3-7 years old. Minor surface surgeries	Sevoflurane	C = saline, D1 = 0.5 mcg/kg dexmedetomidine D 2 = 1 mcg/kg dexmedetomidine	Hemodynamic effects seen with higher doses 1 mcg/kg, but did not exceed 20% of the values before dexmedetomidine infusion	Emergence time prolonged in Group D2(8+3 minutes) and in Group C (8+3 minutes) Recovery time prolonged in Group D2 and Group C (15+6 minutes).
5 Lin et al.	Intranasal dex greatly reduced emergence agitation. Group D1 7/30 patients, Group D2 2/30, Group C 24/30.	Ninety ASA 1 and 2 for cataract surgery	Sevoflurane 0.5% proparacaine eye drops	C = saline. D1 = 1 mcg/kg dexmedetomidine D2 = received 2 mcg/kg of dexmedetomidine	No interventions Reduction in heart rates, but did not require interventions.	Emergence and PACU time all remained the same between the 3 groups