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# Dexmedetomidine Use And Various Techniques Of Administration To Reduce Emergence Delirium In Pediatric Surgical Patients Undergoing General Anesthesia With Volatile Agents

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**Abstract**

This analysis of literature evaluated retrospective chart reviews and randomized controlled trials of school aged children undergoing surgical procedures necessitating general anesthesia with volatile inhalant anesthetic agents. These studies assessed and compared the efficacy of various routes and timing of administration of dexmedetomidine as a pre-medication to determine the most effective technique in reducing the incidence of postoperative emergence delirium (ED). ED presents as a transient, acute episode of delirium occurring during the transition from unconsciousness to complete wakefulness after general anesthesia with anesthetic gases. The results of this review suggested that pediatric patients treated with intranasal dexmedetomidine preoperatively experienced less traumatic separation from parents, smoother anesthetic inductions, avoided hemodynamic instability intraoperatively, had significantly less episodes of postoperative delirium, and had minimal delay to time of discharge when compared with other pre-medications and routes of administration.

*Keywords*: pediatric anesthesia, delirium prevention, emergence delirium, emergence agitation, dexmedetomidine, precedex, pre-medication, pediatric surgery

**Dexmedetomidine Use And Various Techniques Of Administration To Reduce Emergence Delirium In Pediatric Surgical Patients Undergoing General Anesthesia With Volatile Agents**

Emergence delirium presents as a transient, acute episode of delirium occurring during the transition from unconsciousness to complete wakefulness after general anesthesia with volatile anesthetic agents. This disturbance in cognition is heightened in the pediatric population and can manifest as agitation, confusion, disorientation, emotional outbursts, and potentially violent behavior, leading to physical endangerment. Risk factors for emergence delirium include children of preschool and grade school age, use of volatile inhalant agents, the child's level of preoperative anxiety, the presence of an endotracheal tube, postoperative pain, and pre-existing medical conditions that affect cognitive status. In an effort to avoid such adverse postoperative events, pre-medication is frequently used. Dexmedetomidine (Precedex) is a novel pre-medication that is frequently implemented to minimize the incidence of emergence delirium in pediatric patients.

Unlike GABA receptor agonists such as benzodiazepines or propofol, dexmedetomidine produces dose-dependent sedation that closely resembles natural sleep, avoids respiratory depression, and leaves patients more easily arousable postoperatively. Given the general uncooperative nature of the preoperative pediatric population, this literature review investigated a compilation of studies to determine which method was least invasive, and more efficacious in the prevention of postoperative emergence delirium: preoperative administration (intramuscular, intranasal, buccal, sublingual, or oral) or intraoperative administration (intranasal, or intravenous). If dexmedetomidine is to become a standard of care in avoiding emergence delirium in the pediatric surgical population, a more in-depth awareness of the various methods of administration, and specific outcomes of each approach, is necessary. Dexmedetomidine use provides more positive outcomes in the postoperative pediatric surgical population, allowing for less fearful and emotionally traumatic experiences, thereby improving the overall outlook on future anesthesia care by these patients and their families.

## Literature Review

Initially described in the early 1960s (Wong & Baily, 2015), emergence delirium was identified as a dissociated state of consciousness that could occur in adults and children, with heightened incidence and intensified symptoms seen in the pediatric population, most commonly affecting children of preschool age. Although used interchangeably in much of the literature reviewed, emergence delirium and emergence agitation are not one and the same. Emergence delirium (ED) is an altered state of consciousness that begins with emergence from anesthesia and may present as hypersensitivity, irritability, uncooperativeness, inconsolability, crying, moaning, or writhing and kicking that occurs during the early period of recovery from anesthetic sleep to complete wakefulness. Emergence agitation (EA) is defined by excessive motor activity, is more common than ED, and is specifically associated with discomfort, pain or anxiety. Because EA is an umbrella term that includes ED, the two are often confused. Therefore, to correctly diagnose and treat ED, pain must be completely controlled.

Depending on the definition and criteria, the reported prevalence of emergence agitation/delirium ranges from 10% to 80% throughout the literature. While the ability to accurately differentiate between postoperative delirium and agitation is crucial to guide appropriate treatment, the focus of this literature review is to determine the most efficacious technique and timing of dexmedetomidine administration as a pre-medication in order to minimize the occurrence of emergence delirium in the pediatric surgical population.

### Etiology and Risk Factors

While the etiology of ED is not completely understood, the consensus of articles in this literature review is that rapid emergence from general anesthesia with halogenated volatile anesthetics (sevoflurane, isoflurane, and desflurane) is believed to play an integral role. Inhalation anesthesia was not associated with postoperative delirium or agitation until the 1960s, with the advent of cyclopropane and ether to the anesthetic repertoire. Emergence agitation related to the use of sevoflurane was reported as early as 1991 in Japan (one year after its introduction), with the first account of ED described in the United States in 1996 (also one year after its approval

for use). The disruption in brain activity caused by these halogenated inhalant anesthetics leads to a disordered balance between the child's neuronal synaptic excitation and inhibition in the central nervous system, with lower incidences of disruption observed after the use of propofol alone (Wong & Baily, 2015).

Though rapid emergence from anesthesia with volatile agents was originally deemed the causative factor of an increased incidence of ED, surgical factors and psychological factors are also important variables to examine (Martin et al., 2014). The predictability of ED is not always agreed upon, but age, ethnicity, socio-economic background, temperament, psychological or emotional maturity, cognitive skills, previous hospital experience, preoperative anxiety level, parental anxiety level, length of volatile anesthetic exposure, and type of procedure are all considered influential regarding its occurrence (Draskovic et al., 2015). Additional risk factors include children of preschool age, otolaryngology procedures, hypoxemia, nausea and vomiting, and the use of inhalation anesthetics, most specifically sevoflurane (El-Hamid & Yassin, 2017).

The majority of studies in this literature review reported the average incidence of ED to be 60%, of which was a major cause of dissatisfaction among parents and healthcare staff (Mountain et al., 2011; Peng et al., 2014). One of the physiologic consequences associated with preoperative anxiety was noted to be an overall increase in autonomic nervous system activity, resulting in tachypnea and increased motor tone (Draskovic et al., 2015). Though known to be self-limiting with minimal adverse long term events, ED understandably causes distress to the patient, parents, and staff, and may result in physical harm to the child, or those involved in the child's care (Stamper et al., 2014).

**Delirium and Agitation Predictive Tools**

Though there are several scoring systems used to diagnose pediatric emergence delirium to date, the most sensitive tool to quantify the presence and severity of ED, and accurately differentiate its contributing factors, is the Pediatric Anesthesia Emergence Delirium (PAED) scale, which was developed in 2004 for use in children > 2 years of age. This scale incorporates cognitive and agitation assessment items and is generally acknowledged to be

the most valid and reliable method in which to diagnose and quantify the severity of ED. An investigative study performed to examine the diagnostic properties of the PAED scale found that it had a sensitivity of 91% and specificity of 98%, deeming it one of the most valid tools used to measure pediatric delirium (Janssen et al., 2011). This scale allows caregivers to assess patients on five variables, with the total PAED score directly correlating with the degree of ED (1 = child makes eye contact with caregiver, 2 = child's actions are purposeful, 3 = child is aware of his/her surroundings, 4 = child is restless, 5 = child is inconsolable). A score of $\geq$ 10 is deemed the highest specificity for an ED diagnosis (Janssen et al., 2011; Mountain et al., 2011; Wong & Baily, 2015). The PAED scale has proven to be easy to use at the bedside by all clinical practitioners, is not time-consuming, and is suitable for children of all ages (Stamper et al., 2014).

Upon initial recognition of ED, non-pharmacological treatments employed typically involved the exclusion of pain and nausea, ensuring patient safety, providing a quiet environment, and reassuring the patient, parents and healthcare staff of the self-limiting, transient nature of ED (Draskovic et al., 2015). The severity of ED varies from child to child, and although prevention is preferred, effective pharmacological treatments for ED in the postoperative period may include intravenous boluses of midazolam, propofol, or fentanyl (Isik et al., 2006; Wong & Baily, 2015). Additional healthcare costs are incurred when treating ED and are directly related to the need for additional nursing care, and treatment with analgesics or sedatives, which then increased the duration of stay in recovery, further delaying discharge from the hospital (Jannu et al., 2016). Though long term effects of ED have not been studied, with over 50% of pediatric surgical patients experiencing preoperative fear and anxiety, these stressful experiences do have the potential to generate negative postoperative responses which may have long term effects on the child's psychological development and may last weeks to months (Dave, 2019; Keles & Kocaturk, 2017).

**Physiological and Psychological Effects of Delirium**

The initial fear and anxiety can manifests in several ways in the pediatric patient, including difficulty separating from parents and refusal to accept an anesthesia mask once in the operating room. In order to avoid long-term psychological effects, appropriate planning and preparation of the pediatric surgical patient is of utmost importance. Suggestions for such interventions included allowing the child to take a tour of the operating room several days prior to the surgical procedure, or having them watch a video or read a book that explains the activities to be expected on the day of surgery (Draskovic et al., 2015). The results of such preparation are dependent on the child's age and how frequently the subject is discussed with them. Of the few postoperative follow-up studies referenced, adverse outcomes included negative behaviors at home, bad dreams, tearful awakenings, separation anxiety, and temper tantrums.

In an effort to alleviate such adverse effects, anesthesia providers must be proactive in the prevention of emergence delirium. Strategies examined to improve perioperative outcomes included behavior management, distraction with music or electronic devices, and modifications of the anesthetic plan, including the choice of sedatives, anesthetic medications, and techniques and methods of administration (Martin et al., 2014).

**Choice of Pre-medication**

Medications with sedative and anxiolytic effects are often employed in the preoperative patient to ensure a smooth anesthetic induction and potentiate a smooth emergence. When efforts are put in place to reduce or eliminate anxiety, there are fewer instances of postoperative delirium, thereby improving the perioperative experience for both the patient and their family. In an attempt to avoid the incidence of postoperative delirium, several studies recommended to avoid volatile inhalant anesthetic agents altogether, if feasible, and to be cognizant of the postoperative environment, allowing pediatric patients to recover in calm, quiet spaces, with minimal stimuli and their family present. In addition to minimizing the use of halogenated anesthetic agents, pre-medication should be strongly considered in an effort to avoid ED completely. Popular choices of pre-medications that have

proven to be effective in minimizing preoperative anxiety and postoperative delirium include ketamine, midazolam, diazepam, and most recently, dexmedetomidine. The ideal pre-medication is free from adverse effects such as respiratory depression, hemodynamic disturbances, and the potential for delirium (Jannu et al., 2016).

Historically, the most frequently used preoperative medications included diazepam, midazolam, and ketamine, with dexmedetomidine becoming more popular in recent years. Generally, preoperative medications offer significant benefits, such as a lower incidence, severity, and duration of ED, with more stable anesthetic maintenance intraoperatively. With patient safety the priority, the potential for adverse side effects must be taken into account when creating individualized anesthetic plans. Such adverse effects seen with midazolam include restlessness, agitation, hiccups, paradoxical postoperative behavioral changes, and respiratory depression (Peng et al., 2014). Ketamine has the benefit of both sedative and analgesic properties, but due to its sympathomimetic properties its adverse effects include excessive salivation, nausea, vomiting, nystagmus, and hallucinations (Peng et al., 2014).

Aside from disadvantageous side effects, unique obstacles present within pediatric surgical patients. Children are not always cooperative, which poses a challenge to the provider, as preoperative intravenous access is frequently absent, intramuscular injections are frightening, invasive and uncomfortable, and oral medications often have an unpleasant taste.

**Alpha-2 adrenergic receptor agonists.** Alpha-2 adrenergic receptors are found in the cardiovascular and central nervous system and are involved in numerous physiologic functions. The $\alpha_2$ receptors located presynaptically function as autoreceptors in a negative feedback loop, controlling neurotransmitter release. When the presynaptic $\alpha_2$ receptors are stimulated by an agonist such as dexmedetomidine or clonidine, the result is a decrease in catecholamine release, thereby decreasing heart rate and cardiac output. Dexmedetomidine is unique in that it is a highly selective $\alpha_2$ adrenergic receptor agonist that possesses analgesic, sedative, anxiolytic, sympatholytic, and opioid-sparing properties (Lee, 2019; Peng et al., 2014). With $\alpha_2$ receptors found at both

postsynaptic and extrasynaptic sites, the presynaptic $\alpha_2$ receptors are considered of greatest clinical importance due to their ability to regulate the release of norepinephrine via a negative feedback mechanism. The negative feedback is responsible for the inhibitory effects on the secretion of the neurotransmitter. The resultant neuronal hyperpolarization becomes a key element in the mechanism of action of the $\alpha_2$ receptor agonist from an anesthetic viewpoint, as inhibition of norepinephrine release upon the presynaptic activation of the $\alpha_2$ receptor terminates the transmission of pain signals. The postsynaptic (or extrasynaptic) activation of the $\alpha_2$ receptors in the central nervous system exhibit sympatholytic properties.

Due to dexmedetomidines high affinity (94%) to bind to albumin and the $\alpha_1$-glycoprotein, the impacts of its pharmacokinetics have been suggested to be related to body size, hepatic impairment, plasma albumin, and cardiac output (Rosenbaum et al., 2009). It produces sedation and analgesia by acting on the centrally located $\alpha_2$ adrenergic receptors in the locus ceruleus, which has one of the highest densities of such receptors. Stimulation of these central $\alpha_2$ receptors produces a similar effect as opioid receptors at the site of origin for the descending medullospinal noradrenergic pathway, which is an important modulator of nociceptive neurotransmission.

The analgesic effect of dexmedetomidine is weak, but it has proven to be a useful anesthetic adjuvant, decreasing the need for opioids, inhalation anesthetics, and intravenous anesthetics. The sedative response of dexmedetomidine is its most unique characteristic, as it provides for a smooth, more natural transition from sleep to wakefulness while allowing patients to remain in an arousable sedated state, and maintain the ability to cooperate and communicate when stimulated. The research suggested that this more natural awakening from anesthesia produces less delirium, and is the mechanism by which postoperative emergence delirium is avoided. The inhibition of norepinephrine release within the locus ceruleus is the process that creates electroencephalogram activity similar to natural sleep, thereby decreasing the incidence of delirium or agitation upon awakening (Martin et al., 2014).

**Benzodiazepine parallel.** When comparing the efficacy of dexmedetomidine with other commonly used pre-medications, one study compared its buccal administration with diazepam, concluding that there were no significant differences in physiologic measurements, suggesting the two medications are comparable when used as pre-medications. With a higher ratio of specificity for the presynaptic $\alpha_2$ receptor versus the postsynaptic $\alpha_1$ receptor, dexmedetomidine reduces noradrenergic neuronal activity. This decrease in neuronal activity results in less respiratory depression than other choices of pre-medication sedatives, which has proven beneficial for children (Sakurai et al., 2010). Contrarily, Lee (2019) found that sedation induced by GABA receptor modulators such as propofol and benzodiazepines often contribute to an increased incidence of delirium.

In numerous randomized studies of children aged 1-10 years old, an intraoperative dexmedetomidine infusion of 0.2 mcg/kg/hr was shown to decrease the incidence of ED by approximately 26% after general anesthesia with sevoflurane, and did not prolong the time to extubation or discharge from PACU (Kim et al., 2014; Lee, 2019). Although impractical in the pediatric population, preoperative dexmedetomidine infusions have been shown to reduce the incidence of emergence delirium (Wong & Baily, 2015). As interest and research in its use has increased, several studies have concluded that single boluses and continuous infusions of dexmedetomidine reduce the incidence of ED in a similar fashion as the more well-known $\alpha_2$ agonist clonidine (which was initially introduced as a pediatric pre-medication in 1993 (Rosenbaum et al., 2009)). In such studies, dexmedetomidine proved to be a more potent alternative due to its higher receptor specificity, shorter onset time, and faster elimination half-life (Ibacache et al., 2004).

## Technique of Administration, Efficacy, Bioavailability and Dosing

Until recent years, the most commonly used technique of pediatric pre-medication had been the oral administration of the benzodiazepine midazolam, with its beneficial effects including anxiolysis, amnesia, and a rapid onset and offset (Mountain et al., 2011). While benzodiazepines successfully decrease preoperative anxiety, they have not been shown to successfully or reliably decrease ED, and may not be effective for all children.

Several studies reviewed demonstrated examples of failed sedation with oral midazolam that was followed up by safe and effective intranasal administration of dexmedetomidine (Sakurai et al., 2010). When administered 40 minutes before anesthetic induction, the orally administered, flavorless intravenous preparation of dexmedetomidine was more readily accepted by the pediatric population than oral midazolam, which is reported to have a bitter taste (Jannu et al., 2016).

An interesting hypothesis proposed by Qiao et al. (2017) was tested to determine whether or not dexmedetomidine, when used in combination with an additional pre-medication, would prove to be advantageous in improving cooperation of pediatric patients during preoperative intravenous cannulation. Their study found the success rate of 2.5 mcg/kg intranasal dexmedetomidine to be 47%, while 6 mg/kg oral ketamine was successful in 68%. When used in combination (2 mcg/kg intranasal dexmedetomidine with 3 mg/kg oral ketamine), the pre-medications were 80% efficacious, suggesting a reasonable alternative to examine and consider for pediatric pre-medication in clinical practice (Pent et al., 2014; Wong & Baily, 2015). This combination of pre-medications allowed for reasonably calm separation from parents, more successful attempts at venous cannulation, and better acceptance of inhalation induction of general anesthesia. The use of these complimentary pre-medications allowed for the reduction of both the cardiovascular response and adverse postoperative psychiatric events attributed to anesthetic induction with ketamine alone.

Incorporating multimodal avenues of anesthetic management allows for the safe combination of dexmedetomidine with other non-opioid medications with safe and beneficial results. However, when administered concomitantly with other sedatives, hypnotics, anesthetic agents, or opioids, dexmedetomidine causes additive effects, which may increase the risk of hemodynamic compromise, necessitating continuous respiratory monitoring (Weerink et al., 2017). Though sedation is an effect observed due to its action in the locus ceruleus, dexmedetomidine is unlikely to cause respiratory depression when used alone.

**Routes of administration.** Given the various techniques of administration (intranasal [drops, atomizer], buccal, sublingual, oral, intramuscular, intravenous), timing of administration (preoperative, intraoperative, postoperative), and differing results in the prevention of emergence delirium (based on the length and type of surgery and general anesthetic used), the bioavailability of the drug becomes an important variable to evaluate. Unfortunately, because there is such little research into the pharmacokinetics and bioavailability of intranasal dexmedetomidine in the pediatric population, researchers turned to adult studies for a point of reference. One such study by Iirola et al. (2010) was performed in healthy adult volunteers, and found peak plasma concentrations of intranasal dexmedetomidine to be achieved in an average of 38 minutes, with an absolute bioavailability of 65% (Iirola et al., 2010; Santana & Mills, 2017; Yao et al., 2014). A pediatric study investigating the use of intranasal dexmedetomidine as a pre-medication agent prior to intravenous cannulation found that the median onset of time to sedation was 25 minutes, with the median duration of sedation 85 minutes, concluding that this method of administration was effective as long as the medication was given 30-45 minutes prior to the procedure.

Dosage requirements not only differ between the adult and pediatric populations, but also within the pediatric population itself. Younger and older children require different plasma concentrations to achieve similar efficacy due to the larger volume of distribution in children younger than two years of age (Santana & Mills, 2019; Yuen et al., 2012). The bioavailability of dexmedetomidine after oral administration is 16% as compared to 82% for buccal preparations (Keles & Kocaturk, 2017; Mountain et al., 2011), which is likely due to extensive first-pass metabolism. This hepatic metabolic process explains the slower onset of action of oral dexmedetomidine when compared with oral midazolam (Jannu et al., 2016). There is no official oral preparation of dexmedetomidine available at this time, so when given orally, it is the intravenous preparation that is utilized (Mountain et al., 2011).

The intranasal administration of various pre-medications has proven to be simpler than oral sedation within the pediatric population, as it is relatively noninvasive, requires minimal physical restraint, does not require much patient cooperation, and is easier to administer. The intranasal route is the most used extravascular route of pre-

medication administration in clinical practice. Although useful for sedation and pre-medication in the pediatric population, its bioavailability is variable, reported anywhere between 35-93% (Iirola et al., 2011). Several studies compared intranasal administration of dexmedetomidine with an atomizer versus droplets to each nare, both of which were found to be equally as effective in children less than three years of age (Weerink et al., 2017). The optimal volume for intranasal administration of a drug is a total of 1 mL split between nostrils, with larger volumes leading to a partial oral administration when it drips into the oropharynx (Sheta et al., 2013; Yuen et al., 2012). As oral administration of dexmedetomidine has an extensive first-pass metabolism with a bioavailability of only 16%, larger quantities administered intranasally may result in partial oral ingestion, and are presumably the reason for the delayed effects observed in several of the studies reviewed. When compared to commonly used pediatric pre-medications, intranasal dexmedetomidine has proven to be more effective in inducing sleep preoperatively, allowing for smoother endotracheal intubations, a decrease in the frequency of postoperative emergence delirium and no increased length of stay in recovery (Sheta et al., 2013). No significant differences were noted in the PAED scores of patients that were premedicated with intranasal dexmedetomidine when compared to those who did not receive any pre-medication (Santana & Mills, 2019).

Due to the large surface area and vascularity of the nasal mucosa, the absorption rate is rapid, providing for a bioavailability of approximately 65%, as administration via this technique allows for the bypass of the first-pass effect metabolism in the liver (Peng et al., 2014). Minor disadvantages of intranasal administration of any drug are nasal irritation and watering of the eyes, but are more often observed in children who received intranasal midazolam (Sheta et al., 2013). When compared with intranasal midazolam, several studies concluded that the use of preoperative intranasal dexmedetomidine showed no significant differences in the immediate postoperative period for the time it took children to spontaneously open their eyes, the time to respond to a nurse or parent, or the time in which they achieved an Aldrete score of $\geq 9$, which signifies when a patient is responding appropriately enough to be safely discharged from PACU (Sheta et al., 2013).

**Dose and hemodynamic effects.** The most common listed adverse side effects of dexmedetomidine are its potential for long-lasting sedation and hemodynamic changes. Hypotension, transient hypertension, bradycardia, prolonged extubation time, sedation and PACU stay prove to be untoward side effects of its use. These aftereffects were noted to be dose-dependent and were most frequently observed after a large, rapidly administered bolus dose or high dose infusion, and infrequently presented after a slowly administered, single bolus dose (Bedirli et al., 2017). The dose-dependent $\alpha_2$ receptor selectivity exhibited by dexmedetomidine is the reason for these transient cardiovascular complications, and are a result of the drug's peripheral vasoconstrictive and sympatholytic properties. Though the majority of instances of hemodynamic compromise were observed after high intravenous doses, they were also observed after high dose buccal administrations; both intravenous and buccal routes allow for rapid absorption into systemic circulation (Mountain et al., 2011).

Numerous studies examined in this literature review discussed such effects when dexmedetomidine was administered in the absence of pre-medication, and when it was given rapidly via intravenous shortly after intubation. Early studies by Ibacache et al. (2004) observed varied effects dependent on the dose and rate of administration, and reported intravenous doses between 0.15-0.3 mcg/kg as safe for children, with minimal to no significant hemodynamic effects observed. When administered intravenously – either as a continuous intraoperative infusion, a bolus given directly after anesthetic induction, or a bolus given 5-10 minutes prior to emergence – hemodynamic instability, postoperative sedation, prolonged extubation/emergence time, and an increased length of stay were reported in studies by Bedirli et al. (2017), Isik et al. (2006), and Makkar et al. (2015). Conversely, it was reported by both Lee (2019) and Kim et al. (2014) that continuous, low dose (0.2 mcg/kg/hr) intraoperative infusions of dexmedetomidine reduced the incidence of emergence agitation and postoperative pain with minimal hemodynamic compromise or delay of emergence. Incidentally, no known reversal agents are approved for use in human medicine, but a selective $\alpha_2$ antagonist (atipamezole) is currently

used in veterinary medicine (Weerink et al., 2017), which may warrant further studies into its application in human medicine.

*Dose.* Throughout the literature, when dexmedetomidine was used as a pre-medication, a significant reduction in ED was observed after both sevoflurane and desflurane anesthesia, with no momentous difference noted between MAP, HR, $SpO_2$, time spent in PACU, or time to discharge. When administered slowly over the course of five minutes, 0.3 mcg/kg intravenous dexmedetomidine given 15 minutes before surgical completion provided a significant reduction of ED in children after general anesthesia maintained by desflurane, with only a slightly extended period of sedation noted in postoperative recovery (Ibacache et al., 2004). When compared to the oral effects of midazolam, although a slower onset of action, significantly less ED was observed in the patients who received dexmedetomidine. It produced an equally effective preoperative sedation with no physiologic differences, and provided for a smoother recovery period. Of the literature reviewed, 1-2 mcg/kg of intranasal dexmedetomidine proved to be a safe and effective sedative for uncooperative children, with buccal preparations requiring a higher dose (3-4 mcg/kg), likely due to partial oral ingestion. Furthermore, the incidence of postoperative pain, shivering, and emergence agitation was also reduced in the presence of pre-medication with 1 mcg/kg intranasal dexmedetomidine (El-Hamid & Yassin, 2017; Keles & Kocaturk, 2017; Sheta et al., 2013).

*Hemodynamic effects.* Cardiovascular depression has been observed with the intravenous administration of a bolus dose of 1 mcg/kg, temporarily increasing blood pressure with a reflex decrease in heart rate, followed shortly thereafter by a decrease in blood pressure, specifically in young, healthy patients. Peripheral $\alpha_2$ receptor stimulation of vascular smooth muscle explains this initial hemodynamic variation, which can be avoided by administering the drug at a slower rate, ideally over five to ten minutes. Though these sympatholytic actions may be deleterious in hypovolemic patients or those with fixed stroke volume, numerous studies reported an absence of such cardiovascular complications in children who received 1-2 mcg/kg of intranasal dexmedetomidine preoperatively.

**Preoperative Versus Intraoperative Administration**

When administered intranasally at a dose of 1 mcg/kg after mask induction in the absence of pre-medication, the results were a smooth recovery, with comparable emergence and discharge times as other medications with no adverse effects. Satisfactory sedation was achieved when 1-2 mcg/kg dexmedetomidine was administered 30-60 minutes preoperatively as intranasal drops. The age of the child and the bioavailability of the drug must be taken into consideration when dosing the pre-medication, as younger children have a reduced intranasal surface area than that of older children, which may result in less systemic drug absorption (Yuen et al., 2012). Due to their larger volume of distribution, younger children need higher doses to maintain satisfactory levels of sedation when compared to older children. When given as an intranasal pre-medication 45-60 minutes preoperatively, dexmedetomidine produces a dose-dependent reduction in end-tidal sevoflurane requirements, and attenuates acute cardiovascular responses to endotracheal intubation; 1 mcg/kg of intranasal dexmedetomidine has proven to be more effective than intranasal midazolam in the majority of these studies. As previously mentioned, one disadvantage of the intranasal method of administration is the fact that, when administered in a larger quantity, a portion of the drug may drip into the oropharynx, thereby becoming a partial oral administration, decreasing its bioavailability and slowing the expected effects.

Although the absolute bioavailability of intranasal use remains undetermined, the results of its use are clinically significant, and sufficient enough to warrant further investigation, as the ideal pre-medication drug and its most appropriate route of administration remain debatable among researchers (Iirola et al., 2010; Peng et al., 2014). Not only does the intranasal method appear to provide a higher bioavailability than the oral route, but a common theme throughout the literature has proven that an even more successful technique of intranasal administration is with the use of a mucosal atomizer device, as it provides a slightly more rapid onset (23 minutes as compared to 25 minutes) and creates more effective sedation than nasal drops while using the same dose of 1-2 mcg/kg (Xie et al., 2017).

It has been hypothesized that dexmedetomidine aids in the reduction of postoperative delirium, as it preserves the physiologic sleep-wake cycle. Children who have been premedicated with intranasal dexmedetomidine have been observed to require significantly less postoperative rescue analgesia, and the overall incidence of postoperative agitation significantly less pronounced when compared to preoperative midazolam use (Sheta et al., 2013). When administered preoperatively, dexmedetomidine provides an advantageous potentiation of anesthetic agents used, thereby reducing the minimum alveolar concentration (MAC) of volatile agents necessary for laryngeal mask airway insertion or tracheal intubation. Its use as a pre-medication not only facilitates a smooth general anesthetic induction but also allows for minimal emotional distress in children undergoing surgical procedures. Unfortunately, due to its slower onset and peak of action, the fast-paced nature of the preoperative environment may not always allow for adequate timing of drug administration prior to the induction of general anesthesia. When taking the time of its onset into account, if advantages outweigh the urgency of surgical scheduling, the use of dexmedetomidine may be worth considering if a child is refusing oral medication administration.

**Dexmedetomidine, Halogenated Agents, and Opioid Requirements**

The use of dexmedetomidine as a pre-medication has proven to decrease the MAC of inhalation anesthetics, postoperative opioid analgesic requirements, and the frequency of emergence delirium. It also avoids respiratory depression seen with opioid sedation. When used as an intranasal pre-medication, 1-2 mcg/kg dexmedetomidine doses have demonstrated a decrease in the target cerebral concentration of sevoflurane necessary for endotracheal intubation, and also reduce the end-tidal concentration of sevoflurane (Yae et al., 2014). While all halogenated anesthetic agents are considered emergence delirium triggers, there is limited data on the prevention of ED specifically following general anesthesia with desflurane. A handful of studies have demonstrated a reduction in the incidence of emergence delirium following desflurane anesthesia in pediatric patients undergoing strabismus surgery when 0.2 mcg/kg/hr of dexmedetomidine was used as a continuous intraoperative infusion

(without a loading dose) (Kim et al., 2014). Such low-dose dexmedetomidine infusions have also been shown to reduce postoperative pain without hemodynamic compromise or delay of emergence, thus avoiding the need for postoperative opioid analgesics (Kim et al., 2014). One such study was performed without the use of any pre-medication, and found that patients who received a 0.3 mcg/kg intravenous bolus of dexmedetomidine 15 minutes prior to the completion of surgery maintained with desflurane had a 9.4% incidence of ED as compared to 40.6% in the control group (Makkar et al., 2015).

The data suggests that postoperative pain is one of the major causative factors of pediatric emergence agitation and/or delirium, yet pain remains under-assessed and under-treated within the pediatric surgical population; though several studies concluded that the absence of pain does not necessarily guarantee a calm emergence. Of the limited studies performed to assess the effect of various drugs on ED following the use of desflurane, one found that neither propofol nor midazolam was effective in reducing the instance of ED in patients undergoing adenotonsillectomy, yet fentanyl 2.5 mcg/kg successfully decreased the incidence of severe ED without a delay in emergence (Makkar et al., 2015).

As opioid administration treats pain, this author believes that in the instance of decreased ED after fentanyl administration, it was not true emergence delirium, rather emergence agitation, as the presence of pain is the defining characteristic between the two. Physiologically during the postoperative period circulating catecholamine concentrations are elevated, at which time dexmedetomidine use is clearly beneficial, providing sympatholytic and analgesic effects without respiratory depression.

**The History and Future of Dexmedetomidine**

Dexmedetomidine was initially registered in the United States in 1999, and its use later approved by the U.S. Food and Drug Administration in 2003 (Weerink et al., 2017). It has proved useful in multiple off-label applications, such as pediatric sedation, intranasal or buccal administration, and use as an adjuvant to local analgesia techniques. In 2008 additional indications were approved for use in the U.S., allowing for the use of

short-term (< 24 hours) sedation of the non-intubated patient before and/or during surgical and other procedures. Dexmedetomidine had proved to have similar sedative and analgesic effects as benzodiazepines, only with less adverse side effects (Lee, 2019). The pharmacokinetic and pharmacodynamic properties of dexmedetomidine have been studied extensively, both within and beyond the scope of the currently approved indications. Studies suggest that, when used alone, respiratory depression is unlikely, however, when combined with other sedatives or hypnotics, dexmedetomidine demonstrates additive effects, increasing risks and necessitating continuous respiratory monitoring (Weerink et al., 2017). It is apparent that opioid-sparing effects are beneficial, but more research is needed to better characterize the underlying mechanisms of this property.

Regardless of the lack of pediatric labeling, dexmedetomidine continues to be widely studied for its various applications within the pediatric surgical population, with clinically relevant, positive outcomes, as those discussed throughout this literature review. Although the majority of studies reviewed suggest that the intranasal administration of 1-2 mcg/kg dexmedetomidine is superior to that of other medications or routes, the optimal choice of medication (or combination of medications), dose, route, technique, or timing of administration has yet to be agreed upon within the pediatric anesthesia community. This leaves room for future randomized clinical trials to further investigate this topic.

## Recommendations

After careful review of the literature, it can be determined that the goal of using a pre-medication for an operative pediatric patient should be to decrease emergence delirium. When efforts are consciously put in place to reduce or eliminate anxiety, there are fewer instances of postoperative delirium. Ideally, the anesthesia provider should anticipate the high likelihood of ED, and treat preemptively with a multimodal approach, including propofol, ketamine, and an $\alpha_2$ adrenergic receptor agonist such as dexmedetomidine to reduce the probability of ED altogether. The administration of intranasal dexmedetomidine appears to be the most efficacious in reducing both preoperative anxiety and postoperative emergence delirium within the pediatric surgical population, leading

this author to believe that it is highly beneficial when utilized in the preoperative setting. Preemptively reducing preoperative anxiety improves the perioperative experience for both the patient and their family; decreasing anxiety levels preoperatively influences immediate postoperative outcomes by decreasing physiological stress on the body, as well as psychological stress, which can lead to less-than-desirable long-term behavioral outcomes well after discharge.

In addition to utilizing the most effective and least invasive route of pre-medication within the pediatric population, the use of appropriate predictive tools should also be employed to identify emergence delirium and agitation. Concurrent use of the Pediatric Agitation and Emergence Delirium (PAED) score and the postoperative Objective Pain Score (OPS) allow for the accurate prediction of severe emergence agitation. The OPS assesses for pain by evaluating factors such as hemodynamic change, emotions, physical movement, and localization of pain. It is not easy to distinguish pain from agitation in preschool aged children; therefore, as many of the OPS parameters overlap those of the PAED scale, both tools have proven to be effective aides for the early identification of postoperative delirium.

Anesthesia providers and nursing professionals alike are capable of using the PAED scale to effectively identify and respond to episodes of emergence delirium. This author agrees with recommendations by Stamper et al. (2014) that the PAED scale be implemented as a standard of care when assessing for the presence of pediatric emergence delirium in the postoperative setting. Furthermore, as residual sedation can affect PAED scores, the importance of thorough postoperative evaluations are essential in order to appropriately diagnose and treat emergence delirium. Objectives in its identification should be to build upon current evidence based knowledge, encourage communication between health care personnel, the proactive recognition and treatment of postoperative pain, and the prevention of patient and personnel injury when episodes of pediatric emergence delirium do occur.

Due to its prolonged onset of action when used as an intranasal pre-medication, the optimal time in which to administer intranasal dexmedetomidine was determined to be 45-60 minutes prior to the induction of anesthesia.

The studies provided no evidence of intranasal administration being foul tasting, or causing local irritation or bleeding of the nasal mucosa, leading to the belief that the intranasal route is an efficacious and fairly comfortable way to administer the pre-medication, especially in uncooperative, fearful children. The findings indicated that further investigation into appropriate dosing parameters for intranasal dexmedetomidine is warranted. Considerations for future research should include the type of surgical procedure, expected length of the procedure, and the child's age; children younger than two years of age have a larger volume of distribution, and require larger doses than school aged children. A high efficacy of intranasal dexmedetomidine was noted throughout the literature, with observations that it was generally well tolerated, had a bioavailability of 65%, and was deemed suitable for use in clinical situations requiring light sedation.

Based on the research, 1-2 mcg/kg intranasal dexmedetomidine is a safe and effective alternative for pre-medication in children undergoing surgery with general anesthesia maintained either by sevoflurane or desflurane. This is the recommended dose to provide adequate, safe preoperative anxiolysis, while ensuring a significantly decreased incidence of postoperative emergence delirium. As an intranasal pre-medication, dexmedetomidine provides an alternative, less invasive route for pre-medication of children who refuse oral medications, results in satisfactory sedation levels, and improves ease of separation from parents.

As with all medications, thoughtful consideration and careful calculations must be used when selecting patients and determining appropriate dosing of dexmedetomidine. Though a large variation in the efficacy of intranasal dexmedetomidine was reported throughout the literature, it is suggestive that the preoperative intranasal application of dexmedetomidine is likely to become more clinically applicable with the standardization of use of a delivery system such as the mucosal atomizer device. Ideally, a proactive approach to anxiolysis and the prevention of pediatric emergence delirium will prevent the need for postoperative treatment.

## Conclusion

Adverse postoperative events present in the pediatric surgical population as a consequence of stress and fear during the preoperative period, which can have a negative influence on perioperative behavior and clinical

recovery. With a plethora of methods to choose from when reducing preoperative anxiety in children, clinicians need to consider the potential for psychological problems related to surgery and anesthesia in order to best help children and their parents to cope with perioperative stress. Dexmedetomidine is a novel pharmacological option available for use in the prevention of pediatric emergence delirium. With a variety of techniques available in which to administration it, dexmedetomidine has proven to be especially beneficial in the pediatric surgical population, with the chief consideration being the unpredictable nature of children in their willingness to accept oral medication (be it due to a foul odor, taste, or simply fear and distrust) and their lack of cooperation with more invasive routes of medication administration (intramuscular or intravenous).

When administered intranasally in the preoperative setting, dexmedetomidine has been proven to successfully decrease postoperative emergence delirium in pediatric patients while avoiding excessive sedation, respiratory depression, and prolonged discharge times. The data supports intranasal administration (either by drops or an atomizer) as the most efficacious for this population, as the results are similar to those when administered intravenously, although with less adverse physiological effects. Though the onset of action of the drug is more rapid when administered intravenously, the advantages of intranasal administration include more cooperation with ease of management of the child (minimal restraint necessary), providing for less physical discomfort, and the alleviation of distasteful oral solutions. The research indicates that the intranasal administration of dexmedetomidine is more effective in inducing sleep when administered preoperatively; it performed superior to preoperative midazolam, provided for a more agreeable separation from parents, decreased the need for postoperative rescue analgesia, and reduced emergence agitation. Additionally, because dexmedetomidine also exerts an analgesic effect, research suggests that its use may also be an adjunct in the reduction of postoperative opioid requirements and the incidence of complications that accompany opioid use, such as pruritus, nausea, and respiratory depression.

The consensus among the literature is that when administered intranasally at a dose of 1-2 mcg/kg, dexmedetomidine is a safe and effective pre-medication within the pediatric population undergoing various surgical procedures, including tonsillectomy, adenoidectomy, myringotomy, strabismus correction, and dental rehabilitation. At this low dose, cardiovascular complications such as hypotension and bradycardia were avoided altogether, allowing for a smoother perioperative course than observed in pediatric surgical patients that had not received preoperative dexmedetomidine. Though its use within the pediatric surgical population requires continued vigilance and meticulous evaluation to ensure its continued safe use, dexmedetomidine is a useful and attractive non-opioid alternative in the prevention and treatment of emergence delirium and agitation.

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