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**Neurotoxic Effects of General Anesthesia on the Developing Brain and the Use of Spinal
Anesthesia as an Alternative Approach for the Neonate and Infant Undergoing
Genitourinary Surgery**

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Abstract

Spinal anesthesia (SA) in the child under two years old is an excellent option when undergoing short genitourinary procedures. The use of SA in this patient population can avoid the potential deleterious neurocognitive effects on the developing brain that general anesthesia (GA) poses. A comprehensive literature review was conducted via retrospective case study, case control study, integrated review, and prospective study. The objective of this literature review is to examine the potential long-term neurotoxic effects of GA in the infant, as well as the benefits of SA. GA in the younger population has been shown to produce lower gray matter density seen on magnetic resonance imaging, altered listening comprehension, and an increased risk of developing a learning disability later in childhood. Success of SA was defined as the absence of subsequent conversion to GA in multiple studies reviewed. Use of SA in this vulnerable population, as opposed to general anesthesia, resulted in better maintenance of hemodynamics, less perioperative opioid use, and a shorter post-anesthesia recovery stay.

Keywords: spinal anesthesia (SA), pediatrics, neurotoxicity, urologic surgery, general anesthesia (GA), fetus, neonate, neuroapoptosis

Neurotoxic Effects of General Anesthesia on the Developing Brain and the Use of Spinal Anesthesia as an Alternative Approach for the Neonate and Infant Undergoing Genitourinary Surgery

Children who must undergo surgical procedures with anesthesia are exposed to a multitude of stressors capable of interfering with normal brain development during the perioperative period. Pain, stress, inflammation, hypoxia, and ischemia have been shown to adversely affect the immature central nervous system (Cote et al., 2013). Findings from animal studies have indicated that sedatives and anesthetics may undesirably influence brain development by triggering structural and functional abnormalities. These findings have led to an extensive amount of work that has aimed to define this phenomenon, explore theories on the mechanism to which this occurs, and provide potential protective strategies.

Interest in the effect of anesthetics on the pediatric population did not elicit widespread interest until 2016 when the United States Food and Drug Administration (FDA) issued a warning that stated repeated and/or prolonged exposure of general anesthetic agents in children younger than 3 years of age could negatively affect brain development later in life. The potential consequences of GA on the developing brain have led to resurgence in the utilization of SA in the appropriately selected patient population, procedure, and surgical duration. Genitourinary surgery is often elective in nature, short in duration, and limited to the pelvis making SA a suitable option for infants undergoing these procedures. This anesthetic approach also avoids introducing GA to the immature, developing brain and the potential neurotoxic effects that may come with it.

Background

Normal Brain Development in the Fetus and Neonate

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The nervous system is anatomically complete at birth, but functionally it remains immature as the brain continues to undergo myelination and synaptogenesis. The rate of brain growth is different when compared to the growth rate of other body systems in the neonate. The brain has two growth spurts, neuronal cell amplification between 15- and 20-weeks of gestation, and glial cell multiplication starting at 25-weeks and continuing to the second year of life (Cote et al., 2013). Neuronal cell myelination progresses until the third year of life (Cote et al., 2013).

The review by Andropoulos (2017) summarized the rapid brain growth and development in the fetus and neonate. Neurogenesis, or the process by which new neurons are formed in the brain, begins in the early weeks of gestation. The migration of neurons from the germinal matrix and subventricular zone to the developing cortical tissue occurs between 12- and 20-weeks of gestation. After migration, neuroapoptosis, also known as programmed cell death, occurs at an elevated rate from 24 weeks of gestation to four weeks following birth. Infants within this age range have 50% more neuronal synapses than the adult (Andropoulos, 2017).

Neuroapoptosis and synaptogenesis in the second and third trimester fetus reaches its peak during this time, then slows as the fetus nears term. Thus, the effects of anesthetic agents on synaptogenesis and neuroapoptosis render the fetal brain particularly sensitive to this class of drugs (Andropoulos, 2017). Recent controversies concerning the potential adverse effects of GA on the developing brain show just how delicate this organ is and how its growth may be adversely affected by anesthetic agents and other sedatives.

Effects of Anesthetics and Sedatives on the Developing Brain

The first few years following birth pose a critical period of development for many regions within the brain. Gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors play critical roles in the regulation of neuronal maturation and programmed cell death

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(Cote et al., 2013). During normal brain development, GABA guides cell proliferation, neuroblast migration, and dendritic maturation. Stimulation of the NMDA receptor fosters the survival and subsequent maturation of neurons. Anesthetic agents considered to be GABA agonists include volatile gases, propofol and benzodiazepines, while NMDA antagonists include nitrous oxide and ketamine (Andropoulos, 2017).

The most widely studied deleterious consequence of exposure to sedatives and/or anesthetics is neuronal apoptosis (Rosenblatt et al., 2019). In the developing brain, neuronal apoptosis eliminates 50 to 70% of neurons and is a natural process that only affects a small number of cells (Cote et al., 2013). Exposure of sedatives and anesthetics to the mammalian brain, even for a brief period, dramatically increases the number of apoptotic neurons (Cote et al., 2013).

Other Potential Mechanisms for Neurotoxicity

The exact mechanisms that trigger negative responses to anesthetic agents and sedatives in the immature mammalian brain remains unresolved. Cote et al. (2013) explains the possible mechanisms for neurotoxicity following the administration of anesthetics and sedatives. The current hypothesis is that anesthetics and sedatives interrupt normal GABA and NMDA receptor activity, which are the targets in achieving unconsciousness, amnesia, and immobility. Some have also suggested that the administration of GABA receptor agonists and/or NMDA receptor antagonists may cause abnormal neuronal inhibition during a vulnerable period of brain development. It is thought that this process triggers cell death in susceptible neurons, which then leads to neuronal impairment and decreased neuronal density in adulthood (Cote et al., 2013).

Pharmacologic Considerations in the Neonate and Infant

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Immature organ systems are responsible for the pharmacological differences that exist between pediatric patients and adults. Physiologic characteristics in this population that modify pharmacokinetic and pharmacodynamic activity include differences in total body water (TBW) composition, reduced protein binding, immaturity of the blood-brain barrier, greater proportion of blood flow to vessel rich organs, and immature receptor responses (Nagelhout & Elisha, 2018). The following sub-sections discuss some of these differences that are seen within this patient population.

Body Composition

Preterm and term infants have a much greater proportion of TBW when compared to older children and adults (Cote et al., 2013). Due to a dilutional effect, lower plasma concentrations occur rapidly after the administration of water-soluble drugs. The net effect of water-soluble medications is a greater volume of distribution in infants, which ultimately requires an increase in weight-based dosing to achieve the desired target serum concentration and clinical response of the drug (Cote et al., 2013). Conversely, lipid-soluble drugs require a decrease in dosing per body weight as infants have less fat and muscle when compared to adults. Neonates tend to be more sensitive to the neurologic, respiratory, and circulatory effects of many medications and therefore tend to still be responsive to both water-soluble and lipid-soluble drugs at lower blood concentrations (Nagelhout & Elisha, 2018).

Protein Binding

The plasma protein binding of many drugs is decreased in the neonate because of reduced total serum protein and albumin concentrations when compared to the adult. Reduced protein binding increases the free fraction of the medications, thus providing a higher free drug concentration and a greater pharmacologic effect (Cote et al., 2013). Total plasma protein levels

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are lower in infants, reaching equivalent adult concentrations by 5 to 6 months of age (Nagelhout & Elisha, 2018). In contrast to drugs bound to plasma proteins, unbound lipophilic drugs passively diffuse across the blood brain barrier and equilibrate very quickly (Cote et al., 2013).

Drug Metabolism

Drug metabolism usually takes place in the liver, gastrointestinal tract, gastric mucosa, and lungs (Nagelhout & Elisha, 2018). The goal of drug metabolism is to produce a more water-soluble compound that is more easily excreted and occurs in two phases. Phase I metabolism consists of three enzymatic reactions (oxidation, reduction, and hydrolysis) catalyzed by the cytochrome P-450 enzyme system. Additionally, other enzyme systems within red blood cells and plasma are capable of the hydrolysis of many medications, including ester local anesthetic agents. Phase II reactions are immature at birth and consist of conjugation or synthesis (Nagelhout & Elisha, 2018).

Anesthetic and Sedative Agents

Inhaled Anesthetics

The administration of a volatile anesthetic agent, such as sevoflurane or desflurane, produces a state of GA by building up a partial pressure of the agent within the patient's brain and spinal cord. The rapid increase in the alveolar concentration of an inspired anesthetic agent is quantified by the ratio of alveolar concentration (F_A) divided by the inspired concentration (F_I). Factors affecting the F_A/F_I ratio include the delivered inspired anesthetic concentration, the blood-gas partition coefficient of the inhalation agent, alveolar ventilation (V_A), cardiac output and its distribution to vessel rich organs (Nagelhout & Elisha, 2018).

Although tidal volume is similar in both children and adults with an average of 5 to 7 milliliters per kilogram (mL/kg), children have greater minute ventilation (MV) since they have a

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higher respiratory frequency. According to Nagelhout & Elisha (2018), children also have a higher ratio of tidal volume to functional residual capacity (5:1) compared to adults (1.5:1). These differences, a greater MV and a higher ratio of tidal volume to functional residual capacity, account for the rapid inhalation anesthetic uptake and increasing alveolar anesthetic concentrations.

The minimum alveolar concentration (MAC) of an inhalation anesthetic is an indicator of dose and anesthetic requirements that change with age. The MAC is lower throughout the neonatal period, then increases in infants between 1 to 6 months of age as compared to adults (Nagelhout & Elisha, 2018). These requirements for increased amounts of the inhalation agent administered to infants and children are a direct reflection of the increased metabolic rate of this population (Cote et al., 2013). After this, MAC values and basal metabolic rate tend to decrease as the person continues to age (Nagelhout & Elisha, 2018).

Sevoflurane.

The MAC of sevoflurane is 3% for infants up to 6 months of age, decreasing to 2.5-2.8% by one year of age (Nagelhout & Elisha, 2018). It is the inhalation agent of choice in the pediatric population as it produces a rapid inhalation induction and emergence due to its low blood-gas partition coefficient. Sevoflurane is also desirable for infants and children because it is not a potent airway irritant, thus making it feasible for an inhalation induction. This anesthetic agent also depresses MV, and at higher concentrations, will decrease respiratory rate and ultimately cause apnea. Similar to other volatile agents, the degree of myocardial depression with sevoflurane is dependent on the concentration of the drug. Higher concentrations of inhalation agents will contribute to a greater degree of inhibition of myocardial contractility and peripheral

vascular dilation, possibly contributing to adverse neurotoxic effects following GA (Cote et al., 2013).

Desflurane.

Desflurane is another inhalational anesthetic that may be used for longer surgical cases in the pediatric population. According to Nagelhout and Elisha (2018), advantages of desflurane as opposed to sevoflurane include a more rapid rate of uptake and elimination due to its low blood-gas partition coefficient. The blood-gas partition coefficient for desflurane is 0.42, as opposed to sevoflurane which has a value of 0.68 (Nagelhout & Elisha, 2018). Desflurane has also been known to provide a more stable hemodynamic profile intraoperatively and appears to have a wider margin of safety since it undergoes a negligible amount of hepatic metabolism. Despite these advantages, sevoflurane is superior to desflurane for inhalational inductions, as desflurane is known to be a potent airway irritant.

Intravenous Sedatives

Since infants and children have a higher proportion of cardiac output being delivered to vessel rich organs (i.e., heart, brain, kidneys, and liver), intravenous anesthetics are rapidly delivered and absorbed by these tissues. Intravenously administered drugs may have a prolonged duration of action in infants because of decreased hepatic degradation and renal excretion (Nagelhout & Elisha, 2018). Propofol is one of the most widely used intravenous sedatives in anesthesia and is discussed in detail below.

Propofol.

Propofol produces its action through GABA agonism, which results in neuronal hyperpolarization and a more negative resting membrane potential of the cell. Infants require a larger induction dose of propofol per body weight because of their higher degree of volume of

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distribution and increased metabolic rate when compared to older children and adults. According to Nagelhout & Elisha (2018), induction dosing of propofol for the infant should range between 2.5 and 3 mg/kg. Other advantageous effects of intravenous propofol administration include a reduced incidence of postoperative nausea and vomiting (PONV) and, with the addition of an opioid agonist, the ability to provide total intravenous anesthesia, eliminating the need for inhalation agents. Disadvantages to the use of propofol include a burning sensation on injection and a reduction in systolic blood pressure due to myocardial depression and vasodilation (Nagelhout & Elisha, 2018).

Fentanyl.

Intravenous opioids may be administered during a general anesthetic to aid in analgesia and sedation. As Cote et al. (2013) explains, fentanyl is the most commonly used opioid during general anesthesia in infants and children. Fentanyl is a potent mu (μ) receptor agonist with a potency 100x greater than that of morphine. This drug is lipophilic with a rapid onset and intermediate duration of action and can efficiently penetrate the blood brain barrier to exert its effects. Clinical effects associated with μ receptor agonism include analgesia, respiratory depression, bradycardia, sedation, nausea and vomiting, urinary retention, and pruritis. Additionally, fentanyl is available in different routes of administration.

Dexmedetomidine.

Dexmedetomidine provides sedation through alpha 2 receptor agonism which decreases cyclic adenosine monophosphate (cAMP) and results in inhibition of the locus coeruleus. Both dexmedetomidine and clonidine are in the same drug class, alpha 2 adrenoreceptor agonists, but dexmedetomidine differs from clonidine in that its affinity for alpha 2 receptors versus alpha 1 receptors is 8x greater (Cote et al., 2013). The central nervous system manifestations of alpha 2

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agonism include sedation and anxiolysis, making this an ideal drug for preoperative sedation. Analgesic effects of dexmedetomidine are mediated through the dorsal horn of the spinal cord, which ultimately results in a reduction of substance P and glutamate release.

According to Cote et al. (2013), the primary action of alpha 2 receptors on the cardiovascular system is a dose-dependent chronotropic effect in which it slows heart rate by blocking cardioaccelerator nerves and augmenting vagal activity. Actions on the peripheral vasculature depends on the dose of dexmedetomidine – vasodilation is a result of the sympathectomy occurring at low doses, and vasoconstriction which is a direct action on smooth muscle vasculature at higher doses. Dexmedetomidine also does not cause respiratory depression, negating the need for airway manipulation unless necessary. The lack of respiratory depression seen with this drug distinguishes this intravenous sedative from opioids and other GABA receptor agonists (Cote et al., 2013).

Dexmedetomidine administered via nasal and buccal routes have a high degree of bioavailability and can be used with proven efficacy for preoperative sedation in the pediatric population. Dexmedetomidine is also desirable as it reduces the incidence of emergence delirium in children (Cote et al., 2013). Because of these overall effects, dexmedetomidine has become a suitable choice for preoperative sedation in many pediatric institution-based SA protocols.

Regional Anesthesia in the Infant

Regional anesthesia (RA) in the neonate and infant has become increasingly popular as the sole anesthetic for many procedures below the umbilicus that are shorter in duration. As Nagelhout & Elisha (2018) state, the two most common techniques used in the neonate are spinal and caudal epidural blocks. Anatomic differences between a neonate and an adult must be taken into careful consideration. The spinal cord extends as far as L3 in the neonate and does not reach

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the adult position of L1 until one year of age. The dural sac continues from S3 to S4 and doesn't reach the adult position at S1 until approximately one year of age. The volume of cerebrospinal fluid (CSF) is twice that of the adult patient, 4 mL/kg versus 2 mL/kg. This difference in CSF volume promotes dilution of local anesthetics (LA) in the infant and neonate and can explain the higher dose requirements and shorter duration of analgesia in this patient population (Nagelhout & Elisha, 2018).

According to Nagelhout & Elisha (2018), patients within this age group have displayed stable hemodynamic responses to RA as compared to adults. It is hypothesized that this could be from the neonate and infants' immature sympathetic nervous system or the proportionally smaller amount of blood volume in the lower extremities, reducing the amount of venous pooling. Effects on ventilation are dependent on the level of the block, similar to adults. Historically, most neonates and infants have a regional technique performed after the initiation of GA. This was often because of challenges related to the age of the patient and variations in cooperability and agitation of the neonate. With newer techniques and institutionalized hospital protocols, along with a skillful anesthesia provider, SA can be initiated in this patient population in place of general anesthesia for some surgical procedures.

Technique

SA has been in practice since the early 20th century for pediatric patients undergoing surgical procedures on the lower abdomen and lower extremities. Caudal blocks are also common in neonates as they provide excellent analgesia, are easy to perform, and reduce the use of post-operative opioids. According to Nagelhout & Elisha (2018), SA can be implemented in the sitting or lateral position, but the patient's neck must be extended to prevent airway obstruction. The lumbar puncture is performed at the L3 to L4 or L4 to L5 interspace, knowing

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the spinal cord ends at L3 in this age group. Next, a 1½ inch, 22-gauge needle is inserted into the identified interspace and resistance may be met as the needle passes through the ligamentum flavum. A characteristic “pop” is felt when the needle enters the subarachnoid space. The presence of free-flowing, clear CSF indicates the correct placement and next, the appropriate dose of LA is administered. The patient is immediately placed supine following successful SA placement (Nagelhout & Elisha, 2018). Figure 1 depicted in the image below demonstrates proper SA technique in this patient population .

Figure 1

Step by Step SA Technique



“Note: subcutaneous infiltration of local anesthetic (A), proper patient positioning and needle placement (B), verification of clear, free-flowing CSF (C), injection of local anesthetic into the spinal space (D).”

(Taken from: Jefferson et al., 2022)

Eutectic Mixture of Local Anesthetics (EMLA).

As Nagelhout & Elisha (2018) discuss, 5% EMLA cream, an equal mixture of 2.5% lidocaine and 2.5% prilocaine, was present in various hospital-based protocols discussed in this literature review. Transdermal EMLA placement produces analgesia within one hour of administration and achieves its maximum effect within 2 to 3 hours. A clear, occlusive dressing should be applied after topical application to help facilitate absorption. Dosage recommendations for the infant under 1 year of age range from 1 to 2 grams (gm), depending on weight and should be applied to a maximum area of 10 centimeters (cm)² and 20 cm², respectively. Adverse reactions to this drug include skin blanching, erythema, pruritis, and methemoglobinemia (Nagelhout & Elisha, 2018).

Local Anesthetics

According to Apex Anesthesia (2022), local anesthetics exert their action by decreasing neuronal permeability to sodium, thus inhibiting depolarization. After injection of LA into the desired area, it is rapidly dissociated into an uncharged base and an ionized conjugate acid. Only the ionized portion of the LA binds to the alpha-subunit inside of the voltage-gated sodium channel. The sodium channel remains in a closed, inactive state until enough of the LA diffuses away from its site of action. There are two classes of clinically useful local anesthetics, esters and amides. These drug classes differ in their metabolism – the ester class are primarily metabolized by plasma esterase, while amides undergo hepatic degradation via CYP450 enzymes, which are reduced in the neonate and infant (Apex Anesthesia, 2022).

There are additional pharmacologic considerations when initiating RA in the neonate and infant. As Cote et al. (2013) explains, the proportional dose of LA required for SA in neonates and infants is much greater than that required of adults. On a per kilogram basis, there is a 5- to

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10-fold greater drug requirement in neonates as for adults to reach a similar dermatomal distribution. Also, the duration of action for this larger dose in the neonate is approximately half as long as the adult. As discussed previously, it is believed these effects seen in the neonate are a result of the large volume of CSF per kilogram (Cote et al., 2013). The sub-sections below will discuss some of the commonly used local anesthetics and additives in SA for the neonate and infant.

Bupivacaine.

The choice of local anesthetic for SA in the neonate and infant depends on the desired speed of onset and duration of the block. Bupivacaine is among the amide class of local anesthetics and is commonly used for regional blockade in the pediatric population. As Cote et al. (2013) states, it is important to note that this duration of action is decreased in smaller infants because of their differences in CSF volume. Although a higher dose is often needed in the neonate and infant, the dose for SA with isobaric or hyperbaric bupivacaine in this population must be taken into careful consideration given the proposed risk of local anesthetic toxicity with larger doses. This drug is highly protein bound and undergoes hepatic metabolism, which is often underdeveloped in this age group and can potentially lead to LA toxicity (Cote et al., 2013).

Chloroprocaine.

Chloroprocaine is an ester local anesthetic and is reported in one of the studies within the literature review (Nagelhout & Elisha, 2018). Three percent chloroprocaine was selected for its effects intraoperatively via a caudal epidural catheter following the placement of a SAB. This approach was described as an effort to prolong the duration of the block to aid in the completion of longer, more complex surgeries and to provide a route of administration for postoperative

analgesics. Chloroprocaine is desirable for this technique due to its rapid onset, wide safety profile, and ease of titratability (Nagelhout & Elisha, 2018).

Additives.

According to Apex Anesthesia (2021), additives to LA solutions are used to help speed the onset and prolong the duration of the block, provide supplemental pain relief, and improve drug absorption. The alpha agonistic effect of epinephrine makes it a potent vasoconstrictor. When added to a local anesthetic solution, it can help reduce systemic uptake of the drug, prolong block duration, and enhance block quality. Less systemic uptake of the LA allows for a decrease in plasma concentration and a reduction in the incidence of toxicity. Dexamethasone may be added to an LA solution for similar reasons as epinephrine, to extend the duration of blockade (Apex Anesthesia, 2021).

Clonidine and dexmedetomidine, both alpha 2 agonists, may be added to LA solutions to prolong postoperative analgesia and allow for more stable hemodynamics intraoperatively. The addition of 100 mcg of clonidine to a LA solution prolongs the duration of the block by approximately 100 minutes with minimal side effects (Nagelhout & Elisha, 2018). The addition of narcotics may be considered for longer, more complex surgeries. Opioids will intensify the quality of the block produced by LA solutions alone. Complications following SA include total spinal anesthesia, post-dural puncture headache, back pain, and other neurologic sequelae which are further evaluated within this literature review.

Literature Review

Methods

A comprehensive literature search was performed on the following major databases: PubMed, Cochrane Library, Medline, Google Scholar, SCOPUS, and CINHALL. Retrospective

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case studies and systematic meta-analyses published within the last five years, 2017 to 2022, were selected. Relevant search terms included in the initial inquiry were “spinal anesthesia and infant” which resulted in several case studies discussing spinal anesthesia protocols for the infant. The search was then further specified to focus on spinal anesthesia for the use of short, genitourinary procedures. Additional key words included in the search were “urologic surgery” and pediatric spinal anesthesia.” Another purpose for the literature review was to explore the potential neurotoxic effects imposed by general anesthetics in the pediatric population. Additional search terms included “general anesthesia and neurotoxicity,” “neuronal apoptosis and anesthesia,” and “long-term outcomes and anesthesia.”

Exposure to General Anesthesia in the Young Patient

The purpose of the comprehensive literature review by Rosenblatt et al. (2019) was to examine the literature associated with anesthesia exposure in the young child and its long-term effects on brain development and cognition. Following the selection of relevant articles, a total of 41 were chosen to be included in the review. Inclusion criteria consisted of studies examining anesthesia exposure in humans aged birth to 24 years, various types of anesthesia exposures, and differences in surgical duration. Literature that was excluded in this review consisted of animal studies, publications prior to 2000, and studies that did not measure cognition or brain development (Rosenblatt et al., 2019).

The review by Rosenblatt et al. (2019) focused on the long-term effects of anesthesia exposure, age at exposure, and the duration and frequency of exposure. Outcome measures for long-term effects of anesthesia exposure were evaluated through academic assessment, behavioral assessment, brain studies, and neurological testing with the use of a validated neurological assessment tool. The findings suggested an association between longer durations of

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anesthesia exposure and negative outcomes on intelligent quotient (IQ) performance, behavior, and brain development. The articles included within this study reviewed a range of ages for anesthesia exposure, from preterm to 10 years old, and outcomes were measured at ages 2 through 19 years old. Additionally, eight of the 41 studies examined children who were exposed to anesthesia at an age of 5 years old or less. These studies found reduced scores in listening comprehension, performance IQ, and receptive and expressive language. Three of the studies examining children exposed to anesthesia after age 5 found no long-term behavioral difficulties or cognitive effects, except for decreased motor function and an interim drop in IQ scores, which recovered to baseline 1 year postoperatively (Rosenblatt et al., 2019).

Two studies included in the research conducted by Rosenblatt et al. (2019) examined duration of anesthesia. One study found that anesthesia duration was associated with incremental decreases in developmental test scores, and another found differences in procedures lasting longer than 35 minutes, but not less than 35 minutes. Longer cumulative anesthesia exposures were associated with an increased risk of behavioral abnormalities, learning disability, decreased educational achievement, and reduced expressive language scores. It remains unclear if the negative impacts seen are specifically related to the duration of anesthesia exposure, the frequency of anesthesia exposures, or if it is a combination of both (Rosenblatt et al., 2019).

In the comprehensive literature review by Xiao et al. (2022), a total of 72-studies originating from 18 different countries between the years of 2000 and 2022 were analyzed. More than half of the studies included in this review provide evidence of negative neurocognitive effects after GA exposure in young children. Follow up testing occurred at a mean age of 7 years and assessed cognitive abilities such as, memory reasoning, spatial ability, processing speed, and IQ. A majority of the studies utilized anesthetic agents with agonist effects on GABA receptors

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or antagonism of the NMDA receptor. Twenty of the 72 studies found a decline in cognitive function after undergoing general anesthetics of various durations. Additionally, there was an increased risk of behavioral and developmental disorders following surgery requiring general anesthesia in 32 of the 72 studies identified. Learning disability, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) were among the most frequently observed diseases following general anesthesia in 15 of the studies. However, the development of a behavioral disorder can be multifactorial and other causes besides exposure to general anesthesia in childhood must also be considered (Xiao et al., 2022).

In another meta-analysis discussing anesthetic exposure during childhood and the associated neurodevelopmental outcomes by Reighard et al. (2022), 31 studies were analyzed. Studies considered in this literature review were required to include children exposed to GA, as well as an unexposed comparison group (Reighard et al., 2022). Children undergoing surgery with pre-existing comorbidities and congenital anomalies were excluded from this review due to the difficulty in determining whether GA had a measurable negative effect on neurodevelopment in children with significant baseline comorbidity.

When duplicate reports evaluating the same population were identified, only the study with the largest sample size was chosen to be included in this analysis. Outcomes from this comprehensive review were classified into 13 domains: academics, adaptive behavior, behavioral problems, cognition, clinical diagnoses and associated manifestations, executive function, overall physical health, language, motor function, non-verbal reasoning, sensory development, and social cognition. Children with any amount of exposure had reduced scores in academics, cognition, executive function, general development, language, motor function, non-verbal reasoning, and showed an increased incidence of behavioral problems (Reighard et al., 2022).

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Ing and Bellinger (2022) conducted a review of clinical studies evaluating neurodevelopmental outcomes in children following surgery and general anesthesia. According to Ing and Bellinger (2022), although there were minimal differences in intelligence between children exposed to GA and unexposed children, there was an increased incidence of ADHD disorder, particularly following multiple exposures. The prevalence of behavioral issues and ADHD diagnoses ranged from 30% to 50% after a single GA exposure. However, there is lack of definitive linkage that anesthetic agents themselves, not other co-existing factors such as underlying disease, inflammation, perioperative factors, and pain, are the culprit for differences in various neurodevelopmental outcomes (Ing & Bellinger, 2022).

In another review by Olsen & Brambrink (2013), the potential for anesthetic neurotoxicity in the newborn and infant was evaluated. It was concluded that there was not enough evidence available to definitively determine if neuroapoptosis occurs in human neonates or infants who undergo anesthesia or whether anesthesia exposure leads to impairment during further development, such as animal studies have suggested. The basis for this conclusion addresses several key issues that have not yet been systematically approached. One of the major issues presented by Olsen and Brambrink (2013) was the differential effects on neurodevelopment of anesthetics versus those of the simultaneous surgical intervention. There are several ongoing trials in process; the General Anesthesia and Apoptosis (GAS) study, the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) project, and the Mayo Safety in Kids (MASK) study (Olsen & Brambrink, 2013).

Long-term Measurement of Neurodevelopmental Outcomes

The GAS study is an ongoing prospective, randomized, multi-center, international trial comparing RA and GA for inguinal herniorrhaphy in neonates. Inclusion criteria consist of

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greater than 26 weeks gestational age and post-conceptual age of less than 60 weeks. This study defined GA as exposure to sevoflurane, and RA was defined as a bupivacaine caudal block or SAB alone. Enrollment concluded with a total of 722 participants and the study is currently in the phase of 5-year postoperative neurocognitive follow-up (Olsen & Brambrink, 2013).

The PANDA project is a multicenter study comparing American Society of Anesthesiology (ASA) physical status of I or II children exposed to any type of anesthetic for inguinal hernia repair prior to 36 months of age to their unexposed siblings. Study participants were identified retrospectively and then underwent prospective neurocognitive and behavior testing between the ages of 8 and 15 years old. This study is ongoing with a projected enrollment of 960 participants (Olsen & Brambrink, 2013).

Lastly, the MASK study is a collaborative effort evaluating a large cohort of children from Minnesota to identify those with one, multiple, or no anesthesia exposures prior to 3 years of age (Olsen & Brambrink, 2013). Participants undergo extensive prospective neurocognitive testing, including the operant test battery (OTB), which is an array of cognitive tests consisting of positive reinforcement techniques that has been used extensively in the history of neurotoxicology research. Other results of this study suggested differences in reading and fine motor skills in patients who received multiple anesthesia exposures, but no major changes were identified between the group who had a single anesthesia exposure and those who did not.

Olsen and Brambrink (2013) also identified an additional study originating in Australia that found an association between exposure to anesthesia prior to age 3 with language and abstract reasoning deficits detected as early as age 10, even with a single anesthesia exposure. Neurocognitive testing evaluated expressive and receptive language ability, cognition, behavior, and motor function. They found a 2.4-fold increased risk for receptive language disability when

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comparing children with a single anesthesia exposure versus unexposed children. Also, there was a 3.5-fold increase in the incidence of receptive language difficulty following multiple anesthetic exposures (Olsen & Brambrink, 2013). As discussed previously, increasing concern regarding the potential negative effects of early use of inhalational and intravenous anesthetics on neurocognitive development have led to a growing interest in alternative forms of anesthesia in the infant.

Spinal Anesthesia as an Alternative to General Anesthesia

The use of SA in neonates and infants has been explored as a potential alternative to GA in appropriate surgical cases. In the study by Handlogten et al. (2020), the institution based infant spinal anesthesia protocol was introduced in collaboration with pediatric urologic surgeons. The goal of this protocol was to minimize excess sedation and to avoid GA while providing a safe and pain-free anesthetic that lasted as long as possible for infants undergoing urological surgery. Another goal for this protocol was to reduce discomfort and movement for infants during spinal placement due to the challenges that can be associated with pediatric neuraxial anatomy (Handlogten et al., 2020).

As Handlogten et al. (2020) state, preemptive intranasal sedation was achieved with 4 to 5 micrograms per kilogram (mcg/kg) of dexmedetomidine 45 minutes prior to operating room entry, which is similar to the SA protocol described in the case study by Jefferson et al. (2022). Patients had the lumbar area prepped with EMLA cream and then the area was covered with a clear occlusive dressing up to an hour prior to performing the spinal. While initially using 25-gauge Whitacre needles, Handlogten et al. (2020) concluded that it was difficult to keep the side port of the needle in the intrathecal space, evidenced by the frequent loss of CSF flow during injection. After this finding, 25-gauge two-inch Quincke needles were used in this protocol.

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Following placement of the spinal anesthetic, the infant was immediately placed supine, additional monitors were applied, and intravenous access was obtained in the lower extremity (Handlogten et al., 2020).

In the study by Ebert et al. (2019) discussing the advantages of SA in this vulnerable population, 0.2 mL/kg of 0.5% bupivacaine was used for LA. Ebert et al. (2019) also described washing the glass syringe with 1:1,000 epinephrine prior to drawing up the appropriate weight-based dose of local anesthetic to prolong the surgical block and maximize postoperative analgesia. To manage fussiness intraoperatively following the initiation of SA, a pacifier immersed in sucrose 24%, also known as Sweet-Ease, was provided to the infant. If this initial soothing measure failed, small doses of intravenous sedatives, such as dexmedetomidine or fentanyl were administered (Ebert et al., 2019).

The technique for obtaining intrathecal access followed by caudal epidural catheter placement to allow for more complex urological surgery described in the case study by Jayanthi et al. (2019) began with the preoperative administration of 0.5 mg/kg of oral midazolam. Of the patients included in this review, 13 of the 20 (65%) received preoperative sedation at the discretion of the anesthesia provider. Initial dosing of the spinal anesthetic consisted of 1 mg/kg of 0.5% isobaric bupivacaine, with a maximum dose of 5 mg, followed by placement of a caudal epidural catheter. An epidural needle was used to obtain access to the caudal epidural space via the sacrococcygeal ligament. A 20-gauge caudal catheter was then advanced into the epidural space to the desired dermatomal level and secured in place (Jayanthi et al., 2019).

At approximately one hour after the intrathecal injection, a 1.5 mL/kg bolus of 3% chloroprocaine was administered via the caudal catheter to prolong the duration of the surgical block (Jayanthi et al., 2019). Following the bolus dose, an infusion of 3% chloroprocaine was

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initiated at 1 milliliter per kilogram per hour (mL/kg/hr). Prior to the removal of the caudal catheter in the post-anesthesia recovery area, a supplemental bolus dose of either 0.25% bupivacaine or 0.2% ropivacaine was administered through the catheter to provide prolonged postoperative analgesic coverage for 45 minutes after discontinuation of the chloroprocaine infusion. Additionally, a dexmedetomidine infusion at 1 microgram per kilogram per hour (mcg/kg/hr) was selected to be used to provide patient comfort because of its minimal effects on respiratory drive, reducing the potential need for airway manipulation (Jayanthi et al., 2019).

Spinal Anesthesia for Urologic Surgery

Handlogten et al. (2020) implemented a retrospective review of 230 patients undergoing anesthesia for various genitourinary surgical procedures. Infants aged 1 to 14 months who received spinal anesthesia for circumcision, orchiopexy, orchiectomy, hypospadias repair or epispadias repair were compared to unmatched historical controls who received GA. Patients were excluded if their parent or legal guardian did not consent for the use of their medical record for research purposes, if they had previously received any surgical procedures, or if age was greater than 14 months. Of the 230 participants examined, 102 patients received SA and 128 received GA. Surgical duration for SA ranged from 4 to 189 minutes. Spinal anesthesia failure was defined as the requirement of conversion to GA within 15 minutes of surgical start time (Handlogten et al., 2020).

The objective of the retrospective case study conducted by Jefferson et al. (2022) was to characterize the safety and efficacy of SA for urologic surgery in infants lasting longer than 60 minutes, but less than 3 hours in duration in a time frame of May 2018 to March 2021. Urologic procedures considered in this review included circumcision, proximal and distal hypospadias repair, chordee repair, orchidopexy, hydrocelectomy, and urethroplasty. Patients included in this

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study had a mean age of 6 months. Relative contraindications for SA included anatomical abnormalities of the spine, degenerative neuromuscular disease, coagulopathy, bacterial infection, increased intracranial pressure, or the presence of ventriculoperitoneal shunts. These cases were performed by two urologic surgeons and the median procedure duration was 95 minutes, with a maximum of 189 minutes.

According to Jefferson et al., of the 245 cases that implemented SA, 76 (31%) of infants underwent surgery lasting greater than or equal to 60 minutes. Of the 76 infants undergoing SA for urological procedures lasting at least 60 minutes, 73 (96%) were successfully completed with SA alone (Jefferson et al., 2022). In the 3 cases that required conversion to GA, 2 (67%) were completed with mask inhalation of sevoflurane. Of note, these two patients only required mask anesthesia after 96 and 169 minutes, with less than 10 minutes until completion of the surgical procedure. Conversion to GA was due to leg movement, not loss of analgesia. Jefferson et al., (2022) concluded that a single intrathecal injection of $0.8 \text{ mg/kg} \pm 0.2 \text{ mg}$ of 0.5% bupivacaine in infants undergoing urologic surgery lasting an hour and up to 3 hours is safe and effective.

In the prospective study conducted by Whitaker et al. (2017), a SA program was developed and implemented as an alternative to GA in the pediatric population in effort to reduce the theoretical neurotoxic effects of these agents. Data collection for children undergoing SA at a large tertiary pediatric center focused on demographics, procedure, time required for placement of the spinal, length of surgery, success of lumbar puncture, success of attaining adequate surgical anesthesia for pediatric urologic procedures, need for supplemental systemic sedation, conversion to GA, and perioperative complications. SA was attempted in 105 children, with 104 being male and 1 female. Age and weight of the patients ranged from 19 days to 24 months and 3.5-13.7 kg, respectively (Whitaker et al., 2017).

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Of the 105 patients in the study conducted by Whitaker et al. (2017), SA was successful in 93 (89%) patients and was abandoned in 7% of patients with subsequent administration of GA. In instances where SA was successfully placed and surgery had begun, 5 of the 93 patients (5%) required conversion to GA intraoperatively. Reasons for conversion to GA included evisceration of the large intestine through hernia defects related to coughing and abdominal irritation in two patients, lack of motor blockade despite an adequate sensory blockade in an additional two patients, and one patient due to the inability to place an intravenous catheter in the lower extremity as per hospital protocol (Whitaker et al., 2017). Intravenous catheter placement was successful following inhalation induction and the subsequent maintenance of GA. Whitaker et al. (2017) deemed SA a safe and effective technique for routine urological procedures and should be considered in patients with significant cardiac or pulmonary comorbidities when the risks of GA are weighed against the risks of non-intervention.

Trifa et al. (2018) also examined the use of SA for genitourinary surgical cases lasting longer than 60 minutes in duration in children up to three years of age between September 2015 and August 2017. A total of 35 patients met the inclusion criteria to be considered in this study. Patients selected to be a part of this case study were male undergoing genital or groin surgeries with a mean age of 7 months and average weight of 8 kg. Surgical duration ranged from 60 to 111 minutes and SA was determined to be successful in 31 (89%) of patients (Trifa et al., 2018).

After parental consent was obtained, EMLA cream was applied over the intended puncture site, similar to other institutions' pediatric SA protocols. The LA of choice was 1 mg/kg of isobaric, preservative free 0.5% bupivacaine up to a maximum total dose of 7 mg (Trifa et al., 2018). Adjunct agents included in the spinal anesthetic were 1 mcg/kg of clonidine \pm a 1:200,000 epinephrine wash. According to Trifa et al. (2018), all the patients received clonidine,

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and 34 of the 35 patients received epinephrine as an additive to the isobaric bupivacaine. The majority of patients fell asleep following placement of the SAB and the upper extremities were gently restrained. A pacifier dipped in 24% sucrose was provided, and if the child did not respond to this, intravenous sedation with small doses of dexmedetomidine was administered as necessary (Trifa et al., 2019).

The primary outcome from the retrospective review by Trifa et al. (2018) was success of SA for the surgical procedure without the need for conversion to GA. Cases were excluded if they lasted longer than 60 minutes. Additionally, eight cases were excluded because of failure to obtain free flowing CSF or insufficient motor blockade. Spinal anesthesia with 0.5% bupivacaine, clonidine, and epinephrine was deemed to be a feasible technique for appropriately aged children undergoing urological procedures lasting longer than 60 minutes, with a success rate of 89%. Among the patients whom SA was successful, the surgery was completed without the administration of any additional sedative anesthetic agents in 81% of patients (Trifa et al., 2018).

Jayanthi et al. (2019) examined the use of combined spinal and caudal catheter anesthesia to allow for more complex pediatric urological surgery. Surgeries performed under a spinal/caudal catheter technique included seven ureteral reimplantation, two ureterocele excisions and reimplantation, two megaureter repairs, four first-stage hypospadias repairs, one distal hypospadias repair, one second-stage hypospadias repair, two feminizing genitoplasties, and one open pyeloplasty. The procedure duration ranged between 63 and 172 minutes, with an average length of 109 minutes. A retrospective case review was conducted, and additional variables of interest included age, gender, diagnosis, and type of procedure, need for conversion to GA, medications given perioperatively, complications, and outcomes. Of the 23 children who

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underwent attempted spinal/caudal anesthesia, 20 of the children had a successful spinal/caudal catheter placement. All patients remained spontaneously ventilating on room air for the duration of the procedure and none of the children required airway intervention or had any post-operative anesthesia or surgical complications. One child received opioids intraoperatively and 13 (65%) of the patients received a bolus of long-acting LA via caudal catheter in the recovery area for post-operative pain management (Jayanthi et al., 2019).

Table 1 serves as a review of the SA approaches for pediatric genitourinary surgery described in the studies within this literature review. The key points in the institution-based SA protocol are outlined, detailing intrathecal LA dosing and pre-operative medication dosing. The total number of patients in the study, mean age, and mean procedure duration was also recorded, along with the success rate of SA and any anesthesia related complications that may have occurred.

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Table 1

Review of SA Approaches for Pediatric Genitourinary Surgery

Author	Anesthesia technique and preoperative sedation protocol	Number of patients	Mean age	Male gender	Mean procedure duration	SA success rate	Anesthesia related complications
Ebert et al. (2019)	IT 0.5% bupivacaine ± adjunctive epinephrine or clonidine; IV fentanyl or dexmedetomidine if needed	20	48 days	17/20 (85%)	NR	16/20 (80%)	0/20 (0%)
Handlogten et al. (2020)	IT 0.5% bupivacaine ± adjunctive analgesic alpha 2 agonists; IV dexmedetomidine or fentanyl; preemptive IV atropine	102	6.5 months	NR	35 minutes	80/102 (80%)	0/102 (0%)
Jayanthi et al. (2019)	Preoperative oral midazolam; IT 0.5% bupivacaine with adjunctive epinephrine and clonidine, placement of a caudal epidural catheter for a 3% chloroprocaine infusion; IV dexmedetomidine bolus and infusion; 0.2% ropivacaine or 0.25% bupivacaine via caudal catheter in PACU for postoperative analgesia	20	16.5 months	9/20 (45%)	109 minutes	20/20 (100%)	0/20 (0%)
Jefferson et al. (2022)	IT 0.5% bupivacaine; IN dexmedetomidine ± IN fentanyl if over 4 months of age	76	6 months	76/76	95 minutes	73/76 (96%)	0/76 (0%)
Trifa et al. (2018)	IT 0.5% bupivacaine with adjunctive epinephrine and clonidine; IV fentanyl or dexmedetomidine as needed for sedation	35	7 months	35/35 (100%)	71 minutes	31/35 (89%)	0/35 (0%)
Whitaker et al. (2017)	IT 0.5% bupivacaine with adjunctive epinephrine and	105	7.4 months	104/105 (99%)	38 minutes	88/105 (84%)	0/105 (0%)

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clonidine; IV fentanyl or
dexmedetomidine as
needed for sedation

IV, intravenous; NR, not reported; PACU, post-anesthesia care unit; IN, intranasal; IT, intrathecal

Spinal Anesthesia for Non-Urologic Surgery

Spinal anesthesia in the pediatric population is not limited to urinary surgery and can also be effectively implemented for procedures of the lower abdomen, pelvis, and feet. A study examining the use of SA and the need for opioid administration in percutaneous Achilles tenotomy found that patients who underwent this approach received less opioid, did not require an airway device, did not receive potent inhaled halogenated agents, and exhibited faster and better postoperative recovery as evidenced by comparative numerical data between a SA group and GA group (Acquaviva et al., 2021). General anesthesia had previously been the preferred anesthetic of choice for percutaneous Achilles tenotomy (PAT) at this specific institution, but orthopedic surgeons in collaboration with pediatric anesthesiologists deemed SA to be a superior technique in July 2018 (Acquaviva et al., 2021).

Thirty infants (mean age of 2.3 months) undergoing PAT with SA were compared to 15 infants (mean age 2.0 months) undergoing the same procedure with GA (Acquaviva et al., 2021). There were initially 32 patients in the SA group, however, there were two failed spinals because of the inability to achieve CSF flow and these patients subsequently received a general anesthetic. Data collection focused on hemodynamics, perioperative times, time spent in the post anesthesia care unit, and the need for opioid administration. The study found that 10 of the 15 (67%) GA patients received intraoperative opioids as opposed to 1 out of 30 (3.3%) infants who had received SA. The timing from the start of anesthesia to first postoperative oral intake and time spent in the recovery area were both shorter in the group who underwent a spinal anesthetic (Acquaviva et al., 2021).

Acquaviva et al. (2021) concluded that the time from anesthesia start to surgery start, the time from surgery end to anesthesia end, the time from anesthesia end to initial oral intake, and

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the time for phase one recovery were all reduced in the SA group. However, total time spent in the post-anesthesia recovery unit was not different between the two groups. Blood pressure and heart rate changes were variable for both groups. Three of the 15 GA patients had an arterial oxygen saturation below 94% during the surgery as opposed to 0 of the 30 patients who received SA. Heart rates were not statistically different between either group at any point during the procedures (Acquaviva et al., 2021).

According to Acquaviva et al. (2021), additional benefits of SA included no need for airway manipulation reducing the risk of perioperative respiratory complications and improved operating room efficiency. This study also found that SA had less impact on blood pressure, as opposed to the infants undergoing GA with sevoflurane who demonstrated a reduced blood pressure which may contribute to cerebral hypoperfusion and have potentially negative effects on neurodevelopment later in life (Acquaviva et al., 2021).

In a meta-analysis by Jones et al. (2015), researchers aimed to determine if SA reduces post-operative bradycardia, the use of assisted ventilation, and neurological impairment in comparison to GA for preterm infants undergoing inguinal herniorrhaphy repair at a postmature age. Seven small trials were selected to be incorporated into this review and inclusion criteria consisted of studies evaluating preterm infants born before 37 weeks gestational age undergoing inguinal hernia repair prior to 60 weeks post-gestational age. Primary outcome measures were grouped into respiratory and neurological effects of GA versus RA. Respiratory outcomes were further separated into the number of episodes of apnea, defined as cessation of breathing for more than 20 seconds in the first 24 hours post-operatively, any episodes of desaturation less than 90% for more than 10 seconds in the first 24 hours postoperatively, and the use of postoperative respiratory support for more than one hour following the administration of a

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neuromuscular blockade antagonist. There was no statistical difference in the risk of postoperative apnea and bradycardia, postoperative desaturation, the use of postoperative analgesics, or the need for postoperative respiratory support between the two groups (Jones et al., 2015).

In a retrospective study by Heydinger et al. (2022), outcomes of SA in infants less than 6 months of age undergoing ambulatory surgery were reviewed. Data collection focused on the success rate of intrathecal injection, the presence of any adverse events, time spent in the post-anesthesia care unit, and emergency department returns within the first seven days postoperatively. The study included a total of 173 infants receiving SA for outpatient procedures such as urologic surgery, inguinal herniorrhaphy, Achilles tenotomy, or other pelvic or lower abdominal surgeries. Heydinger et al. (2022) explained 162 (93%) of patients were able to undergo their respective surgical procedures under SA without the need for conversion to GA. Additionally, 136 (78%) of patients did not require additional sedation or analgesic agents, which was defined as the administration of intravenous dexmedetomidine or fentanyl (Heydinger et al., 2022).

Benefits of Spinal Anesthesia

Ebert et al. (2019) conducted a retrospective analysis to determine if there were any potential benefits of SA in the infant population. Goals for this review included the identification of the success rate of SA, complications related to spinal placement, need for supplemental medications or oxygen, and the impact on length of hospital stay. Infants less than 90 days old who underwent SA for four surgeries (inguinal hernia repair, scrotal exploration, posterior urethral valve ablation, and ureterocele puncture) were identified from the institution's database

and compared to a matched cohort of patients who underwent GA for the same types of urological procedures (Ebert et al., 2019).

Of the 40 patients identified, 20 underwent SA while the other half underwent general anesthesia (Ebert et al., 2019). There were no significant differences between the groups in age, gender, weight, history of prematurity, or presence of additional comorbidities. Ebert et al. (2019) reported successful implementation of SA in 80% of the selected patients. It was also found that patients in the SA group were less likely to receive narcotics and supplemental medications intraoperatively (Ebert et al., 2019). Supplemental medications consisted of the administration of bronchodilators, corticosteroids, acetaminophen, dexmedetomidine, and glycopyrrolate.

Ebert et al. (2019) explained reasons for conversion to GA included failure of spinal needle placement in 75% of patients and intraoperative agitation in 25% of patients. Of the 20 participants in the SA group, there were no reports of complications related to spinal needle placement. Additionally, there were no significant differences in the length of hospital stay between the two cohorts. It was concluded that SA had evident advantages in this patient population as it obviates the need for airway manipulation and management and avoids the potential consequences of GA on neurocognitive development (Ebert et al., 2019).

Disadvantages of Spinal Anesthesia

Disadvantages to the implementation of SA for the neonate and infant are related to surgical duration and the possibility of a failed or insufficient blockade. As Trifa et al. (2018) explains, one of the major limitations to SA is the relatively short duration of surgical anesthesia. Reasons for unsuccessful SA consisted of sustained coughing during surgery, failure to obtain peripheral intravenous access in the lower extremity, and a surgeon's decision to convert to a

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laparoscopic procedure requiring conversion to GA 30 minutes following the start of the operation (Trifa et al., 2018).

According to Acquaviva et al. (2021), most of the complications of SA in infants are self-limiting and include bradycardia and respiratory insufficiency resulting from a high level of sensory and motor blockade. One child aged 29 months and weighing 13.6 kg developed a high spinal shortly after the intrathecal administration of 7 mg of isobaric 0.5% bupivacaine with 14 mcg of clonidine and 1:200,000 epinephrine. This complication was effectively managed by positioning the patient in reverse Trendelenburg and providing supplemental oxygen administration, without the conversion to GA (Trifa et al., (2018).

In the retrospective study by Heydinger et al. (2022), two perioperative adverse events were identified. One patient required conversion to GA following an inadequate motor blockade and a brief laryngospasm prior to removal of the supraglottic airway device. No escalation of care was required, and the laryngospasm was resolved with a single dose of intravenous propofol. A second event was related to a penile block performed by the surgeon at the conclusion of the procedure for postoperative analgesia. If SA has already been performed, the dose of the LA in the penile block administered by the urologic surgeon must be decreased to avoid administering a toxic dose. It is believed that there was inadvertent intravascular injection of LA as evidenced by a transient oxygen desaturation and mild neurological deficit of limited duration in the patient (Heydinger et al., 2022). Heydinger et al. (2022) reported there was full resolution of symptoms after the initiation of bag mask ventilation and the administration of intravenous midazolam and propofol. The patient reportedly remained hemodynamically stable and was discharged home on the same day without any further issues. Additionally, one patient presented to the emergency department on postoperative day 2 with poor oral intake and

fussiness. Ultrasonography suggested a sunken fontanelle and a possible CSF leak. The patient was ultimately discharged the next day after receiving intravenous fluids and no further care was necessary for the presumed CSF leak (Heydinger et al., 2022).

Discussion

The purpose of this comprehensive review was to describe the literature associated with anesthesia exposure in the young child and its long-term effects on brain development and cognition. Overall, studies were consistent with their findings regarding the effects of anesthesia exposure in the neonate and infant. Repeated or multiple exposures that were longer than 3 hours in duration showed an increased incidence in the development of a neurocognitive disability, such as ASD and ADHD (Ayoï et al., 2022). The occurrence of these disorders later in childhood are multifactorial and single or multiple exposures to GA in these vulnerable patients cannot take all the responsibility. The use of GA for some pediatric patients undergoing surgery may be necessary, whether it be the nature of the procedure or for the presence of any comorbidities (Rosenblatt et al., 2019). Children with co-existing comorbidities or those who had a history of a pre-term birth were often excluded from these studies, making results difficult to interpret. One must take into consideration that premature infants may already be at a higher risk for developing alterations in their neurocognitive abilities later in life (Jones et al., 2015).

This review also serves to determine the success rate, benefits, and possible disadvantages of SA as an alternative approach for infants undergoing genitourinary procedures lasting approximately an hour in duration. The implementation of a SA in this patient population has proven to be a safe and effective method as a sole anesthetic in many elective procedures (Whitaker et al., 2017). Spinal anesthesia produces a reliable level of anesthesia inferior to T6 and T8 dermatomes, making it an ideal option for use in procedures involving the lower

extremities, genitalia, and lower abdomen (Ebert et al., 2019). Successful SA placement requires a skilled provider and meticulous attention must be paid to the differences neonates and infants have on pharmacodynamics and pharmacokinetics of a drug, as well as their anatomy when compared to the adult patient (Cote et al., 2013).

Limitations

The studies analyzed in this comprehensive literature review pose several similar limitations. These studies have reported mixed results, likely attributable to significant heterogeneity in study designs, type and number of anesthetic exposures, patient populations evaluated, and the outcomes that were assessed. Another limitation commonly present in the case studies evaluated in this review was provider variability (Acquaviva et al., 2021). Some protocols consisted of one or two pediatric anesthesia providers, while others had multiple providers. Additionally, many of the studies are retrospective and observational in nature, deeming any associations made between anesthetic exposure and behavioral deficits not directly attributable to anesthetic agents (Jefferson et al., 2022). Limitations of prospective studies included in this review are mainly due to the significant number of resources necessary for long term follow up (Ing & Bellinger, 2022). Further research is warranted to determine the mechanism behind reported associations and whether these differences in neurocognitive development can be attributed to childhood exposure to anesthetic agents.

Conclusion

Human studies regarding effects of GA on the developing brain have found mixed evidence for an association between surgery requiring anesthesia in childhood and subsequent neurodevelopmental delay. Cumulative anesthesia exposures were found to be associated with increased risk of behavioral abnormalities, learning disability, decreased educational

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achievement, and decreased expressive language scores (Rosenblatt et al., 2019). The effect of inhaled sevoflurane in combination with reduced blood pressure may have potentially detrimental consequences on cerebral perfusion and subsequent neurodevelopment later in childhood which may account for the neurodevelopmental changes that have been described (Acquaviva et al., 2021). In addition, the sympathectomy and resulting hypotension often observed in adult patients with spinal anesthetics does not occur in infants, who are primarily parasympathetically driven (Acquaviva et al., 2021). The avoidance of GA in this particularly susceptible patient population removes the concerns on the developing brain that have been raised by the FDA in 2016.

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