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Sedative Premedication in Preschool Children Undergoing Magnetic Resonance Imaging

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Abstract

The frequency of magnetic resonance imaging (MRI) scans in pediatric patients has increased in recent years. The MRI has become the preferred diagnostic procedure for many conditions because it is a noninvasive and radiation-free diagnostic procedure. An MRI scan can take ~10 to 30 minutes. It is quite noisy, and the patient is moved into a narrow cylinder with limited access. The patient must lie motionless inside a tunnel-like magnetic coil during the MRI scan. Several factors related to MRI can cause fear, agitation, and anxiety in patients, including an unfamiliar environment, the presence of unknown staff, and lengthy scan times. Magnetic resonance imaging (MRI) scans for children are a challenge for anesthesiologists since the child must be sedated enough to stand still. But anesthetic drugs used for sedation might have serious side effects and monitorization resources and accessibility to the patient during MRI scan is limited.

Keywords: Sedative Premedication, Children, Magnetic Resonance Imaging.

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1. Introduction

Magnetic Resonance Imaging (MRI) MRI is a common modality used to diagnose and monitor many different acute and chronic pediatric medical problems. Increased MRI utilization has also expanded the need for pediatric sedation in recent years, partially motivated by the interest to avoid the use of CT and its associated ionizing radiation exposure [1]. The MRI procedure itself is not painful, but it can be distressing given the relatively small diameter and long length of the machine bore and loud noises produced, creating challenges for many young and claustrophobia-prone patients. A key procedural requirement is for the patient to remain as motionless as possible throughout the scanning duration to facilitate high-quality diagnostic images. Depending upon the protocol required, the imaging time can vary from a few minutes to several hours long, causing variability in which scans require sedation [2]. MRI uses extremely strong magnetic fields that are always on, creating special safety and equipment concerns when sedating in this environment. Any ferromagnetic items can become life-threatening projectiles when placed within the MRI magnetic field. Special MRI-compatible equipment including medication poles, wheel chairs, oxygen tanks, stretchers, and all materials that enter Zone IV (the room containing the MRI machine) must be carefully chosen and labeled to clearly identify them as MRI-compatible. Similarly, MRI-compatible sedation monitoring equipment (pulse oximetry, electrocardiogram with MRI-compatible pads, blood pressure monitoring, temperature probes, capnography, etc.) are available and necessary to use to monitor patients within the scanner with the same level of care as in other sedation locations. MRI-compatible infusion pumps may be used with remote control devices able to direct the pumps from outside the scanner room; alternatively, medication extension tubing can carry sedatives to the patient from infusion pumps placed outside the MRI Zone IV room. The use of sedation increases the risk of an MRI-related safety issue; vigilance is necessary to prevent thermal injuries in sedated patients who may be unaware of these burns occurring during the procedure [3].

2. Drug Selection and Administration

Sedatives and Analgesics

Dexmedetomidine

Indications:

Dexmedetomidine (Precedex), a pharmacologically active dextroisomer of medetomidine, is a selective α-2 adrenergic receptor agonist. The food and drug administration (FDA) approved indications for dexmedetomidine are sedation of intubated and mechanically ventilated patients in the intensive care unit (ICU) and peri-procedural (or peri-operative) sedation

of non-intubated patients. Over time, usage has expanded to off-label uses, including treatment and prevention of delirium, adjunctive analgesia, therapy for insomnia in the ICU, and treatment of alcohol withdrawal [4]. Dexmedetomidine can markedly reduce the anesthetic requirements of inhaled and intravenous anesthetics. It can also decrease the dose of opioids required, perioperatively and postoperatively, in patients undergoing a variety of surgical procedures. This opioid-sparing effect of dexmedetomidine decreases opioid use and thereby reduces the risk of opioid-induced respiratory depression in bariatric patients or those with significant respiratory disease [5].

Mechanism of Action:

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist (selectivity ratio for α2: α1 is 1600:1). The sympatholytic effect of dexmedetomidine made it attractive to be used as a hypotensive drug during surgery because of decrease in heart rate (HR) and cardiac output with no decrease in stroke volume unless the plasma concentrates reaches above 5.1 μg/mL. The cardiovascular effects of dexmedetomidine begin with initial hypertension following the administration of a loading dose, due to the activation of α-2B receptors located on vascular smooth muscle, with subsequent hypotension and bradycardia due to centrally mediated decrease in sympathetic tone. Dexmedetomidine also has sedative, amnesic, anxiolytic, hypnotic, and analgesic effects with minimal changes in respiratory variables. Furthermore, it reduces postoperative nausea, vomiting, and shivering. It also reduces delirium in patients after cardiac surgery [6-7]. Receptors for α2 are found in platelets, the liver, pancreas, kidney, eye, and heart. From an anesthesiologist point of view, neuronal hyperpolarization is a key element in the mechanism of action of dexmedetomidine and is achieved by efflux of potassium and suppression of calcium entry. Loss of intracellular potassium and inhibition of calcium entry suppress neuronal firing and can inhibit signal transduction [8].

Administration:

Injection: may be administered IM or IV

- Intramuscular: IM injection (2.5 mcg/kg) of dexmedetomidine has been used for premedication.
- Intravenous: loading dose of 1 mcg/kg over 10-20 minutes followed by a maintenance infusion in the range of 0.2-0.7mcg/kg/hr. The rate of infusion can be increased or titrated up to 1.5 mcg/kg/hr.
  - **Spinal:** 0.1-0.2 mcg/kg.
  - **Epidural:** 1-2 mcg/kg.
  - **Peripheral nerve block:** 1 mcg/kg.
  - **Buccal:** 1-2 mcg/kg.
  - **Intranasal:** 1-2mcg/kg [9].

Side Effects:

The most frequently reported treatment-emergent adverse events that occurred with ≥2% frequency across the clinical studies were bradycardia, dry mouth, and hypotension.

According to the US manufacturer's prescribing information, clinically significant episodes of bradycardia and sinus arrest have been observed following the administration of dexmedetomidine to healthy volunteers with high vagal tone and following the administration of dexmedetomidine via different routes, including rapid intravenous or bolus administration [10].

Contraindications:

There are no absolute contraindications to the use of dexmedetomidine. However, it should be used cautiously in patients with bradycardia and hypotension as the medication may exacerbate these findings. Additionally, it should be used cautiously in patients with known heart failure as there is level B evidence showing dexmedetomidine can potentially exacerbate myocardial dysfunction [4].

Toxicity:

There have been reports of over dosage of dexmedetomidine, in which higher doses ranging from 10 to 60 times the recommended infusion dose. Hypotension, bradycardia, deep hypnosis, miosis and hypoglycemia can be expected in these patients.

Severity of side-effects of dexmedetomidine seems more related to the speed of injection and less to the actual dose administered by infusion.

At present, there is no chemical reversal or antidote for dexmedetomidine. Supportive care and close monitoring are the staples of treatment for overdose [11].

Midazolam

Indication:

Midazolam is a short-acting, water-soluble benzodiazepine that has anxiolytic, sedative, amnestic, and muscle relaxant effects [12].

Mechanism of Action:

It is a gamma-aminobutyric acid (GABA) agonist and functions by enhancing chloride conductance and subsequent hyperpolarization of the postsynaptic cell membrane, which leads to neurons that are more resistant to excitation [13]. Midazolam becomes more lipophilic at physiologic pHs, which facilitates its transit across the blood–brain barrier and is the primary reason for rapid onset of action in the central nervous system. Typically, onset of action after an oral dose of midazolam is 10–30 min compared with 3–5 min after an intravenous dose [14]. Rapid redistribution means midazolam has a short duration of action and elimination half-life—particularly advantageous properties for when continuous midazolam infusions are used [13]. Oral midazolam is commonly administered to alleviate distress in children. A single dose of intravenous midazolam (0.05 mg/kg) is regarded as sufficient sedation in oncology practice, providing either complete or partial amnesia for nearly all procedures [15].

Administration

Administration routes vary from

- **oral** (0.5–1.0 mg/kg—not to exceed 20 mg),
- **intramuscular** (0.1–0.2 mg/kg—not to exceed 10 mg),
- **intranasal** (0.1–0.2 mg/kg—not to exceed 10 mg),
- **intravenous** (0.05–0.15 mg/kg—not to exceed 6 mg)
- **rectal** (0.5–1.0 mg/kg) [16].

Side effects:

Midazolam causes dose-dependent respiratory depression that is markedly increased with concurrent opioid administration. Paradoxical reactions, such as hyperactivity and agitation have been reported with midazolam at a rate of 1.2–3.4% [17]. Medical professionals skilled in pediatric airway management should be readily available and the proceduralist should understand the potential need for ventilation assistance[15].

Toxicity:

Flumazenil is a benzodiazepine antagonist used to reverse somnolence and/ or respiratory depression caused by midazolam. Initial dosing is 0.01 mg/kg intravenously. Dosing can be repeated until adequate reversal of midazolam is noted, not to exceed a total dose of 1 mg [14].

Propofol

Indication

Propofol (2,6-disopropylphenol) was originally introduced into clinical practice in the 1980s, It is a potent, ultra-short-acting intravenous hypnotic agent associated with rapid progression in sedation levels, ultimately leading to general anesthesia. Propofol is easily titratable but has a notably narrow therapeutic window. Elimination is primarily via hepatic metabolism [18].

Mechanism of Action:

Propofol induces unconsciousness partly by GABA-A mediated inhibition of histamine (arousal-promoting neurotransmitter) release in the hypothalamus, inhibition of NMDA receptors, and modulation of calcium influx to inhibit postsynaptic neurons [19]. Elimination is primarily via hepatic metabolism, there is also extensive extra-hepatic elimination via the pulmonary and renal systems [20]**.** The elimination half-life ranges from 13 to 44 h [19]. Propofol has a fast onset of action (10–50 s) and a short distribution half-life (approximately 9 min in pediatric patients) [21]. The typical intravenous dose to induce general anesthesia is 1.5–2.5 mg/kg; higher dosing is often required for younger pediatric patients because of their higher volume of distribution, shorter elimination half-lives, and higher plasma clearance. Continuous infusions can be initiated to maintain sedation/anesthesia at 75–200 mCg/kg/min [16]. Propofol has advantages including antiemetic properties and a lower incidence of emergence delirium in children [21].

Side effects:

Disadvantages of propofol use include hypotension, which is commonly seen and is more pronounced in volume-depleted patients. In addition, ventilation is negatively impacted with dose-dependent hypoventilation, apnea, and airway obstruction [22]. Pain with injection affects up to 60% of patients and is often recalled by patients as a distressing event. Pain can be tempered by using an antecubital vein instead of a hand vein and by co-administering lidocaine, opioids, or ketamine [23]. Propofol has minimal to no analgesic properties and therefore should be combined with additional medications, such as short-acting opioids or ketamine, for brief painful procedures [18]. Concerns relating to the administration of propofol to patients with known food allergies (soy, egg) are prevalent in the medical community. As more children are diagnosed with food allergies, more of these individuals will invariably require procedures such as endoscopy for diagnostic and therapeutic purposes [24]. Despite a narrow therapeutic window, there are multiple reports of the safety of propofol in pediatric procedural sedation [25]. Utilization of propofol remains a subject of controversy between anesthesiologists and physicians in other specialties. Its use outside the OR by non-anesthesiologists has increased over the past years, with many professional societies making claims to the relative safety of propofol administration by non-anesthesia-trained providers despite the FDA warning on the package insert [26].

Ketamine

Ketamine is a phencyclidine derivative that achieves its function as an N-methyl-D-aspartate (NMDA) receptor antagonist at the dorsal horn of the spinal cord [27]. It induces dissociative amnesia and analgesia [14]. Administration routes are intravenous (1–2 mg/kg), intramuscular (2–10 mg/kg), oral (3–6 mg/kg), intranasal (2–4 mg/kg), rectal (5–10 mg/kg) [16]. Adverse reactions associated with ketamine include dreams, hallucinations, delirium, agitation, vomiting, increased salivation, and laryngospasm [28]**.** Clinically, ketamine is one of the more frequently used medications to facilitate short, painful procedures in the emergency department [29].

Fentanyl

Mechanism of Action:

Fentanyl is an opioid receptor agonist (mu, delta, and kappa) at pre- and postsynaptic sites in the central nervous system. It mimics endogenous peptide opioid ligands such as enkephalins, endorphins, and dynorphins [30]**.** At the molecular level, potassium conductance is enhanced. This causes axonal hyperpolarization and/or calcium channel inactivation, which leads to a decrease in neurotransmitter release [31].

Administration

Administration routes are

- **oral** (15–20 lg/kg),
- **intravenous** (0.5–2.0 lg/kg)
- **intramuscular** (50–100 lg/ kg)
- **intra-nasal** (0.5–2.0 lg/kg) [16]**.**

The use of oral transmucosal fentanyl citrate (OTFC) for painful diagnostic procedures in children is more frequently associated with vomiting and itching than is intravenous fentanyl **(32).** OTFC has a significant delayed onset of sedation (45 min), and no improvement in cooperation at induction compared with placebo was observed when used as a premedication prior to general anesthesia [32].

Toxicity

Naloxone is the reversal agent of choice for opioid-induced respiratory depression and apnea. Typical dosing starts at 1–2 lg/kg. Onset of action occurs within 1–2 min, and duration of action is around 45 min [14]. Fentanyl is often co-administered with midazolam for sedation [33].

Side effects:

Noted adverse events included apnea (0.2%), vomiting (5%), and mild oxygen desaturations (9%). Patients aged \6

years were more likely to develop adverse respiratory events[33].

Diazepam

Diazepam is an anxiolytic benzodiazepine, it is a fast-acting, long-lasting benzodiazepine commonly used to treat anxiety disorders and alcohol detoxification, acute recurrent seizures, severe muscle spasms, and spasticity associated with neurologic disorders [34]. Benzodiazepines exert their effects by facilitating the activity of gamma-aminobutyric acid (GABA) at various sites [35]. Diazepam is available in multiple formulations, including oral tablets: 2 to 10 mg orally 2 to 4 times a day, intramuscular injections (IM): 5 to 10 mg IM once 30 minutes prior to the procedure intravenous injections (IV): Usually less than 10 mg, but some patients require up to 20 mg IV, especially when narcotics are omitted , IV titration: The IV dose should be titrated to desired sedative response (e.g., slurring of speech) with slow administration immediately before the procedure, rectal gel: 0.2 mg/kg rectally, rounded upward to the next available dose. A 2.5 mg rectal dose may be given as a partial replacement if patients expel a portion of the initial dose [36]. Like most benzodiazepines, the adverse reactions of diazepam include CNS and respiratory depression, dependence, and benzodiazepine withdrawal syndrome [38]. Overdose in adults manifest as CNS depression and are very rarely fatal. In mild cases, lethargy, drowsiness, and confusion are common symptoms. In cases of severe overdose, symptoms manifest as ataxia, diminished reflexes, hypotonia, hypotension, respiratory depression, coma (rarely), and death (rarely) [37]**.** Treatment of benzodiazepine overdose involves protecting the airway, fluid resuscitation, and the use of flumazenil if indicated [38].

- **Intranasal administration variable techniques**

Nasal mucosa has been considered as a potential ad-ministration route to achieve faster and higher level of drug absorption because it is permeable to more com-pounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents [39]**.** Many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called “NASAYA KARMA” [40].

The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible and suitable for self-medication. The large surface area of the nasal mucosa affords a rapid onset of therapeutic effect, potential for direct-to central nervous system delivery, no first-pass metabolism, and non-invasiveness; all of which may maximize patient convenience, comfort, and compliance [41]. It is non-invasive, essentially painless, does not require sterile preparation, and is easily and readily administered by the patient or a physician, e.g., in an emergency setting. Furthermore, the nasal route may offer improved delivery for “non-Lipinski” drugs [42].

ADVANTAGES

1) Drug degradation that is observed in the gastrointestinal tract is absent.
2) Hepatic first pass metabolism is avoided.
3) Rapid drug absorption and quick onset of action can be achieved.
4) The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
5) The nasal bioavailability for smaller drug molecules is good.
6) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
7) Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
8) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
9) Drugs possessing poor stability in g.i.t. fluids are given by nasal route. 10) Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery [43].

3. NASAL DRUG DELIVERY SYSTEM

A. Liquid Nasal Formulations

Liquid preparations are the most widely used dosage forms for nasal administration of drugs. They are mainly based on aqueous state formulations. Their humidifying effect is convenient and useful, since many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. Microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water-based dosage forms because the required preservatives impair mucociliary function [44].

Instillation and rhinyle catheter

Catheters are used to deliver the drops to a specified region of nasal cavity easily. Place the formulation in the tube and kept tube one end was positioned in the nose, and the solution was delivered into the nasal cavity by blowing through the other end by mouth [45-46].

Compressed air nebulizers

Nebulizer is a device used to administer medication in the form of a mist inhaled into the lungs. The compressed air is filling into the device, so it is called compressed air nebulizers. The common technical principal for all nebulizers, is to either use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device [47-48].

Metered-dose pump sprays

Most of the pharmaceutical nasal preparations on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically, see nasal administration. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism. The three main types available for local effect are: antihistamines, corticosteroids, and topical decongestants Metered- dose pump sprays include the container, the pump with the valve and the actuator [49].

B. Powder Dosage Forms

Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation. Compared to solutions, the administration of powders could result in a pro-longed contact with the nasal mucosa.

Insufflators

Insufflators are the devices to deliver the drug substance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient de aggregation of the particles and results in a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules [50].

Dry powder inhaler

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales[51].

These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough [52].

C. Pressurized MDIs

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. Other medications less commonly used but also administered by MDI are mast cell stabilizers, such as (cromoglicate or nedocromil) [53]. The advantages of MDIs are their portability and small size, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use [54]. Propellants in MDIs typically make up more than 99 % of the delivered dose. Actuation of the device releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are then inhaled [55].

D. Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there was not much interest in this system. The advantages of a nasal gel include the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption [56]. The deposition of the gel in the nasal cavity depends on the mode of administration, because due to its viscosity the formulation has poor spreading abilities. Without special application techniques it only occupies a narrow distribution area in the nasal cavity, where it is placed directly. Recently, the first nasal gel containing Vitamin B12 for systemic medication has entered the market [56].

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