2 Anesthetic Considerations in the Evaluation of Children with Glaucoma and Associated Conditions

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Introduction

Each year in the United States, more than 6 million infants and toddlers require some form of anesthesia to facilitate a wide array of examinations, procedures, and surgeries. Unlike adults, who are able to submit to all but the most invasive examinations and diagnostic procedures awake or with mild sedation, most children are unable to tolerate all but the most minor medical procedures in an awake, non-sedated state. In this population, even detailed eye exams can be challenging without the assistance of some sedation, and in many cases general anesthesia is required to complete necessary diagnostic and treatment interventions. These sessions often occur in an ambulatory surgical environment and are not always coupled with an actual surgical intervention.

Given the importance of sedated examination in the unique setting of childhood glaucoma, this chapter is devoted to the practice of pediatric anesthesia and what every pediatric glaucoma specialist should know about bringing their smallest patients to the operating suite, including the preoperative, intraoperative, and postoperative components of a visit, a discussion of optimizing patients prior to undergoing anesthesia, and possible complications that may arise during an anesthetic. Lastly, as the breadth of practice and age range is wide in the treatment of childhood glaucoma, there are some salient points regarding the child's age and the comorbidities one will encounter in anesthetizing those with systemic syndromes that affect multiple organ systems.

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Preoperative Assessment

Pediatric Anesthesia in the Ambulatory Setting

Most children undergoing examination or surgical intervention with anesthesia will do so in the ambulatory setting. Each year, over 3 million children receive anesthesia care on an outpatient same-day basis, many of which occur in a free-standing facility separate from a hospital [1]. There are specific guidelines for the pediatric

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ambulatory setting with regard to appropriate criteria for same-day surgery, preoperative workup, and discharge. Specifically, current or recent upper respiratory tract infection, apnea risk in those with sleep apnea or in infants, and potentially undiagnosed myopathies or cardiac disease are special areas of concern during triaging pediatric cases for same-day surgery [2]. In this setting, the plan is for same-day discharge; in order to ensure that this approach is efficient and safe, short-acting drugs, multimodal pain control, and regional anesthetics when possible are utilized at every opportunity [2].

Routine management of childhood glaucoma consists of serial exams and/or surgical interventions when warranted from the time of diagnosis onward. In some cases, these children present soon after birth and thus will undergo comprehensive examinations under anesthesia (EUAs) repeatedly throughout their early childhood. Children are almost twice as likely to experience any perioperative adverse event (incidence 35%) as adults (incidence 18%) [3]. Neonates, high-risk patients (American Society of Anesthesiologists [ASA] level III and above), and children with congenital heart disease have a higher relative risk of cardiac arrest [4, 5] and subsequent mortalities, especially neonates [6], and require the specialized knowledge of pediatric anesthesiologists.

Pediatric Patient Selection and Optimization

Prior to each scheduled anesthetic session, every child must have an evaluation and clearance from an anesthesiologist to ensure that they are fit and optimized for anesthesia. The details of optimization are individualized to each child and specifically consider the presence of any additional medical problems, co-associated syndromes, cardiopulmonary dysfunction, and recent or acute illness, all of which may increase perioperative risk.

The child's medical history, birth and perinatal history, recent hospitalizations, and current post-conceptual age are factored into the above assessment to calculate risk and to formulate a plan for the anesthesiologist's approach to their flow through the perioperative day. Medical history review includes perinatal events and hospitalizations with review of relevant medical records, specifically including any pertaining to neonatal intensive care unit (NICU) or pediatric intensive care unit admissions. An assessment of functional capacity with a focused physical exam includes, at minimum, heart, lungs, and airway assessment and review of applicable laboratory values. A discussion with parents or caregivers and the patients, when applicable, addresses risks and benefits of the planned anesthesia, as well as reviewing anesthesia-related instructions for the day of the procedure [7].

A thorough risk assessment considers co-associated disease states, pervasive developmental disorders, metabolic disorders, neuromuscular disorders, muscular dystrophies, congenital syndromes, and genetic disorders when formulating the anesthesia plan. The presence of an unexplained murmur should undergo possible evaluation. Untreated congenital cardiac disease may require a pediatric anesthesiologist with subspecialty training in congenital heart disease, as these patients may exhibit cardiac physiology vulnerable to administered anesthetics. This categorical assessment of disease states will allow for a more organized preoperative assessment of anatomical dysmorphology, with special attention given to craniofacial abnormalities and metabolic and end-organ compromise [8, 9].

The patient and their caregivers will undergo this pre-anesthesia workup either in the days leading up to the scheduled procedure in an ambulatory anesthesia preoperative clinic or over the phone when indicated for otherwise healthy patients. The final details will be discussed in person on the day of the procedure with the members of the anesthesia care team.

Physical Exam and Airway Considerations

The Mallampati classification is a key component of the airway examination. It is the gradation assessment of the oral aperture and the hard and

soft palate and is one of several objective findings that assist the anesthesiologist in predicting airway complications. Children who are cooperative with examination of their oropharynx will receive a Mallampati classification, but it is expected that infants and typically toddlers will not cooperate with this exam (Fig. 2.1). Neonates and infants have several anatomical differences of the mouth and airway compared to older children and adults, which should be familiar to the pediatric anesthesiologist. Briefly, this includes a large tongue in relation to the area of the mouth, obligate nose breathing for the first 3 months of life, a large oblong-shaped epiglottis, anteriorly slanted vocal cords, and a glottis opening situated higher in the neck at the level of C3–C4 of the cervical spine. These differences result in a higher incidence of obstruction and difficult mask ventilation in children less than 1 year of age. However, overall the incidence of difficult mask ventilation in children is 0.2% compared to 1.4% in adults [10–14].

Anesthesia Assessment and Plan

American Society of Anesthesiology Physical Status Classification Each patient, child and adult alike, receives a numeric score referring to the ASA physical status classification system (Table 2.1) [14–17]. The ASA status is a subjective assessment of a patient's risk of adverse cardiopulmonary complications while receiving sedation or general anesthesia. Pediatric patients who are categorized ASA I and II are considered at lower risk for procedural sedation and general anesthesia. Patients with ASA status III or higher have significant systemic dysfunction and typically are quite ill. These patients usually require careful medical optimization of their systemic conditions prior to elective surgery, and in most cases their surgeries are best performed in a hospital operating suite and not in a strictly ambulatory setting.

Preoperative Fasting, *nil* per os (NPO) Status Once appropriate review and examination have taken place, a plan for the anesthetic approach will be formulated. Patients will receive their presurgical instructions with regard to fasting times, which medications to withhold versus which to take, and any other specific orders for preparation [18]. The ASA guidelines recommend fasting times prior to surgery, which can be reviewed in Table 2.2 [19]. Pediatric patients and parents should be given specific instruction to follow fasting guidelines, which allow for clear liquids 2 h prior and breast milk 4 h prior to surgery. Infants and neonates are especially sensitive to fluid shifts and rapidly dehydrate and therefore are not able to tolerate depleted intravascular states that accompany the prolonged fasting periods expected of adults.

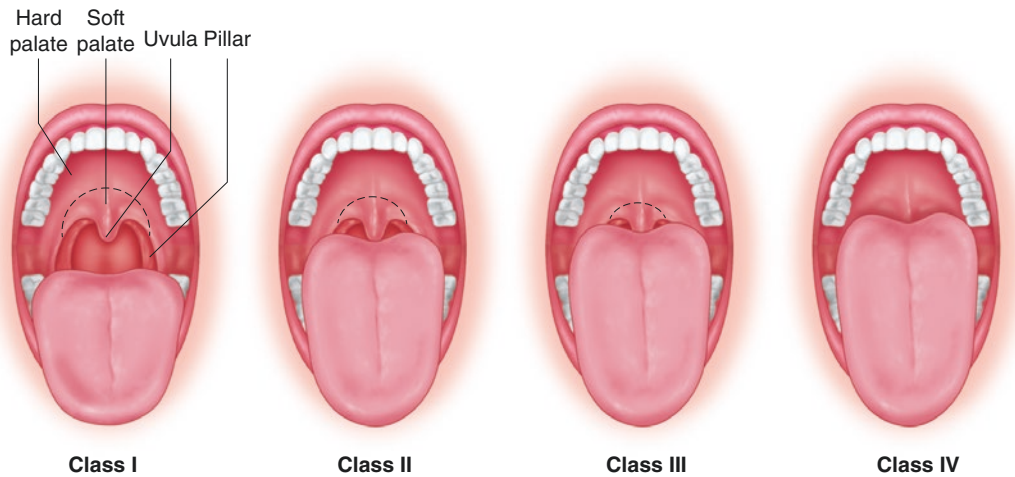

Fig. 2.1 Mallampati assessment of the oral aperture. (Courtesy of Jacqueline L. Tutiven, MD)

Table 2.1 Adapted from the American society of anesthesiologists modified ASA physical status classification system 2013 [15, 16]

Class	Physical status	Example
I	A healthy patient	A fit patient with an umbilical hernia
II	A patient with mild systemic disease	Mild diabetes and controlled hypertension
III	A patient with severe systemic disease that is a constant threat to life	Moderate to severe COPD and angina
IV	An incapacitating disease	Congestive heart failure
V	A moribund patient not expected to live	Ruptured aortic aneurysm
E	Emergency case	–

Table 2.2 American society of Anesthesiologists preprocedure fasting guidelines

Ingested material	Minimum fasting period (h)
Clear liquids (water, pedialyte, apple juice, black coffee/tea)	2
Breast milk	4
Formula (nonhuman milk, juice with pulp, light meal)	6
Light meal (toast and clear fluid)	6
Heavy meal (high fat content)	8

Data from the American Society of Anesthesiologists Committee [19]

Aspiration Aspiration intraoperatively can be a fatal complication, and about 50% of patients who do aspirate end up developing various levels of lung injury, including aspiration pneumonia [20]. Almost all of the medications routinely used in anesthesia will decrease lower esophageal sphincter tone and potentially increase the risk of aspiration [21]. There are many predisposing conditions that can also increase the risk of aspiration; while some are anatomic abnormalities that may relate to the child's specific syndrome (Table 2.3), others include obesity, hiatal hernia, or need for emergency surgery, to name a few. For emergency surgeries, when the appropriate NPO time cannot be honored, a technique of cricoid pressure with rapid administration of induction agents and paralytics is used to secure the airway as quickly as possible after loss of lower esophageal sphincter tone and protective airway reflexes. This rapid sequence induction technique requires the use of a cuffed endotracheal tube (ETT) and avoidance of bag mask ventilation to avoid insufflation of the stomach. Therefore, no breath is delivered to the apneic patient until the ETT is secured and placement has been confirmed with inflation of the cuff in order to limit regurgitation of stomach content into the lungs.

Table 2.3 The effects of anesthetic medications and techniques on intraocular pressure

Drug or procedure	Intraocular pressure change
Induction/sedation agents	
Propofol	↓↓
Etomidate	↓↓
alpha-2 agonists—dexmedetomidine	↓
Ketamine	+/–
Benzodiazepines	
Midazolam	↓↓
Opioids	↓
Inhaled anesthetics	
Volatiles (sevoflurane)	0/↓
Nitrous oxide	↓
Neuromuscular blockade	
Depolarizing agents (succinylcholine)	↑
Non-depolarizing agents	↓
Direct laryngoscopy	↑↑
Valsalva maneuver (coughing, "bearing down")	↑↑

Delivery of Anesthesia Care and Anesthetic Technique

Sedation for Examinations and Induction of General Anesthesia

Sedation of pediatric patients should be provided by specialists who have acquired an advanced set of skills, knowledge, and certification to practice with absolute adherence to published guidelines. Risk assessment for procedural sedation should not be taken lightly. In the United States, the American Academy of Pediatrics, the American Academy of Pediatric Dentistry, the American College of Emergency Medicine, and the ASA have published revised guidelines for the

procedural sedation in infants and children. Similarly, in the United Kingdom, guidelines have been produced by the National Institute for Health and Care Excellence (NICE). Irrespective of the level of sedation that is intended, pediatric sedation exemplifies a continuum. As such, it may consequentially result in respiratory depression with a loss of protective airway reflexes.

Therefore, procedural sedation must be provided within an area that provides necessary resuscitation and supportive equipment. Unexpected complications may arise, and practitioners should not be fraught with the inability of rescuing a patient due to lack of skill, appropriate resuscitation equipment, medicines, or specialized ancillary staff. Every patient is administered oxygen, via nasal cannula, while receiving intramuscular (IM) or intravenous (IV) sedation. Observation and monitoring of vital signs of a sedated pediatric patient include heart rate, pulse oximetry, respiratory rate, and blood pressure recorded at regular intervals. Because sedation is a continuum of a phase of anesthetic somnolence and analgesia, purposeful responses may wane to a point where intervention is required [22]. Infants, as opposed to older children, have greater total body volumes of distribution for certain water-soluble pharmacologic agents while less total body volume of distribution for liposoluble agents. This may present difficulty in predicting how a patient, in this case an infant, will respond to a continuum of sedation. Practitioners administering moderate to deep sedation and analgesia should be ready to rescue patients who may enter into a deeper level of sedation and analgesia. This requires specialized airway management skills. Anesthesiologists are usually best suited to administer sedation to infants and toddlers [17, 19, 23].

There are only a few drugs that are used for pediatric sedation, but more often than not, one sole agent may not be enough to provide adequate sedation. A cocktail of drugs may be needed, as some drugs suppress the ability to breathe, while others may not. Using more than one complementary agent can also decrease the narcotic dose required to maintain a deep enough level of sedation [24].

Midazolam Midazolam is a widely selected benzodiazepine, chosen for its anxiolytic effects, its amnestic properties, and its ability to decrease eye muscle tone along with minimally affecting IOP [25]. Midazolam can be administered orally, intravenously, rectally, or intranasally and is used as a premedication to encourage a child's cooperation. In addition to providing sedation, anxiolysis, and anterograde amnesia, midazolam can help combat emergence delirium after general anesthesia. The side effects of midazolam can be minor, including hiccups to paradoxical hyperactive reactions [26].

Midazolam has a rapid onset of action, within 15–20 min after oral ingestion. A brief half-life time, 1–4 h, gives it a safer margin than using chloral hydrate, for instance, which has a much longer half-life and may not be the best sedative on an outpatient basis [25, 27]. Midazolam is frequently used in conjunction with the following sedative medications, as it is usually insufficient to provide adequate sedation for examination, e.g., as part of premedication.

Ketamine A N-methyl-D-aspartate (NMDA) receptor antagonist and phencyclidine derivative, ketamine has been and continues to be a commonly used anesthetic for procedural sedation. Its pharmacokinetic profile gives it particular properties that have allowed it to be used in infants and children for noninvasive diagnostic exams and minor emergency room procedures. Ketamine is a "dissociative anesthetic," in that it provides sedation and analgesia through NMDA receptor antagonism, potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1) receptor antagonism, and a balanced modulating interplay among cholinergic, aminergic, and opioid systems. Dissociation occurs between the cerebral cortex and the limbic system, resulting in antinociception or *analgesia*, increasing levels of sedation, hypnosis, and unconsciousness with marked adrenergic sympathetic activity. Ketamine also causes cerebral excitation with evidence of seizure-like activity in susceptible individuals, transient increase in IOP [26, 28], and elevation of heart rate and systemic blood pressure. Ketamine can be adminis-

tered by IV or IM with the former being preferred, as its effects are longer-lasting. The overall incidence of severe adverse complications and events remains low as long as risk assessment for adverse events is considered and discussed prior to sedation. Green et al. pooled data from 8282 pediatric ketamine sedations in the emergency departments and demonstrated that an overall incidence of upper airway and pulmonary adverse events was 3.9% [23]. Clinical variables shown to increase risks among this age group include patients younger than 2 years of age, young adults aged 13 or older, high IV dosages greater than 2.5 mg/kg or a total dose of 5 mg/kg, and concurrent use of anticholinergic or benzodiazepines [29–31].

The potential benefit of ketamine is that there is little to no risk of apnea, as it does not interfere with breathing, in contrast to the more commonly used agent, propofol. However, it does have the potential to cause laryngospasm and rapid desaturation. Anticholinergic use, such as atropine or glycopyrrolate, can help reduce the increased laryngeal secretions associated with ketamine use. Glycopyrrolate is most often used due to its short half-life and because it does not cross the blood-brain barrier as atropine does. Hemodynamic compromise is not a concern with ketamine as it is with other agents; therefore, ketamine is considered safer to use in those with hemodynamic instability. Ketamine is generally well tolerated in the pediatric population and is sometimes the only option for sedation in those who carry too high a risk to receive agents that could cause hemodynamic or respiratory compromise [23].

Propofol Propofol is an IV sedative-hypnotic agent that, when given as a bolus, will quickly result in a loss of consciousness followed by a quick and smooth awakening. Propofol causes cardiovascular and respiratory depression, decreases cerebral metabolic uptake of oxygen, and decreases cerebral blood flow and intracranial pressure (ICP). Its depressant effect is uniformly distributed in the central nervous system, decreasing synaptic transmission, and will also act as an anticonvulsant, mediated via gamma-aminobutyric acid receptors. Changes in IOP have been noted with low-dose IV sedation with propofol. An IOP decrease of 20–25% can be expected after an initial bolus of propofol with 0.5 mg/kg and is likely due to extraocular muscle relaxation [28, 29, 31, 32].

Pain on injection is a common adverse event that can be decreased by adding lidocaine to the IV line. Anaphylaxis is rare. The incidence of airway obstruction and apnea is very high in infants and children undergoing continuous sedation with propofol; hence credentialed providers of deep sedation/anesthesia must demonstrate appropriate skills in airway rescue management. A report from the Pediatric Sedation Consortium Research group presented data on more than 49,000 sedation/anesthesia encounters utilizing propofol. Their analysis found it unlikely for propofol to yield worrisome adverse outcomes when well-motivated and appropriately supported sedation/anesthesia services are in place [33–36].

Dexmedetomidine Dexmedetomidine is an α-2-adrenergic agonist approved in the United States by the Food and Drug Administration as an IV sedative for patients intubated in the ICU and for patients requiring procedural sedation without intubation. As an off-label medication, dexmedetomidine has been used in children, in and out of the operating room, for surgical, medical, and procedural sedation in the pediatric ICU. Dexmedetomidine provides sedation, maintains respiratory drive, and attenuates analgesia, emergence delirium, and pain in the postoperative period. Notably, upper airway patency is maintained with dexmedetomidine infusions during sedation in children. This is also noted in children with obstructive sleep apnea when compared to propofol [37]. In children, 93% of IV dexmedetomidine is protein bound, and its redistribution half-life is approximately 7 min. It is biotransformed in the liver to inactive metabolites. Adrenoceptors in the central nervous system mediate the cardiovascular effects of dexmedetomidine, mainly causing systemic hypotension and bradycardia, through central sympatholysis. A slow loading infusion is recommended to

attenuate the drop in blood pressure. A loading dose of 0.5 μg/kg, infused over 5 min, can give modest 10% decrease in systolic blood pressure [37, 38]. Dexmedetomidine-induced bradycardia can decrease heart rates up to 30% from awake states. Intravenous glycopyrrolate yields unexpected responses and does not attenuate the bradycardia, and transient systemic hypertension has been reported [39, 40].

Oral dexmedetomidine (2.6 μg/kg) has been used as a preoperative sedative, achieving sedation within 30 min, comparable to midazolam at 0.5 mg/kg, and has a similar recovery profile, but it is slow and unpredictable [36, 40]. Intranasal (IN) dexmedetomidine, 1 μg/kg, can provide adequate sedation in approximately 50% of children within 1 h. Preoperative anxiolysis, provided by IN dexmedetomidine, decreases heart rate by 11% within the hour and has been found to assure effective sleep in patients before they enter the operating room. Although dexmedetomidine is available and used in children, specific indications are not in place for its use in the pediatric population, and more clinical research is needed on the hemodynamic challenges, analgesia, and anesthesia recovery in infants.

Sedation may not be well tolerated in the pediatric population as incomplete anesthesia of the globe may elicit discomfort during examination, causing the patient to move, cry, and elicit higher than normal IOPs due to agitation. In contrast, general anesthesia ensures a stable airway and an akinetic globe; however, it usually lowers the IOP.

General Anesthesia

General anesthesia is most often used in preference to sedation in childhood glaucoma patients requiring a comprehensive examination (including IOP), since a procedure may follow the EUA if needed. Establishment of general anesthesia renders the patient unconscious and static in order to obtain clinical findings. Vascular access can be easier to obtain and may be required prior to advancing airway support and for surgical procedures. General anesthesia is also beneficial in that the anesthesiologist can control ventilation via various modes available for use on the ventilator and has the ability to change the respiratory rate of the patient. Hypoventilation or hyperventilation can change arterial partial pressure of carbon dioxide (P_{aCO2}) and cause changes in IOP. Therefore spontaneous ventilation can be overridden with controlled ventilation in the patient with an endotracheal tube (ETT), a laryngeal mask airway (k), or via bag mask ventilation by the anesthesia provider and with titration of anesthetic agents. The disadvantage of general anesthesia is that all volatile agents and most IV anesthetic agents will cause a change, usually a decrease, in IOP, which can lead to falsely reassuring IOPs. The exception to this is ketamine, which may potentially and transiently increase IOP.

At 6 months of age, infants under general anesthesia often need a higher minimum alveolar concentration (MAC) of volatile anesthetics to produce an optimal depth of anesthesia and avoid Bell's phenomenon (palpebral oculogyric reflex) on the eye being examined and operated on. Bell's phenomenon denotes light anesthesia and will increase IOP. Higher MAC of volatile anesthetics often results in unstable hemodynamics reflected by low mean arterial pressures. Cardiovascular changes seen in infants under general anesthesia include hypotension, tachycardia, and decrease in venous pressure. For patients who exhibit Bell's phenomenon while under an appropriate amount of general anesthetic, it is advised to consider a balanced anesthetic, protecting the airway with an ETT and adding a muscle relaxant to attenuate this reflex. This will decrease nociceptive stimulus on the eye being examined, decrease the anesthetic requirements through volatile anesthetics or IV anesthetics, and provide akinesia for surgical procedures [41, 42].

General anesthesia has been reported to cause a significant and often time-dependent decrease in IOP after anesthetic induction. The timing of IOP measurement under anesthesia is important and should be consistent with serial examinations. IOP tends to fluctuate, with the lowest IOP occurring after induction of anesthesia and prior to instrumentation of the airway and the highest IOP occurring 1 min after extubation [43].

Bag Mask Ventilation In certain scenarios (i.e., short EUAs), the patient will need to be anesthetized, but actual placement of an airway device is not necessary, and maintenance of anesthesia can be simply sustained through bag mask ventilation. This technique involves placement of a face mask over the patient's nose and mouth, with or without the use of an oral airway, to deliver anesthetic gases to patients while they breathe spontaneously. It is the least invasive but does not provide for selective entry of air into the trachea. The major disadvantage is that peak airway pressures must remain relatively low so as not to insufflate the stomach and cause regurgitation of stomach content that can be aspirated into the lungs. This decreased amount of airway pressure will not allow for adequate-sized breaths to be delivered to the patient, and hypercarbia could ensue. Light plane of anesthesia and laryngospasm remain disadvantageous to this technique in addition to possibly increasing IOP from external compression of the globe by the face mask. This method is nonetheless vital to performing inhalational induction so that venous access and future placement of an airway can be obtained. IOP may be measured once the patient has entered stage III depth of anesthesia and before IV access is obtained. One-hundred-percent oxygen is delivered prior to removing the mask. The face mask may be removed, especially in infants and children with small faces, to obtain IOP measurements, while the anesthesia provider maintains airway patency maneuvers, such as a chin lift during IOP measurement. If the mask is kept in place, the anesthesiologist avoids positive pressure ventilation through the mask during the actual IOP assessment. Once the IOP measurements are taken, IV access is secured, and an advanced airway or supraglottic airway is placed for continued EUA or surgery [42, 44].

The Supraglottic or Laryngeal Mask Airway (LMA) Supraglottic airways sit above the glottic opening and do not pass through the vocal cords. The LMA is the most commonly used supraglottic airway device in spontaneously ventilated patients. Positive airway pressure is required to perform adequate ventilation with the LMA, and it has a higher success rate with a lower complication rate than ETT [45]. The LMA remains in the supraglottic area and does not go through the vocal cords. This reduces the cough reflex seen with endotracheal intubation. Therefore, a lighter plane of anesthesia is required when compared to placement of an ETT. This has less effect on the patient's hemodynamics and preserves blood pressure, while it also avoids the sympathetic surge that follows placement of an ETT. This effect is proven by the lack of change seen in IOP from baseline after insertion of the LMA [46].

The disadvantage is similar to the bag mask ventilation technique; insufflation of the stomach can occur at high airway pressures leading to aspiration. Although the complication rate is lower than with placement of an ETT, partial airway obstruction can occur, and inadequate ventilation can ensue. Ill-fitting LMAs can induce edema of the airway, especially if used for a prolonged procedure [47, 48]. Prolonged procedures (>2 h) are typically not the ideal cases to be performed with a supraglottic airway. There are increased risk of regurgitation and increased amount of gastric volume as surgery time increases [48]. There is also a potential risk for pharyngeal ischemia when higher than recommended cuff pressures are used [49]. These complications are rare, and more recent studies and reviews are showing that even prolonged surgeries have a very low risk of the previously described complications [34]. During emergence from general anesthesia, the LMA does not protect against laryngospasm. Therefore, placement and removal should be performed when a patient is no longer in the hyper-reactive phase of their anesthetic, or phase II.

LMA failure is more likely in children with acquired or congenital airway syndromes. The LMA was designed for the normal airway anatomy. Craniofacial dysmorphology, seen in many syndromes that present for glaucoma and other eye surgeries, can alter the airway anatomy. This would predispose the patient to an ill-fitting LMA [50]. The LMA is part of the pediatric difficult

airway algorithm and can be a lifesaving device in children with difficult airways. Every pediatric airway should be thoroughly examined and assessed for appropriate airway management as a case-by-case/risk to benefit ratio decision. Hence, the "best" approach to airway management will vary for all children and especially those with craniofacial abnormalities and airway anomalies.

Endotracheal Intubation Placement of an ETT involves use of a laryngoscope, which allows visualization of the patient's vocal cords and epiglottis. Placement of the ETT requires operator experience, especially in the pediatric patient with a difficult airway that can be caused by syndromic variations in anatomy. The major advantage of an ETT is that ventilation is easier to control with minimal concern for stomach insufflation and laryngospasm, as occur with light anesthesia. The cuff can also help prevent regurgitation of stomach content from being aspirated into the lungs, which the supraglottic airway devices do not prevent. Ventilation can be controlled via a pressure or volume mode of ventilation, avoiding barotrauma. Patients may still breathe spontaneously with an ETT, although a deeper plane of anesthesia may be required to avoid emerging to stage II of anesthesia, leading to coughing against the ETT, which will increase IOP and risk interfering with intraocular procedures for glaucoma. Maintaining a patient under deep anesthesia could also lead to hypoventilation and hypercarbia. The benefit of a spontaneously breathing patient is the ability to draw air into the lungs via negative pressure that will decrease central venous pressure (CVP) and allow for an IOP more similar to the patient's baseline when they are not anesthetized. Positive pressure ventilation will increase CVP and in turn increase IOP, as it limits venous drainage from the head and neck. The use of spontaneous and controlled ventilation with their advantages and disadvantages is also applicable to the LMA, while pulmonary respiratory parameters are adjusted to deliver adequate volumes [50].

Perioperative Physiology Affecting Intraocular Pressure

Intraocular pressure and its measurement can be greatly affected when a patient is anesthetized or sedated. The point at which IOP measurement occurs is essential for accurate assessment of glaucoma, and it may vary from the preinduction phase, where a patient may receive premedication of an anxiolytic, such as midazolam, to the extubation phase where coughing on an ETT can greatly raise IOP to up to 34–40 mmHg [41]. It is essential to understand how anesthesia medications—both IV agents and inhaled volatile anesthetics—as well as how the time point during an anesthetic may impact the measurement of IOP. These effects are briefly summarized in Table 2.3.

Intraocular pressure can be affected by external pressure on the eye, venous congestion, and changes in intraocular volumes. The patient, surgeon, and anesthesiologist can influence these three factors in a multitude of ways.

External Compression External pressure to the eye will increase IOP [42]. Careful attention must be paid to patient positioning. Eyes must remain free of pressure in all positions (prone, supine, or lateral). Elevation of the head, such as placing a patient in the reverse Trendelenburg position, can also ameliorate increased IOP because it allows for venous drainage [51, 52].

An increase in extraocular muscle tone can increase IOP from external compression. This has been seen with spasms, mediated by the depolarizing muscle blocker, succinylcholine [53].

Venous Congestion Venous congestion can impede drainage of the head and neck, which in turn can increase IOP and ICP. Increasing CVP can inhibit efflux from the eye and increase IOP [54, 55]. CVP can be greatly affected by patient positioning, choice of anesthetic, and parameters set on the patient ventilator. High peak airway pressures and use of high levels of positive end-expiratory pressure (PEEP) while a patient is under general endotracheal anesthesia will impede venous drainage from the head and neck due to

increasing CVP. Any positive pressure application in the ventilated patient has the potential to increase CVP. This is in contrast to a patient who is breathing spontaneously, creating negative inspiratory pressures, without the assistance of the ventilator, which decreases CVP [56].

The spontaneously breathing patient has a negative airway pressure with each inspiration, thereby reducing CVP and increasing venous drainage from the head and neck, reducing IOP. Work of breathing and airway resistance plays an indirect role on IOP. Depending on the type of airway support in use, i.e., face mask, an LMA, or an ETT, and if a patient is left spontaneously breathing or on a mechanical ventilator, the IOP will be affected [56, 57]. Placement of an oral airway device to permit unobstructed flow will decrease inspiratory work of breathing and measurements of IOP in infants and children and should be performed after an appropriate depth of anesthesia is achieved and before definitive airway manipulation.

Changes in Intraocular Volume Blood volume and aqueous humor formation and drainage affect intraocular volume and IOP. The basal intraocular blood volume is determined by intraocular vessel tone, which is affected by P_{aCO2}. An increase in P_{aCO2} will increase IOP because of increasing choroidal blood volume [54]. This effect can be manipulated under anesthesia where hypoventilation results in an increase in arterial CO_2, a mild acidotic state, and vasodilation of cerebral vessels with concomitant increase in choroidal blood volume. Alternatively, hyperventilation will reduce P_{aCO2} and produce vasoconstriction of choroidal blood vessels and a lowering of IOP. Generally, arterial pressure has very little effect on IOP [55, 58, 59].

Autonomic Stimulation and Changes in Aqueous Humor Volume and Drainage Peripheral autonomic fibers from the pterygopalatine ganglion (parasympathetic) and the superior cervical ganglion (sympathetic), along with local influences from trigeminal sensory fibers, innervate structures that maintain IOP in a complex interrelated way. Aqueous humor is formed by the ciliary epithelium, and its production is increased with sympathetic stimulation and decreased with parasympathetic stimulation. The adrenergic nervous system plays a significant and complex role in the regulation of IOP. Autonomic nerve fibers innervate the ciliary processes, the trabecular meshwork, and the episcleral blood vessels. These last vessels are actually arteriovenous anastomoses. Their vascular tonicity or episcleral venous pressure (EVP) is afforded to the episcleral blood vessels via parasympathetic, sympathetic, and trigeminal fibers. This EVP needs to be overcome in order to allow for proper outflow of aqueous humor; internal adrenergic stimulation and locally applied β agonists (epinephrine) will decrease IOP. Clonidine, an α-2-adrenoreceptor agonist, will also directly decrease IOP when placed as a topical treatment. Yet, β-adrenergic antagonists can also decrease IOP. This occurs as there may be different sites of action for a β agonist (reabsorption areas) and antagonist (decreases secretion) [60, 61]. Further physiologic research may contribute to understanding the complex interrelationship of the central pathways, ascending neuromodulatory pathways, the extrinsic system, and the local autonomic nervous system (intrinsic system) on the neuromodulation affecting IOP [62, 63].

Changes in Volume of the Vitreous Humor The volume of vitreous humor is generally constant but can be affected by hydration and osmotically active agents such as mannitol, which can create a significant reduction in IOP. Preoperative dehydration, seen in infants with prolonged NPO status before being examined under anesthesia, may reflect a mild decrease in IOP [63–65].

Anesthetic Agents and Their Effect on Intraocular Pressure

Inhaled Anesthetics Volatile anesthetics that are in current use today include the halogenated agents of sevoflurane, isoflurane, and desflurane. Halothane is no longer available for use in the United States but could be found in other parts of the world. Nitrous oxide is the oldest inhaled anes-

thetic that is available but must be used with other halogenated agents due to its low potency [66].

Nitrous oxide requires a high minimum alveolar concentration in order to provide reliable anesthesia, but giving high concentration of nitrous oxide is limited due to its ability to cause hypoxia. Nitrous oxide has greater solubility than nitrogen and can expand in air-filled spaces, in addition to causing diffusion hypoxia when given in concentrations greater than 3:1 with oxygen. Therefore, nitrous oxide has been used as a sole agent in concentrations of 70% or less to provide anxiolysis to patients. The benefits include its rapid onset and offset, minimal changes on hemodynamics, and minimal effect on IOP [67]. When used as a sole agent, there is no concern for malignant hyperthermia or possibly even emergence delirium [68]. Nitrous oxide is controversial because of its increased risk of postoperative nausea and vomiting, its potential of inactivation of vitamin B_{12}, and the possibility of expansion of air-filled structures. This is of concern when surgeries involve the inner ear or with the use of an intraocular gas. Perfluoropropane (C_3F_8), sulfur hexafluoride (SF_6), and filtered room air are commonly used in retinal surgery, which, when coupled with the use of nitrous oxide, can expand the intraocular gas leading to increased IOP and potentially permanent visual loss. The avoidance of nitrous oxide for 3 months is recommended after ophthalmic surgery involving the use of an intraocular gas unless the intraocular gas has become completely absorbed [69].

Sevoflurane is the halogenated agent of choice for both the typical pediatric inhalational induction and for the maintenance phase of a general anesthetic, as it is fast-acting and the least irritating to the airways. Other agents are less useful in this setting; desflurane, while fast-acting, is the most pungent; isoflurane has a slower onset to achieving a deep anesthetic level and is also very unpleasant for inhalation induction. Both will induce harsh coughing and significant airway irritation in patients of all ages [70, 71]. Desflurane induces sympathetic stimulation, with transient increases in blood pressure and tachycardia [70]. However, such fluctuations are not linked to increases of IOP when compared to the use of sevoflurane. The mechanism for lowering IOP, upon the use of halogenated agents, is likely related to an increase in the outflow of aqueous humor and decreased aqueous production, along with relaxation of extraocular muscles [72]. Schäfer and colleagues described the mechanism of decreased IOP after the use of sevoflurane as being due to a decrease in heart rate and blood pressure, which would also decrease CVP and potentially choroidal blood flow [32]. Since there are many factors that can influence the IOP of a child under anesthesia, the timing of IOP measurement related to inhalational anesthesia is important. It is generally recommended that IOP should be checked immediately after inhalational induction, as IOP continues to decrease with time [32].

Intravenous Agents Intravenous agents for the induction of anesthesia include propofol, etomidate, ketamine, and thiopental (although thiopental is no longer available in the United States). Dexmedetomidine is also commonly used for the maintenance of anesthesia when volatile agents may be contraindicated. As previously described, all of these agents will decrease IOP except ketamine. Ketamine is a dissociative anesthetic that can also cause an increase in blood pressure and heart rate. Controversy exists whether or not induction dose ketamine causes an increase in IOP or has no effect at all. Older studies examined ketamine without the use of premedication, such as midazolam, and found that IOP was increased after administration possibly due to causing nystagmus and increased extraocular muscle tone [32]. More recent studies have been unable to replicate this when premedication was given and found that IOP measured under ketamine fairly accurately represents IOP in the awake state [32, 73, 74]. Ketamine has unpleasant side effects, including increased oral secretions, which could potentially cause laryngospasm (reduced with atropine or glycopyrrolate), nystagmus, and unpleasant dreams or hallucinations. The use of midazolam can help mitigate these unpleasant dreams. Premedication of atropine and midazolam given 20–30 min prior to attending the operating suite is recommended.

Propofol is the most commonly used induction agent, as its profile has fewer side effects compared with other agents. Propofol is rarely contraindicated unless there is a history of a mitochondrial disorder; prolonged exposure may lead to propofol infusion syndrome [75, 76]. Propofol formulations commonly include a soybean oil emulsion and egg lecithin, which have previously been contraindicated in patients with soy or egg allergy. Most patients with egg allergy are actually allergic to the proteins found in egg white, but not the yolk. Multiple studies have confirmed the safety of propofol use in egg or soy allergy [77]. When compared with etomidate and thiopental, all of which decrease systolic blood pressure and IOP after induction, propofol was found to decrease IOP the most and to prevent an increase in IOP when an LMA was inserted [78]. Propofol has also been found to cause a significant decrease in IOP when compared to sevoflurane alone [33].

Local Anesthetics for Analgesia

Local anesthetics (LAs) play a key role in reducing the need for opioid-based analgesia and are especially useful in ophthalmic ambulatory surgery. The application of LAs to the surface of the pediatric globe, or placement along periocular tissues, should be performed by specialty-trained physicians on children under general anesthesia, almost always by the operating surgeon in cases of childhood glaucoma. LAs are classified as either amino-esters or amino-amide compounds, both of which possess characteristics unique to their class. Common agents used in pediatric eye surgery are summarized in Table 2.4.

Amino-Esters Amino-esters are hydrolyzed by plasma cholinesterases. Cholinesterases, enzymes found ubiquitously in plasma and tissues, quickly metabolize these esters, giving them a low toxicity profile in older children. Neonates and infants have decreased levels of plasma cholinesterase and, as such, are susceptible to a buildup of toxic levels when given in summative fashion. Fortunately, ester LAs are short-lived, being metabolized within minutes. Tetracaine and proparacaine are two common ester LAs utilized in ophthalmic surgery on infants and children.

Amino-Amides Amino-amides are eliminated by hepatic enzymatic degradation. The amino-amides include lidocaine, bupivacaine, ropivacaine, and levobupivacaine. The neonatal hepatic system is immature at birth, with limited enzymatic metabolism of such agents, which increases the risk of drug buildup causing LA toxicity. Hepatic clearance of LAs approaches adult levels by 8 months of age [79]. Bupivacaine is a common agent used in infants and children eye blocks at concentrations of 0.25–0.5%. It is typically bound to plasma-binding proteins, α-1-glycoprotein and albumin. Neonatal levels of these proteins are less than those in adults, resulting in a greater free fraction of bupivacaine and other circulating highly bound drugs, thus rendering the potential cardiotoxicity a key consideration in dosing in neonates and children under general anesthesia. A single-dose slow bolus

Table 2.4 Local anesthetics commonly used in eye surgery with recommended maximal dosages

Local anesthetic	Class	Maximum dose (mg/kg)	Duration of action (min)
Procaine	Ester	10	60–90
2-Chloroprocaine	Ester	20	30–40
Tetracaine	Ester	20	30–60
Lidocaine	Amide	1.5	180–600
Bupivacaine	Amide	2–4	180–600
Ropivacaine	Amide	2–4	180–600
Levobupivacaine	Amide	2–4	180–600

Data adapted from the American Academy of Pediatrics; American Academy of Pediatric Dentistry, Coté CJ, Wilson S; Work Group on Sedation [15].

injection for ophthalmic blocks may range from 2 to 4 mg/kg. Ropivacaine is an S(−) enantiomer and a racemate of bupivacaine and exhibits fewer cardiovascular and central nervous system side effects [80].

Local Anesthetic Systemic Toxicity Local anesthetic systemic toxicity involves the cardiovascular and central nervous systems with symptoms that include tinnitus, perioral numbness, dizziness, agitation, and seizures [76]. The most feared complication involves complete circulatory arrest that does not respond to normal resuscitative efforts. The treatment of choice is a lipid emulsion 20%, with avoidance of most vasopressors and a much reduced dosage of epinephrine (<1 μg/kg) [80–82].

Postoperative Analgesia

After invasive surgery that is likely to be painful, such as glaucoma drainage device surgery or laser cyclodestruction, a long-acting local anesthetic via the sub-Tenon or peribulbar route at the end of the procedure significantly reduces postoperative pain and postoperative nausea and vomiting (PONV). The size of the globe is an important consideration for peribulbar blocks. The anteroposterior length of a typical adult globe is approximately 22–24 mm. A premature neonate may have an axial length of 15 mm, while a full-term neonate's globe is characteristically 16–17 mm in length. The globe continues to grow until reaching full size at approximately 3 years of age. A short-beveled needle or angled cannula can be used with an amide anesthetic; our institution uses ropivacaine 0.375% for an inferotemporal approach to a peribulbar block (Fig. 2.2) [83].

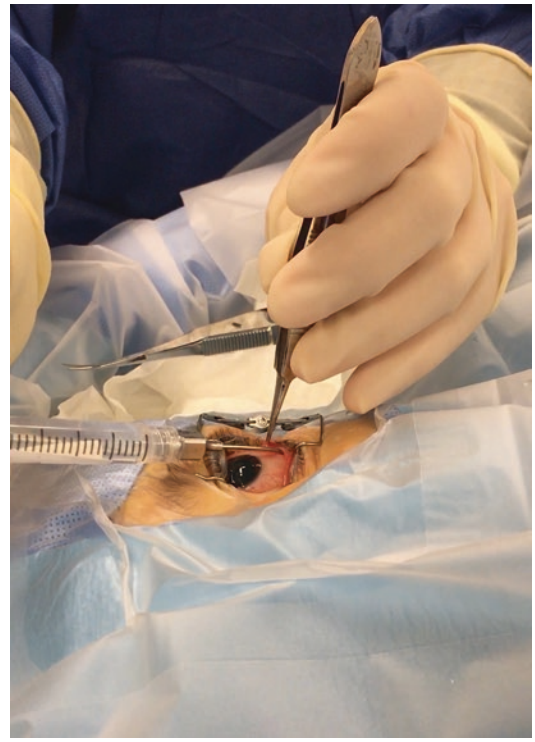

Fig. 2.2 Sub-Tenon pediatric eye block. A short-beveled needle or angled cannula can be used with an amide anesthetic; our institution uses ropivacaine 0.375% for an inferotemporal approach to a peribulbar block useful for postoperative analgesia at the end of major surgery. (Courtesy of Jacqueline L. Tutiven, MD)

Topical Anesthesia and Neonatal Intensive Care Unit Patients

Neonates and premature infants residing in NICUs do not typically require sedation for the brief measurement of IOP. Diagnostic modalities that require minimal movements can fuel discussion on how best to provide immobility in NICUs without exposure to anesthetics. Most academic centers in the United States and United Kingdom conduct *feed and swaddle* techniques for magnetic resonance imaging (MRI) and other noninvasive diagnostics, avoiding sedation altogether [84]. A topical local anesthetic, usually a very short-acting ester anesthetic eye drop, is applied, not only to decrease possible discomfort but to depress the corneal reflex upon achieved surface analgesia. Common topical preparations are lidocaine, tetracaine, and proparacaine. Studies in healthy adults have demonstrated that episcleral venous pressure is not affected by topical anesthetics [85]. Systemic absorption is increased in neonates and infants. The thin keratin layer of the newborn's skin around the eyes, conjunctiva, nasal mucosa, and gastrointestinal tract increases

the systemic absorption of these and many other ocular medications, easily contributing to toxic effects of these or other ocular medications. Punctal occlusion over the nasal lacrimal canal can reduce up to 90% of this absorption. Excess medication overflow should be immediately cleaned and punctal occlusion placed for 3 min to decrease systemic absorption [85, 86].

Postanesthesia Care Unit and the Recovery Period

Monitoring and documentation of all types of anesthetic given to patients must be continued into the recovery phase within the postanesthesia care unit (PACU).

Post-extubation Croup

Small children and infants recovering from general anesthesia are at risk for post-extubation complications such as stridor and dyspnea due to laryngeal swelling. This is seen especially in children convalescing from upper respiratory infections that required an ETT during surgery. The supraglottic airway or LMA may be superior in the aspect of maintaining laryngeal airway patency with less postoperative laryngeal swelling [87].

Postoperative Nausea and Vomiting

Postoperative nausea and vomiting is a major concern following general anesthesia. The risk of PONV may also be elevated due to the type of surgery and its duration even when only sedation is involved, as with surgery on the eye. Children undergoing ocular surgery experience increased incidence of PONV, likely due to a trigeminal-medullary oculo-emetic response, especially following emergence from general anesthesia. Use of inhaled volatile anesthetics, e.g., nitrous oxide, and the inclusion of opioids for pain control are associated with a greater incidence of PONV as is a history of motion sickness. Age of onset of PONV occurs after 2 years of age and increases until puberty, and the risk of PONV in children is thought to be twice that of adults [88]. Prophylaxis against PONV is recommended for those at high risk, and it includes the use of 5-HT_3 antagonists such as ondansetron, the glucocorticoids such as dexamethasone 0.15 mg/kg, and hydration, unless there is a contraindication [88]. Other ancillary medications that can be used effectively to reduce the risk of PONV include clonidine, metoclopramide, droperidol, and substitution of general volatile anesthesia with total IV anesthesia (TIVA) using propofol or dexmedetomidine or some combination thereof.

Ophthalmic surgeries carry one of the highest risks of PONV with an elicitation of the oculocardiac reflex during surgery thought to be predictive of PONV [89]. PONV most frequently occurs in the first 3 h following general anesthesia but can occur up to 24 h after. Persistent PONV in the PACU may herald ongoing acute pressure/volume changes occurring within the eye that may need immediate attention from the surgeon or surgical team [90, 91].

Postoperative Pain

The dissection of extraocular and intraocular tissues is painful and often complicated with postoperative PONV, stressful hemodynamics (high mean arterial pressures), and increased incidence of oculocardiac reflexes (OCR) reflected in the PACU area as moderate pain scores. As mentioned above, the use of a long-acting local anesthetic given via the peribulbar or sub-Tenon route just before emergence from general anesthesia reduces surgical pain and the incidence of PONV. This is due to an effective nerve conduction block of the efferent fibers of the trigeminal nerves that disrupts the trigemino-emetic reflex.

A multimodal approach to pain control best decreases opioid requirement and possibility of PONV. Ketorolac is a nonsteroidal anti-inflammatory drug that can be used topically, via IV or via IM. Acetaminophen is also available in a wide array of formulations, including IV, rectal, pill, or liquid with a low side effect profile.

Intravenous acetaminophen is a novel analgesic for pediatric use in the perioperative period. It offers an alternative or supplement to opioid analgesia when treating surgical pain in term neonates or former preterm infants in whom the reduction of opioid-associated side effects is desirable. Neonates greater than 10 days of age and children weighing up to 33 kg can receive 15 mg/kg every 6 h without evidence of hepatotoxicity. An increase in unconjugated hyperbilirubinemia reflects a low drug clearance, which would dictate lowering the dose [92].

Malignant Hyperthermia

Malignant hyperthermia (MH) is a fatal, unless treated, complication from the use of succinylcholine or volatile anesthetics. There is a hypermetabolic response from these anesthetic triggering agents, which leads to increased intracellular calcium concentration causing an overwhelming metabolic stimulation resulting in increased carbon dioxide and lactic acidosis. This is manifested as tachycardia, tachypnea, and an elevation in body temperature being a late and ominous sign [89]. Treatment involves early recognition with the only antidote, dantrolene. Dantrolene helps to decrease intracellular calcium concentration and should be continued continuously over the next 24 h [93]. An MH reaction often occurs in the operating room but can be delayed to the recovery room after the anesthetic has been terminated. Therefore, there must always exist an index of suspicion when there is unexplained tachycardia, tachypnea, or elevated body temperature that does not respond to normal interventions. Patients that have had previous general anesthetics without an episode of MH are not immune from MH during future anesthetic sessions. Patients on average require three exposures to triggering anesthetic agents to have an MH episode [94, 95].

The suspicion for MH offers a variety of presentations, from sudden death under anesthesia in a family member or the patient may provide a vague history of a family member having an "allergy" to anesthesia. Routine testing is not recommended unless a family member had an MH episode.

The confirmation test for MH is offered only in five centers across the United States and Canada, is extremely expensive, and may not be covered by some insurance plans. The gold standard for diagnosis is the caffeine-halothane contracture test. A person is considered MH susceptible if contracture tests are positive to both caffeine and halothane, and they are considered not susceptible to MH if both tests are negative [95]. Genetic testing is also available for MH as it is autosomal dominant, and the mutation can result de novo. Even if a patient has a negative mutation result, they may still have a positive muscle contracture test deeming them MH susceptible as there are at least 30 causal mutations for MH [96].

Therefore, a diagnosis of MH prior to the operating room is extremely rare unless the patient personally has had a previous reaction. Due to the insidious onset of MH, and difficulty in diagnosis, there is a 24-hour hotline available to anesthesia providers to offer advice regarding symptoms and treatment. If there is a high suspicion for MH, the patient should be scheduled as the first case of the day, and anesthesia machine should be prepared. The vaporizers should ideally be removed from the anesthesia machine, and fresh gas flow should be kept at 10 liters per minute for at least 10 to >90 min depending on the machine. The carbon dioxide canister, breathing circuit, and fresh gas hoses should be new. Each anesthesia machine has different recommendations regarding preparation for a malignant hyperthermia-susceptible patient [96]. Total IV anesthesia (TIVA) should be used to avoid anesthetic vaporizers, and depolarizing muscle relaxants, succinylcholine, should be avoided.

Special Considerations

Many of the children who require anesthesia in the management of childhood glaucoma are healthy and otherwise free of systemic disease such that most anesthesiologists may manage their anesthesia. However, there are those that

will require the specialized knowledge of a pediatric anesthesiologist. The following section summarizes the approach to the more complex patients who may exhibit physiologic and/or anatomic abnormalities that occur with various etiologies of secondary glaucoma and present added risk during induction, airway management, and emergence and postoperatively.

Anesthetic Considerations of Pediatric Glaucoma in the Neonate

Primary congenital glaucoma is the commonest glaucoma seen in infants; however many will develop increased IOP secondary to manifestations of syndromes and systemic disease or as a consequence of prematurity [97]. Neonates share a unique physiology that is shifting from that which is adapted to an in utero environment to life outside the uterus, which requires close and careful intraoperative management. Despite vast improvements, perioperative complication rates, morbidity, and mortality remain disproportionately high in neonates undergoing general anesthesia [3, 5, 97, 98]. The incidence of perioperative neonatal (less than 30 days of life) mortality after cardiac arrest is estimated to be 144.7 per 10,000 anesthetics (0.014%) compared to 2.1 deaths per 10,000 anesthetics (0.00021%) in children aged greater than 10 years (overall mortality 6.8 per 10,000 anesthetics) [5]. Factors which contribute to higher mortality rates include level of preoperative illness, neonatal/infant physiology with depressed cardiopulmonary reserves, and surgical complexity. Neonates, infants, and preterm infants are at an increased risk of apnea due to immaturity of their respiratory center, underdeveloped chemoreceptor responses to CO_2 levels in the blood, and delayed laryngeal reflexes.

While glaucoma surgery in the neonate is considered low risk for adverse cardiopulmonary events, carrying the neonate through an anesthetic brings to the forefront several issues of concern which are unique to the population and include intracardiac shunting with patent foramen ovale or ductus arteriosus open, immature cardiopulmonary physiology that is heart rate dependent, tendencies toward rapid desaturation, and a narrow range of temperature and glucose homeostasis. Furthermore, immature renal function with decreased glomerular filtration rates, compared to adults, impacts many administered anesthetic drugs and sensitivity to opioids and inhaled agents. Anatomical differences of the airway lend to difficult intubation and ventilation in the inexperienced provider, and finally a large percentage of these neonates will have associated congenital anomalies requiring increased vigilance and care [99].

Neurotoxicity and the Neonate Newborns are very susceptible to anesthetics, and the requirement needs to be measured carefully against the urgency, type, and length of surgery. For the past decade, anesthesia-related neurotoxicity risks in newborns and infants have been a topic of interest worldwide. Although epidemiological evidence has not been consistent, it does appear to indicate that neurotoxicity may result after prolonged or repeated exposures to anesthetics early in life [99, 100]. The decision to subject a child to an EUA should not be taken lightly and should be performed with the view to aiding clinical decision-making. Concerns of neurotoxicity should be considered in the context of a disease, which is potentially blinding if not adequately assessed or managed.

Programmed cell death, apoptosis, is an important factor during the development and remodeling of all multicellular organisms, in this case, neuronal tissue. Commonly used anesthetic agents increase neuro-apoptosis and have neurodegenerative effects after exposure in the neonatal period of rodents [99]. Systematic reviews of preclinical and clinical studies have suggested a strong indication of increased neuronal apoptosis after general anesthesia exposure in piglets and nonhuman primates. Studies on rodents and primates support a causal relationship between anesthesia and neonatal neurotoxicity [101]. Retrospective clinical human data in epidemiologic studies saw 10,450 siblings born in 1999, enrolled in the New York State Medicaid program, and found that the incidence of behavioral and developmental problems was 128.2 diagno-

sis per 1000 person-years for the exposed group compared to 56.3 diagnosis per 1000 non-exposed group. The FDA gave a safety alert advisory to health-care professionals. Health-care professionals are to "balance the benefit of appropriate anesthesia in young children and pregnant women against the risks." This is markedly important for cases that may run longer than 3 h or when multiple procedures are required in one patient less than 3 years of age.

These studies were compromised by methodological issues and have been deemed important but nonconclusive. The GAS study (general anesthesia vs. spinal) and the PANDA study (Pediatric Anesthesia and Neurodevelopmental Assessment study) were able to support that a single short anesthetic exposure was not associated with neurodevelopmental compromise [102, 103]. Thoughtful consideration should be given to brain developmental stages. General anesthetics may have an impact on future cognitive and behavioral milestones in humans.

Anesthetic Implications of Childhood Glaucoma Associated with Systemic Disease

A majority of childhood glaucoma cases presenting to the operating suite can be considered to be primary glaucoma with defects limited to one or both eyes and no systemic syndrome or disease. Secondary childhood glaucoma occurs when an independent disease process impairs the ocular filtration system [104–106] which results from an impressive array of clinical conditions, some of which are associated with systemic abnormalities affecting one or more organ systems.

The classification of childhood glaucoma has undergone multiple iterations [99–101], with the latest system as that proposed by the Childhood Glaucoma Research Network and validated by the World Glaucoma Association Consensus on Childhood Glaucoma [107]. Regardless of classification method, it is apparent that a significant proportion of childhood glaucoma is an ocular manifestation of systemic disease. Upward of 36% of all eyes with the diagnosis of childhood glaucoma have secondary glaucoma, i.e., glaucoma associated with non-acquired systemic disease/syndrome, or have an association with an acquired condition [96], and over 45 unique syndromes have been linked to childhood glaucoma [104]. As such, it is imperative for the diagnosing clinician as well as the consultant pediatric anesthesiologist to recognize associated systemic disease or syndromes because of the potential problems for those who require anesthesia, surgery, or intensive acute care management. Children born with these rare syndromes may have problems associated with cardiopulmonary disease and congenital malformations, facial dysmorphisms resulting in difficulties with intubation and/or ventilation, and neurologic effects such as seizure disorders and increased ICPs [108]. These phenotypic manifestations present significant risk during general anesthesia and require careful planning and specific modifications to the anesthetic technique to ensure safe perioperative care. Several of the most common disorders and conditions associated with childhood glaucoma are summarized in Table 2.5 [109–116].

The Cardiopulmonary System in a Syndromic Child Congenital heart disease is a prevalent finding in this cohort of syndromic children. Because the association is so strong, neonates born with dysmorphic features and heart murmur undergo detailed cardiac evaluation and imaging to rule out congenital cardiac disease [117]. A typical childhood glaucoma practice will encounter infants and children who carry structural and functional cardiac defects because many of the syndromes associated with non-acquired glaucoma carry strong associations with congenital cardiac defects, as well. For example, trisomy 13 (Patau syndrome) and trisomy 21 (Down syndrome) each are at high risk for cardiac involvement; in fact, 80% and 50% of afflicted children will have significant congenital cardiac involvement, respectively [115, 116].

The presence of congenital heart disease alone adds considerable perioperative risk and increases perioperative mortality by twofold [118, 119]. Accordingly, children with congenital heart

Table 2.5 Systemic effects and corresponding anesthetic considerations of several common etiologies of secondary childhood glaucoma

Systems affected						
	Cardiovascular	Respiratory	HEENT/airway	Neurologic/ neuromuscular	Metabolic/endocrine	Anesthetic considerations
Glaucoma associated with non-acquired systemic disease or syndrome						
Phacomatoses (64%)						
Sturge-weber (involves the brain, skin, and eyes; ipsilateral vascular anomalies of meninges [leptomeningeal angioma], port-wine stain)	Coarctation of the aorta, visceral/ intraoral angiomatoses, cutaneous hemangiomata, possible AV shunting and HF	–	Hemangiomas of the lips, buccal mucosa, macrocheilia, palate and tongue involvement	Seizures beginning in infancy, intracranial calcifications, leptomeningeal angiomas (98%), hemiparesis, hemianopia, cerebral cortex atrophy	–	Evaluate neurological function closely (EEG imaging), and evaluate heart and airway for malformation presence. Baseline blood and coagulation lab values. Intraoperatively, consider oral vascular involvement and potential for bleeding when planning for intubation. Avoid regional anesthesia due to meningeal hemangioma. Pulse oximetry may be difficult due to capillary anomalies. Avoid medications that reduce seizure threshold, continue anti-epileptic medications up to surgery, and consider neurology consultation for seizure management in severe cases
Klippel-Trenaunay-weber (port-wine stain, abnormal overgrowth of soft tissues and bones, and vein malformations)	Venous and cutaneous capillary malformation, lymphatic abnormalities	Vein malformations → risk of DVT and PE	–	Cerebral aneurysms, spinal cord AVM	Soft tissues/bony hyperplasia	80% of spinal cord lesions rupture/bleed at some point. Avoid cough/Valsalva maneuvers. Baseline blood lab values should be obtained. Obtain neurologic evaluation to localize malformations and avoid perioperative hypertension. Blunt hemodynamic responses to laryngoscopy/surgical stimulation and extubation. Central neuraxial techniques are contraindicated. Avoid triggers and institute prevention techniques for PONV

Neurofibromatosis (skin pigmentation [cafe au lait spots] and benign nerve tumor growth along the skin, brain, and other parts of the body)	Possible thoracic/abdominal aorta coarctation, renal artery stenosis → HTN	–	Macrocephaly, possible laryngeal/pharyngeal neurofibromas → difficult ventilation/intubation	Multiple neurofibromas of the skin and nerves, scoliosis, seizures. Frequent involvement of spinal cord	Possible association with pheochromocytoma/MEN IIB	Consider reviewing MRI to r/o tumor formation in the cervical spine, brain stem, airway or anterior mediastinum. Avoid neuraxial techniques because of possible spinal column involvement. Nerve monitoring is essential, and one may need to tailor the use of muscle relaxants
Chromosomal disorders						
Trisomy 13 (specific midline dysmorphic features, severe intellectual disability, and abnormalities affecting multiple body systems)	Highly associated (80%), VSD/ASD, aortic coarctation, PDA, cardiomyopathy, dextrocardia	Apneic episodes possible. Bi-lobed lung	Cleft lip (60–80%) +/− palate, deafness, airway and nose abnormalities, choanal atresia	Severe development delay, motor seizures, microcephaly, microphthalmia, absent corpus callosum, spina bifida	Feeding difficulties, failure to thrive	Evaluation of cardiac, urologic, neurological function and anatomy for potential airway difficulties. Challenging mask ventilation. Latex precautions with spina bifida. Consider postoperative inpatient observation. Death often occurs before 6 months of life
Trisomy 21 (associated with intellectual disability, a characteristic facial appearance, and hypotonia in infancy)	Congenital heart disease (50%): VDS, ASD, AV canal defect, endocardial cushion defect	Recurrent lung infections	Microphthalmia, macroglossia, pharyngeal hypotonia, subglottic stenosis, obstructive sleep apnea, midface hypoplasia, high narrow arch	Atlantoaxial instability, cognitive and motor delay with hypotonia	Congenital hypothyroidism, immune deficiency	Anticipate difficult intravenous access. Potential for perioperative airway obstruction. Cervical instability may cause post-intubation subluxation. If symptomatic, cervical spine films and smaller endotracheal tube should be used for intubation. Preoperative cardiac evaluations should be considered in view of potential bradycardia on inhalation inductions. Consider post-op observation or admission if airway difficulties/obstruction exists

(continued)

Table 2.5 (continued)

Systems affected						
	Cardiovascular	Respiratory	HEENT/airway	Neurologic/ neuromuscular	Metabolic/endocrine	Anesthetic considerations
Connective tissue disorders						
Stickler syndrome (progressive arthro-ophthalmology condition affecting eyes, face, and joints)	Mitral valve prolapse (50%)	–	Flat distinctive face, sensorineural deafness (10%), myopia, PRS (10%) → retrognathia, glossoptosis, airway obstruction +/−cleft palate	Intracranial calcifications, normal intellect	Bony enlargement of joints at birth, hypermobility	Cardiac evaluation preoperatively. PRS strongly associated—Prepare for difficult intubation. Examine joint mobility, and position carefully. Consider regional anesthetic
Marfan syndrome (generalized connective tissue disorder with weakness of the connective tissues)	Valvular (MVP, TR, MR) or aortic root dissection (progressive into adulthood)	Intrinsic lung involvement—Emphysema, bronchogenic cysts → spontaneous/ tension pneumothoraces, restrictive lung disease from vertebral/chest wall deformities	Temporomandibular joint at risk of subluxation or dislocation → difficult intubation	High-arched palate	Hyperextensible joints, disproportionately long extremities, pectus excavatum, kyphoscoliosis	Cardiopulmonary evaluation. Careful mechanical ventilation to avoid barotrauma-induced pneumothoraces. Careful positioning and protection of joints. Control blood pressure and lung pressures under anesthesia. Neonatal/infantile form: Lax skin, scoliosis, adducted thumbs, extremity contractures, micrognathia, muscle hypoplasia, ectopia lentis, severe cardiac valve insufficiency/aortic dilatation resulting in early death
Craniofacial						
Rubinstein-Taybi (short stature; moderate/severe developmental delay distinctive facial features; broad thumbs and first toes; and other cardiac, digestive and respiratory malformations)	33% cardiac defects (PDA, ASD, or VSD)	Frequent respiratory infections, asthma	Characteristic facies (100%)—Microcephaly (84%), micrognathia (100%), choanal atresia, narrow mouth/palate, frontal bossing, hearing loss/low-set ears; feeding/swallowing difficulties	Significant development delay (100%), corpus callosum agenesis, hypotonia, hyperreflexia, seizures. Association with neurological tumors (neuroblastoma, meningioma)	Short stature (94%), scoliosis	Evaluate cardiac function and thorough airway examination. Risk of pulmonary aspiration due to GI anomalies. Difficult laryngoscopy with facial malformations

Glaucoma associated with non-acquired ocular conditions						
Rieger syndrome/ SHORT syndrome (short stature, hyperextensibility of joints or hernia or both, ocular depression, Rieger anomaly, and teething delay) when *without* dental/skeletal defects	–	–	Maxillary > mandibular hypoplasia, midface hypoplasia, dental hypoplasia	Myotonic dystrophy (rare reports with Rieger syndrome), sensorineural deafness, development and speech delays	Pituitary deficiencies: Adrenal insufficiency, short stature, low birth weight dwarfism, lipoatrophy, DM	Perioperative glucose monitoring—Fasting and glucose/ insulin requirements will depend on severity of DM. Hyperextensible joints—Manipulate the neck and joints during positioning with care. Look out for low birth weights in neonatal period. Cautious use of NDNMB due to unpredictable paralytic response. Dental and craniofacial abnormalities may lead to difficult airway
Glaucoma associated with acquired conditions						
Retinopathy of prematurity (common blinding disease in neonates associated with delayed retinal vascular growth and hypoxia-induced pathological growth)	Immature sympathetic nervous system, proclivity of bradycardia	Apnea of prematurity risk with anemia and GA, BPD, history of prolonged intubation secondary to lung immaturity	Anatomic variation of the neonatal airway	Intravertebral hemorrhage, seizures in the extreme prematurity	Possible hypotonia, immature glucose regulation, immature hepatic metabolism of medications	Avoid hypoxemia. May require overnight stay if outpatient procedure. EUA may be done at bedside in NICU if inpatient

(continued)

Table 2.5 (continued)

Systems affected						
	Cardiovascular	Respiratory	HEENT/airway	Neurologic/ neuromuscular	Metabolic/endocrine	Anesthetic considerations
Intraocular neoplasms						
Retinoblastoma (familial malignant ocular tumor of the retina caused by defect in specific Rb regulatory gene)	–	–	–	Potential local invasion or into optic nerve	Late disease with bone metastasis	Can be associated with other primary malignancies (leukemia, lymphoma, pinealoma, Ewing or osteogenic sarcoma) and 13q syndromes. Caution during administration of laser therapy (safety risk) and during intra-arterial chemotherapy → a severe bronchospastic reaction (autonomic cardiorespiratory reflex) and hemodynamic instability, which requires treatment with epinephrine). Children undergo many anesthetics and likely develop significant associated anxiety

ASD Atrial septal defect, *AV Arteriovenous, AVM Arteriovenous malformation, BPD* Bronchopulmonary dysplasia, *CHD* Congenital heart disease, *DM* Diabetes mellitus, *DVT* Deep vein thrombosis, *EEG* Electroencephalography, *EUA* Examination under anesthesia, *GA* General anesthesia, *GI* Gastrointestinal, *HEENT* Head, ears, eyes, nose, throat, *HF* Heart failure, *HTN* Hypertension, *MEN* Multiple endocrine neoplasia, *MR* Mitral regurgitation, *MRI* Magnetic resonance imaging, *MVP* Mitral valve prolapse, *NDNMB* Non-depolarizing neuromuscular blockade, *NICU* Neonatal intensive care unit, *PDA* Patent ductus arteriosus, *PE* Pulmonary embolism, *PONV* Postoperative nausea and vomiting, *PRS* Pierre Robin sequence, *SHORT* Mnemonic for short stature, hyperextensibility, ocular depression (deeply set eyes), Rieger anomaly, and teething delay, *TR* Tricuspid regurgitation, *VSD* Ventral septal defect

Note: For neurofibromatosis type 1, Klippel-Trenaunay syndrome, Sturge-Weber syndrome, trisomy 13, Down syndrome, and Stickler syndrome, see also the US Dept. of Health and Human Services, US National Library of Medicine, Genetics Home Reference. https://ghr.nlm.nih.gov/about

disease must undergo careful evaluation and optimization prior to entering the perioperative setting, which will include detailed records of the structural and functional anatomy. Additionally, all procedural and surgical history—palliative versus corrective—and current cardiac function should be provided for review and appropriate risk assessment [120].

Several factors will impact the plan for the anesthetic care of these patients. The nature, complexity, and status of surgical repair, as well as the presence of significant intracardiac shunting of blood, will determine whether the additional expertise of pediatric anesthesiologists with subspecialty training in congenital cardiac anesthesia will be necessary. Furthermore, the choice of anesthesia medications, IV access location, and need for invasive monitoring in those with limited hemodynamic reserve and careful choosing of location of perioperative care (i.e., choosing a hospital operative setting rather than outpatient ambulatory surgery center) which should be at a pediatric center with those familiar with the care of these individuals will be tailored accordingly [121]. After anesthesia exposure or surgical intervention, some of these children may require extended observation in the postanesthesia recovery unit or inpatient admission for close continuous monitoring. With appropriate and complete preoperative evaluation, experienced anesthesiologist care, appropriate use of agents, techniques, and invasive monitoring, anesthetic care in children with congenital heart disease can be safe and effective during the bulk of noncardiac surgeries.

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