RESEARCH ARTICLE

Anesthetic Agents in Pediatric Patients: A Comprehensive Review of Pharmacological Considerations in Clinical Practice

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Abstract

Pediatric anesthesia is a specialized subset of general anesthesia that differs in several important ways from adult anesthesia. This field focuses on the routine care of neonates, infants, children and adolescents and includes a thorough preoperative evaluation, patient and parent preparation, induction of anesthesia, maintenance of anesthesia and emergence from anesthesia

There are important differences pharmacodynamics and pharmacokinetics that must be considered and a thorough understanding of the differences between anesthesia in children and adults. In this review these important differences between pediatric anesthesia and adult anesthesia are discussed. The present investigation also describes relevant pharmacology and the techniques required for the preparation, intubation, induction of anesthesia, and maintenance of anesthesia in pediatric patients. Finally, newer drug considerations in the pediatric population, such as magnesium sulfate as an adjuvant drug and albuterol for children undergoing tonsillectomy, are reviewed.

Keywords: pediatric, pediatric pharmacology, pediatric anesthesia

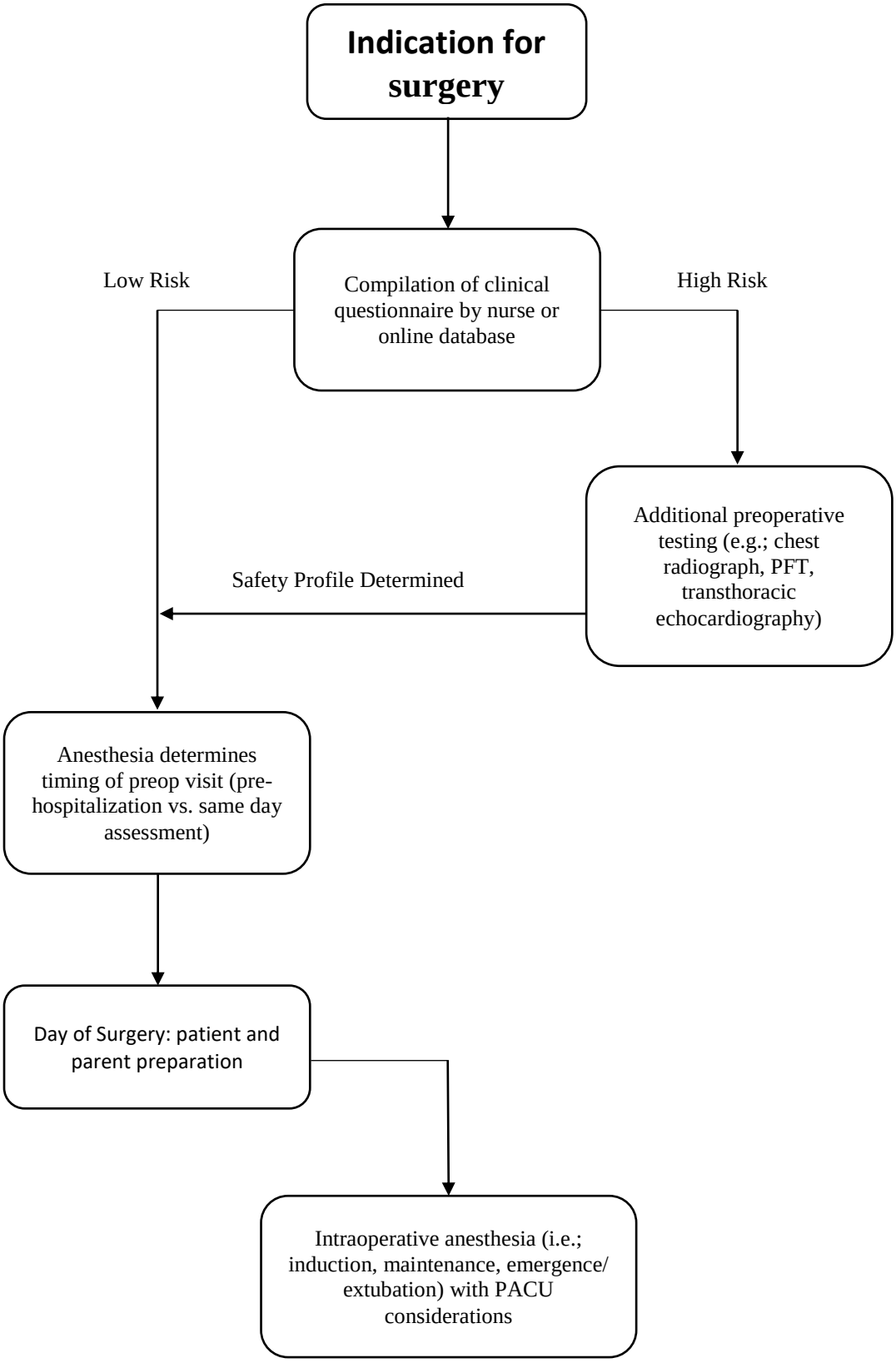
1.1 Introduction

Pediatric anesthesia is a unique specialty of anesthesia that focuses on neonates, infants, children, and adolescents, and its practice differs in several important ways from anesthesia in adults. Overall morbidity and mortality surrounding anesthesia are higher in infants compared to adults (1,3). A thorough understanding of the differences between children and adult anesthesia is important for anesthesiologists managing pediatric patients.

Because of the small number of clinical studies reviewing the suggested dosing of anesthetic agents in pediatric patients, anesthesiologists often have limited evidence to draw from when calculating dosing for this group of patients (3). Even within this age group, anesthesiologists must be cognizant of intra-populational variation between neonates, infants, children, and adolescents. Due to wide distributions in age and weight, the practice of pediatric anesthesia is often without a “familiar” or “usual” dose. This contributes to the observation that life-threatening drug errors are more common in children compared to adults (4).

Anesthesia is a stressful experience for pediatric patients and their parents, and preoperative anxiety regarding the duration of and recovery from anesthesia may increase levels of stress hormones and hinder postoperative wound healing in patients (5,6). A unique consideration in pediatric patients is the fact that informed consent for anesthesia is obtained after parents have given consent for surgical intervention. Oftentimes patients and parents meet the anesthesiologist on the day of the procedure, and this may provide inadequate time to explore patient and parental concerns for anesthesia. Also, this hinders the ability of the anesthesiologist to establish rapport and asses adequate understanding of the information provided (7,8). According to one survey of patients and parents undergoing surgical procedures, the most frequently requested information included the postoperative regimen, recovery from anesthesia, postoperative pain management, and duration of anesthesia. Patients and parents preferred that information be given in written form and on the days prior to surgery (8). See **Figure 1**.

Figure 1. Flow chart of pediatric anesthetic care



1.2 Pediatric pharmacology considerations

Pharmacokinetic Considerations

Pediatric pharmacokinetics vary with age and are significantly different than those of adults, contributing to the difficulties of pediatric anesthesia. Pharmacokinetic considerations are typically broken down into drug absorption, distribution, metabolism, and excretion. Absorption is the rate at which a drug enters the bloodstream from the site of administration. Important considerations of absorption are the rate and extent of absorption. These parameters affect the onset of action and the dosing of a drug (29). Volatile anesthetics are introduced to the body via inhalation into the alveoli of the lungs, where they then enter the capillary beds. This uptake is quicker in neonates and young children due to their elevated alveolar ventilation and relatively lower functional residual capacity (30,31). Drugs introduced to pediatric patients enterally are typically absorbed slower than in adults due to children's smaller gastrointestinal tracts, higher gastric pH in early life, delayed gastric emptying, immaturity of secretions, and fewer protein transporters (29,32).

Distribution refers to the drug delivery to target tissues throughout the body. Factors that affect distribution include rate of blood flow, drug molecular size and solubility, and plasma protein and tissue binding of the drug. Pediatric patients typically have lower plasma protein concentrations, lower body fat percentage, and higher water body composition, altering the rate of distribution of drugs (29). Lower plasma protein levels results in more free active drug molecules, and lower body fat percentage increases drug concentration in the bloodstream due to decreased volume for drug distribution (33). Conversely, greater total body water percentage increases volume of distribution. The immature blood-brain barrier of neonates also affects the distribution of drugs and contributes to the increased sensitivity of neonates to anesthetic agents (34).

Metabolism is the breakdown of a drug into smaller compounds. Most metabolism of anesthetic agents is done in the liver, although other sites of drug transformation include the kidney, intestine, lung, and skin (29). Hepatic metabolism is primarily completed by the cytochrome P450 system. At the cellular level, these enzymes are located within the endoplasmic reticulum and mitochondrial membranes. Drugs can exist in prodrug form, in which metabolism results in the biologically active form, although most drugs are inactivated by metabolism. Neonates have significantly reduced hepatic enzyme levels and hepatic blood flow, resulting in drugs existing in a metabolically active state for longer than in adult patients.

Drug metabolites are then excreted, or removed from the body, in urine, feces, or exhaled air. Metabolites from the liver are excreted into bile, which moves from the alimentary tract to the intestines where they can then be excreted in feces. Some metabolites are reabsorbed from the gastrointestinal tract to be ultimately eliminated via the kidneys in urine. Slower gastrointestinal movement of children increases time for reabsorption of metabolites from the intestines. The kidneys do not become near fully functional until the 20^{th} week of life and have reduced glomerular filtration rates, causing metabolites to take longer to be excreted (34).

Potential Medication Errors

Medication errors are a noteworthy risk to children undergoing anesthesia. These medication errors are often preventable, and ongoing efforts aim to understand and

reduce the frequency of errors causing potential harm to pediatric anesthesia patients. Evidence-based practices to reduce errors include careful reading of legibly labeled syringes prior to administration, formal organization of the drawers and workspaces, two-person checks before administration, and careful measurement of patient weight, as pediatric dosing is often weight dependent (35). Use of medication safety checklists have also been demonstrated to reduce medication errors in the perioperative period (36).

The Society for Pediatric Anesthesia created the Wake Up Safe quality improvement initiative in 2016, which analyzed 6 years' worth of medication error events in pediatric anesthesia (37). The investigation included data from 32 institutions on 2087 adverse events during 2,316,635 anesthetic procedures. The initiative aimed to describe and characterize common patterns of errors to target for prevention of adverse events. The study classified medication errors by:

> (1) medication category; (2) error type by phase of administration: prescribing, preparation, or administration; (3) bolus or infusion error; (4) provider type and level of training; (5) harm as defined by the National Coordinating Council for Medication Error Reporting and Prevention; and (6) perceived preventability" (37).

The most common error reported was accidental administration of the wrong dose, followed by swapping syringes resulting in administration of the wrong agent. More than half of the analyzed errors resulted in patient harm, with 5% of events ultimately requiring a life sustaining intervention. Among all errors in the study 97% were deemed certainly or likely preventable (37). The study suggested strategies such as barcoding, prefilled syringes, and two-person checking of medications to reduce future medication errors

A retrospective analysis of all anesthesia patients at Boston Children's Hospital system from January 2008 to June 2016, also found that incorrect dose and incorrect medication administration were the most common error in anesthetic cases (38). The study also found that after the introduction of the 2009 Medication Safety Program, the incidence of errors declined, with a logistic regression demonstrating a 13% reduction per year in the odds of a medication error throughout the time of the study. This analysis confirms the need for clinicians to be aware of the medication errors that are possible, and that formalized medication safety programs help to prevent overall adverse events for pediatric patients undergo anesthesia.

1.3 Anesthetics in the pediatric population

Preoperative evaluation, a first step in safe anesthesia care, has evolved from surveying admitted patients in the hospital the night before surgery to a largely outpatient exam conducted either via nurse over the telephone or via online survey. The goals of preoperative testing are to procure medical information that may indicate additional preoperative testing prior to the day of surgery and establish patient-provider rapport, outline anesthetic risks and discuss the comprehensive anesthesia plan including any postoperative analgesia (48). The final result of proper preoperative care is to optimize medical conditions while minimizing morbidity and mortality. As part of preoperative examination, it is the anesthesiologist responsibility to evaluate medications, allergies, and past medical history. Prescription medications are reviewed and adjusted on an individual basis. Chronic pain patients are often

encouraged to continue non-NSAID analgesic regimens perioperatively so as to optimize postoperative pain control (49,50). The withholding of any psychiatric drugs must also be decided on an individual basis using complex cost-benefit analysis. Food allergies should be given appropriate attention as well given that they often correlate with anesthesia agent reactions (e.g.; peanut allergies correlate with propofol, seafood allergies correlate with contrast dyes, immunization allergies correlate with topical thrombotic agents) (50). Medical history evaluation in the pediatric population may typically include obstructive sleep apnea syndrome, bronchopulmonary dysplasia, difficult airway, upper respiratory tract infection, diabetes, seizure disorders and sickle cell disease (51). Moreover, special consideration in the pediatric population must be given to those with psychiatric or developmental past medical histories such as autism or depression (52). The perioperative setting can be a fearful time for the child and their family and even more so with pediatric patients on the autism spectrum. Therefore, anesthesiologists must take time to establish strong patient-provider rapport through clear setting of expectations and perioperative timelines (51). The final component of the preoperative visit is the physical exam which is focused on three systems: cardiovascular, pulmonary and neurologic. Special consideration is given to any loose teeth or congenital anomalies (53). Moreover, vital signs are important in the planning of sedation agents (midazolam 0.5 mg/kg, ketamine 3-8 mg/kg), induction and maintenance agent dosing.

Additional steps of pediatric anesthesia include induction and maintenance of anesthesia intraoperatively. In this regard, the majority of pediatric patients do not start out with intravenous access and different than typical adult inductions, mask inhalational anesthesia with sevoflurane is largely the technique of choice. Therefore, the anesthesiologist must prepare for induction by readying warming devices and any emergency drugs (e.g.; intramuscular succhinylcholine and atropine if the pediatric patient developed bronchospasm resulting in inability to ventilate without iv access). The parent may be allowed to be present during induction after making it clear that this period may induce stress for the parent. There are a variety of pharmacologic agents available for pediatric sedation/ anesthesia that can be summarized broadly into inhaled anesthetics (e.g., sevoflurane the least pungent inhalational agent, IV administered anesthetics, e.g. propofol, opioids, and neuromuscular blocking agents (**Table 1**). Inhalation mask induction is the standard of care with pediatric populations because needles and injections can traumatize children and negatively influence the postoperative pain course (54). Inhaled anesthetics include sevoflurane, and to a far less incidence, isoflurane, desflurane, and halothane with augmentation with 70 % nitrous oxide (NO) related to the increased rate of induction with supplemental NO (55). However, there has been a change in recent years away from NO related to its association with nausea and vomiting. Conversely, IV induction is preferred for emergency patients at risk for cardiovascular instability during induction and those with contraindications to inhaled anesthetics. IV agents include as midazolam, fentanyl, ketamine, dexmedetomidine, etomidate and propofol. Case reports show increased favorability of *ketofol* (combination of propofol and ketamine) for short and painful pediatric procedures (56,57). Of note, recent revelations in the medical literature demonstrate improved safety profile when limiting sedation plans to single agent pharmacy rather than multi-drug regimens. Anesthesia maintenance is

predominately performed utilizing volatile inhaled anesthetics but can also use IV agents such as propofol such as in the setting of a patient with a family history of malignant hyperthermia. Other pediatric maintenance considerations include neuromuscular blocking agents when required, opioids to augment other anesthetic agents (see next section) and antiemetics (3).

Emergence and extubation with appropriate PACU care are the final steps of pediatric anesthesia. The goal of this period is to achieve smooth, controlled emergence from anesthesia without oxygen desaturation, coughing, vomiting, laryngospasm or bronchospasm. Typically it is standard practice to ensure spontaneous and regular respirations with conjugate eye/ pain grimacing to oropharyngeal suctioning before extubating (58). Of special interest in the immediate postoperative period is *emergence delirium*, a complex of perceptual disturbances and psychomotor agitation. Frequency of pediatric emergence delirium is reported to be between 10 and 80 % (59). Recent case reports have validated pre-medication of single dose dexmedetomidine (2 µg/ kg), a selective alpha-2 agonist, as a highly effective modality of limiting emergence delirium (60,61).

The role of opioid medications in intraoperative anesthesia care of children and infants has been emphasized as an irreplaceable component of pain control and a primary factor contributing to perioperative complications (62). On recent recommendation, the society of pediatric anesthesia made the following suggestions regarding opioid use. A) opioid prescriptions should be limited to that required for the expected period of severe pain after surgery. B) Acetaminophen use should be considered as an adjunct to patient controlled anesthesia (PCA) for perioperative pain control. C) PCA opioid delivery is safe, efficacious and correlated with higher patient satisfaction when compared with intermittent IV opioid anesthesia. D) regular pain assessments should be part of the perioperative treatment of pediatric patients receiving opioid medications. Each assessment should consider unique circumstances of the child's psychological state (63). These up to date guidelines supported appropriate administration of perioperative opioids on an individual basis.

The influence of general anesthetics on developing brains in pediatric anesthesia have long been debated and researched. Early animal studies (ranging from roundworms to nonhuman primates) found that NMDA antagonists and GABA agonists have immediate neuroanatomical consequences in addition to long term- perhaps permanent- functional neurotoxic effects. In 2016 the FDA warned that general anesthesia and sedation drugs used in children < 3 years old undergoing more than 3 hours of anesthesia or repeated short anesthesia "may affects children brain development" (64,65). In contrast, the PANDA study in 2019 revealed that brief single exposure to general anesthesia was not associated with worse neurodevelopment outcomes (66). Overall, the consensus on the safety profile of pediatric general anesthesia is still out, and undoubtedly demanding of further investigation.

Table 1. Summary of induction agents used in pediatric anesthesia.

Anesthetic Induction Agents	**Dose**	
Nitric Oxide (NO)	70 % by volume	Volatile Inhaled Anesthetic Agents
Sevoflurane	2.2 MAC	
Desflurane	8.0 MAC	
Isoflurane	1.5 MAC	
Halothane	1.0 MAC	
Atropine	0.02 mg/ kg	IV Administered Anesthetic Agents
Propofol	3.0 mg/ kg	
Dexmedetomidine	0.5 – 2.0 µg/ kg	
IV Ketamine	2.0 mg/ kg	
IM Ketamine	5.0 – 10.0 mg/ kg	
Fentanyl	1.0 – 2.0 µg/ kg	IV Administered Opioids
Remifentanil	1.0 – 2.0 µg/ kg	
Lidocaine	1.0 mg/ kg	
IV Succinylcholine	1.0 – 1.5 mg/ kg	NMBA

*All MAC values for volatile inhaled anesthetics are provided for MAC of 1.0 (anesthetic concentration at which 50 % of patients show motor inhibition) in 10-year-old patient mixed with 100% room air.

1.4 Newer drug considerations in the pediatric population

Magnesium

Magnesium is an important element in all organisms. It plays several rolls including acting as a cofactor in over 300 enzyme systems, modulating transmembrane ion transport, and participating in energy metabolism. Because of its diverse physiologic actions, magnesium has become a highly valued element in the perioperative setting and in pediatric anesthesia including sedation, analgesia, muscle relaxation, and organ protection (67). The pharmaceutical form of Mg is magnesium sulfate heptahydrate. One can achieve immediate onset of action through IV with a peak effect in 10 minutes and duration of 30 minutes. When using the IV form, it is important to monitor the neuromuscular, respiratory, and hemodynamics status of the patient (67).

The side effects of $MgSO_4$ vary, are dose dependent, and may occur at doses above 3-4 mg/dl. Reaching this dose can lead to nausea, vomiting, dizziness, headache, lethargy, hyporeflexia, hypotension, and 1st degree AV block. As doses reach above 10-12 mg/dl, symptoms become severe. This includes flaccid palsy, coma, respiratory depression, apnea, complete AV block, and even asystole. Considering this, treatment of Mg toxicity includes supportive care with hemodynamic and respiratory support. Calcium gluconate and calcium chloride can be used as an antidote. Furthermore,

furosemide, hydration, and hemodialysis can be used to reduce Mg levels (67).

Mg has anticonvulsant and sedating effects. Mg can reduce the minimal alveolar concentration requirement of sevoflurane by 50%. It can also reduce the propofol induction dose. In pediatric cases, particularly adenotonsillectomies, IV $MgSO_4$ has been shown to reduce emergence agitation and shivering in the recovery period from anesthesia. This is important as both of these phenomena are related to increased seizure activity associated with Sevoflurane. Lastly, $MgSO_4$ has been shown to successfully treat refractory epileptic seizures thus this may be a viable option to reduce perioperative seizures (67).

Magnesium can alter pain signaling and perception through inhibition of NMDA receptors and calcium channels in the brain and spinal cord. In the pediatric population, $MgSO_4$ may reduce pain in locoregional anesthesia. For instance, the addition of peritonsillar $MgSO_4$ with local anesthesthetics decreases pain in tonsillectomies. Furthermore, it has been shown that gauze instilled with $MgSO_4$ can reduce pain in these types of surgeries if placed in the tonsillar fossa for 3 minutes. Moreover, epidural $MgSO_4$ can be used as an adjuvant to caudal blockade to improve and lengthen analgesia of local anesthetics. Finally, several studies have shown that intrathecal $MgSO_4$ decreases analgesic consumption in regards to open heart surgery and shorten postoperative extubation time (67).

Magnesium has spasmolytic attributes and induces muscle relaxation. This is achieved by blocking presynaptic acetylcholine release and increasing the threshold for postsynaptic depolarization. $MgSO_4$ decreases onset time, dose needed for intubation, and over all requirement of nondepolarizing muscle relaxants such as aminosteroids and bencylisoquinolines while prolonging duration of action. In cases of patients with cerebral palsy, $MgSO_4$ adjuvant can prevent worsening of spasticity in perioperative stress while reducing the requirement of non-depolarizing blockers. In the pediatric population, $MgSO_4$ appeared to decrease postextubation laryngospasm in adenotonsillectomies through IV form and peritonsillectomy local infiltration. Furthermore, magnesium reduces bronchospasm and bronchial hyperresponsiveness. It has been shown that IV forms of $MgSO_4$ with inhaled bronchodilators and systemic steroids yield impressive results. In cases of high severity, beginning therapy early, and with high doses has reduced the need for ventilatory support, pediatric intensive care unit stay, and cost. Finally, adjuvant magnesium has proven effective in treatment of tetanus induced muscle spasm- a potentially life threatening event in terms of laryngeal muscle involvement (67).

Hypomagnesemia is associated with cardiac surgery with cardiopulmonary bypass in the pediatric population. This predisposes patients to arrhythmias, a risk factor for late morbidity and mortality. It has been shown that when $MgSO_4$ is given during rewarming and weaning from cardiopulmonary bypass, it reduces the risk of ectopic junctional tachycardia (the most common arrhythmia). Further expanding on its antiarrhythmic properties, $MgSO_4$ can stabilize cell membranes in Long QT syndrome and digoxin-induced ventricular arrhythmias (67). The vasodilating effect of magnesium can be beneficial in patients with neonatal persistent pulmonary hypertension. It involves significant increase in pulmonary artery pressure leading to a right to left shunt leading to persistent hypoxemia. $MgSO_4$ has shown benefit in these cases when it is refractory to nitric oxide and mechanical

ventilation as it can dilate the pulmonary artery(67).

For anesthesiologists, management of patients during a pheochromocytoma resection can be challenging. Magnesium can help facilitate hemodynamic treatment during these cases through several properties. This includes preventing the release of catecholamines from the adrenal medulla, directly block adrenergic receptors, acting as an antiarrhythmic, and arterial vasodilation (mixed vasodilators such as nitroprusside and nitroglycerin can cause harmful venous dilation especially in patients with low volume). Over all, adjuvant $MgSO_4$ decreases need for alpha-beta blockers and other vasodilators perioperatively (67).

Magnesium is also vital for organ protection. This is attributed to its physiology including maintaining ATP levels via ATP-Mg complex, blocking influx of intracellular calcium, inhibiting cellular edema, and reducing free radical production. Lastly, there is an increase in cytokines with hypomagnesemia thus $MgSO_4$ may help with reduction in inflammation (67). Magnesium has been successful in preventing (antenatal maternal administration in preterm birth) and treatment (postnatal newborn administration) of hypoxic ischemic encephalopathy. Prior clinical trials have shown effective treatment in short term immediate outcomes including lethargy, seizures, and hypotonia/hyporeflexia (67). **See Table 2**.

Table 2: Magnesium Sulfate Pharmacologic Effects versus Side Effect Profile:

Drug: Magnesium	
Available Routes:	
-IV	- Intrathecal
-Peritonsillar local form	- Nebulization
-Caudal	
Pertinent Effects:	
-Reduction of CNS activity (anti-seizure and sedation)	- Reduction of Pain
-Apposition of effect of sympathetic nervous system	- Dilation of Arteries
-Inhibition of uterine contractions	- Mitigation of arrhythmias
-Relaxation of bronchial smooth muscle	
Pertinent Side Effects:	
-Reduction in CNS activity	- Cardiac Blockade (1^{st} degree – Complete)
-Decrease in respiratory effort	- Reduction in blood pressure

Albuterol

Albuterol Sulfate can be beneficial in pediatric anesthesia especially in children undergoing tonsillectomies, a common surgery. It primarily works as a Beta 2 adrenergic agonist and has historically been used for bronchodilation and prevention of increasing respiratory resistance during intubation. The capabilities of albuterol sulfate have been further expanded through a randomized, triple-blind, placebo-controlled trial in Australia. It had shown that pre-administering inhaled albuterol (total of 200µg) reduced the likelihood of cough, laryngospasm, and oxygen desaturation in children up to age 8 undergoing tonsillectomy with or without adenoidectomy. In fact, it was found that children who did not receive albuterol prior to their tonsillectomy had 2.5 greater odds of having a respiratory adverse event compared to children receiving albuterol prior to

surgery. Further results showed that children with moderate to severe obstructive sleep apnea had the most pronounced benefit (68). It should be noted that beta 2 agonists, including terbutaline, are extremely effective in relaxing smooth muscle but also cause a dose-dependent decrease in potassium levels. A high index of suspicion for patients with identified arrythmias intraoperatively or postoperatively might well lead to the diagnosis of hypokalemia mediated by the use of beta 2 agonists.

Clonidine

Clonidine, a selective alpha 2 agonist, has many indications in the pediatric population and can be useful in the operative and perioperative setting. It can treat withdrawal symptoms from opioids and benzodiazepines, prevent postoperative emergent agitation, facilitate analgesia, act as an anxiolytic, facilitate sedation, reduce shivering, and decrease nausea and vomiting (69).

Clonidine can be administered orally, through nasal spray, rectally, and IV. Oral administration is associated with quick absorption with peak plasma levels within 60-90 minute. However, bioavailability through this route is around 85% with a half-life near 12 hours thus making it difficult for dose down-titration. The IV form has the most predictable bioavailability and also is the most easily dose-adjustable (69).

Clonidine can be useful in managing withdrawal symptoms and sedation in the pediatric intensive care unit (PICU). In the PICU, it is common to combine opioids and other analgesics with sedatives such as midazolam. However, this carries an inherent risk of tolerance, withdrawal, hemodynamic depression, and respiratory depression. Knowing this, Clonidine may be a valuable alternative to benzodiazepines. In the safety profile, efficacy, and equivalence in pediatric intensive care sedation study, clonidine was proven to be superior to midazolam when both were given in conjunction with morphine. Clonidine was more cost effective with fewer side effects compared to midazolam. However, neither combination had yielded satisfactory sedation. In the ICU setting, there is potential for the use of clonidine (69).

Clonidine has been shown to have utility in mitigating emergence agitation. This is a phenomenon that is secondary to general anesthesia and described as involuntary physical over activity, crying, moaning, restlessness, delirium, and hallucinations. This can lead to complications such as self-harm, accidental removal of surgical dressings, and disruption in surgical lines and drains. In a Cochrane systematic review, sevoflurane was compared with other general anesthetics, with or without pharmacological or non-pharmacological adjuvants to observe their capability to avert emergence agitation. This included a total of 158 trials with 14,045 patients. The results showed that propofol, alpha 2 agonist (clonidine and dexmedetomidine), ketamine, and opioids reduced emergence agitation. Nine other studies in a Meta-analysis further supported this (RR 0.45, 95% CI .31-0.66) (69).

In the PREVENT AGITATION Trial, 379 children (1-5 years old) were given either 3 µg/kg or saline 20 minutes prior to completion of surgery. It was shown that 25% of the clonidine versus 47% of placebo groups experience one or more episodes of postoperative agitation with no hemodynamic side effects reported. Effects were significant in boys. Through this trial, clonidine had reduced postoperative opioid consumption and prolonged time to first analgesic administration. Lastly, clonidine reduced postoperative nausea and vomiting. In the literature, intraoperative doses of clonidine ranges from 1 to 3 µg/kg with benefits being more prominent with higher

doses (69). It should be noted that dexmedetomidine is an even more selective alpha 2 agonist with similar effects and side effect profile. Both agents have also shown prolonged beneficial effects when added to regionally local anesthetic nerve blocks.

In some small RCTs including children from age 1 to 10 with a sample size of 60 to 90, clonidine (1-3 µg/kg) was given to study the impact on prolonging duration of action of caudal epidural nerve blocks. It was found that clonidine as an adjuvant vs saline, fentanyl or midazolam, increased the time to first rescue analgesic, decreased pain score, and lead to fewer patients requiring analgesic medication in the first postoperative day (69). **See Table 3**.

Table 3: Clonidine administration route, receptors, effect, and side effect profile

Drug	Available Routes	Receptors	Pertinent Effects	Pertinent Side Effects
Clonidine	-IV -Oral (tablet, transmucosal, liquid form) -Intranasal form -Caudal -Oral -Epidural -Skin patch	-Alpha 1A, 1B,1D	-Blood vessel constriction -Raise in blood pressure	-Decreased heart rate -Decreased blood pressure (Dose of <1 ng/ml) -Increased blood pressure (Dose of >2mg/ml
		-Alpha 2A	-Sedation	
		-Alpha-2B	-Blood vessel constriction	
		-Alpha 2C	-Control of sympathetic nervous system neurotransmitters	
		Imidazole Receptors	Decrease in blood pressure	

1.6 Summary

Pediatric anesthesia has important and distinguishable differences from adult anesthesia. Furthermore, and sometimes more so than in adults, anesthesia is a stressful experience for pediatric patients and their parents, and anxiety related to anesthesia may increase levels of stress hormones and hinder postoperative wound healing in patients. One major concern for conducting anesthesia in pediatric patients is medication errors. Therefore, it is important that anesthesiologists practice evidence-based guidelines s to reduce errors. These practices include careful reading of legibly labeled syringes prior to administration, formal organization of the drawers and workspaces, two-person checks before administration, and careful measurement of patient weight. There are also some newer promising drugs that can be used in anesthesia for pediatric populations including magnesium, albuterol, and clonidine that show promise for making the pediatric patient more comfortable and the overall experience of anesthesia for the patient and family less stressful.

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