Anesthesia for pediatric ophthalmologic surgery

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SUMMARY This review presents updated recommendations, based on existing clinical research, for anesthetic management of strabismus surgery in children. In children, unlike adults, eye surgery nearly always requires general anesthesia, even for brief procedures. Recommendations for preoperative anxiolysis, fasting guidelines, and management of upper respiratory infections are discussed. Airway considerations and the oculocardiac reflex are highlighted. The prevention of postoperative complications, including those related to opioid prescription therapy, is also addressed. Finally, given the 2016 warning from the Food and Drug Administration about anesthesia neurotoxicity in children, we discuss recent studies on anesthetic neurotoxicity in children undergoing general anesthesia. (J AAPOS 2019;23:127-131)

Most children presenting for ophthalmologic surgery are in overall good health. Routine anesthetic evaluation should review chronic medical problems and screen for any family history of complications from anesthesia, in particular a familial history of malignant hyperthermia (MH). Children with strabismus were once thought to be at higher risk for MH because of a suspected possible link between strabismus and coexisting muscle disease. This concern was never validated, and strabismus is no longer considered an independent risk factor for MH. Strabismus is associated with a multitude of other genetic syndromes, however, each presenting unique risks from anesthesia.[1] Syndromes associated with strabismus include higher risk of difficult intubation (Cri du chat syndrome, Goldenhar syndrome), congenital heart disease (Down syndrome, Rubinstein-Taybi syndrome), and metabolic abnormalities (homocystinuria).

Preoperative fasting guidelines have been developed in order to lessen the risk of pulmonary aspiration of gastric contents during elective surgery. Serious pulmonary aspiration is rare, but risk factors include high volume of gastric fluid, low pH of stomach contents, and presence of aspirated solids/particulate matter. Traditional "NPO after midnight" rules have been challenged for pediatric patients, particularly infants, because prolonged fasting leads to irritability, thirst, and physiologic derangements (hypoglycemia, low blood pressure) on the day of surgery. Currently most institutions follow some variation of the 8-6-4-2 rule for preoperative fasting: 8 hours for solids, 6 hours for infant formula, 4 hours for breast milk, and 2 hours for clear liquids.[2] After a light meal, 6 hours of fasting is reasonable, but a large or fatty meal may require longer fasting (eg, 8 hours). Clear liquids include water, apple juice, and pediatric oral rehydration fluids[3] While ongoing research investigates whether the 2-hour limit on clear liquids is unnecessarily restrictive, most clinicians are reluctant to reduce these fasting intervals. For patients with severe gastroesophageal reflux or other abdominal diseases, more prolonged fasting before elective surgery may be advised.

Pediatric patients presenting for surgery frequently arrive with recent upper respiratory tract infections (URIs).[4] During active or recent URIs, many studies find an increased risk of respiratory complications—bronchospasm, laryngospasm, prolonged coughing, and oxygen desaturation—events are related to active inflammation, increased secretions, and increased airway reactivity. Adverse respiratory events can lead to increased costs and higher rates of postoperative hospitalization.[5] Although airway hyperreactivity following a URI decreases over time, there is no clear consensus as to when it is safest to proceed with surgery. The increased risk persists for 2-6 weeks after acute URIs. The decision of when to delay surgery must also take into account that children will average a URI every 6-9 weeks; thus children may fall ill again at the next surgery date.[6-8] Specific factors that increase the chance of respiratory complication are the presence of fever, productive cough, nontransparent rhinorrhea, and change in baseline functional status (energy/appetite/sleep). Young age (infants at highest risk), a history of reactive airway disease, airway anomalies, and secondhand smoke exposure at home also increase risk.[9] Most experts agree that waiting for at least 2 weeks after URIs can substantially lower the risk. Management by a specialist pediatric anesthesiologist has been shown to further reduce risk of complications by almost half.[10]

Preoperative anxiety is common in children. Up to 60% of young children undergoing surgery and anesthesia report significant anxiety.[11] Preoperative anxiety can lead to

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postoperative morbidities, such as difficulties with eating and sleeping, regression in toilet training (eg enuresis), negative behavioral changes, and worse postoperative pain control.[12] Managing preoperative anxiety to reduce psychological trauma involves a multimodal approach. Numerous studies have demonstrated the utility of preoperative preparation programs, including tours, videos, books, and modeled play.[13] On the day of surgery, child life specialists can continue the preoperative preparation with games and other reassuring techniques. Distraction and attention redirection using electronic aids (eg, tablets and smartphones) can successfully lower anxiety, in some cases as effectively as premedication with midazolam.[14-17] Pharmacological anxiolytics provide a common method for reducing preoperative anxiety. Optimal efficacy depends on selection of an appropriate medication, proper dose, as well as properly timing the administration of the medication for onset prior to induction of general anesthesia. The routes for anxiolytics delivery are oral, intranasal, intravenous, and intramuscular.[18] A child's anxiety can be further lessened by effectively managing parents' anxiety.[19] In many institutions, a parent is given the option of joining the child in the operating room, called "parent present induction of anesthesia." Whereas this option has been demonstrated to consistently increase parental satisfaction in a number of studies, it is probably most effective when a child is accompanied by a calm parent.[20,21]

Intraoperative Considerations

Whether or not a preoperative anxiolytic medication is administered, most children undergo an inhalational induction of anesthesia on arriving at the operating room. This avoids the stress of intravenous (IV) catheter insertion for most children. For eye surgeries of short duration, some anesthesiologists may forego IV placement throughout the entire surgery. Avoiding IV placement can improve workflow efficiency and may boost parental satisfaction. On the other hand, establishing a peripheral IV facilitates medication administration (eg analgesics, antiemetics) and may increase safety during surgery or postoperative care. Whether safety is truly improved by having an IV has been specifically evaluated. Two recent studies did *not* find more complications without an IV for routine ophthalmologic examinations, including laser and injection procedures.[22,23] For longer surgeries or in patients with a higher risk of complications (recent illnesses, airway abnormality, history of postoperative nausea/vomiting), placement of an IV is still warranted. Intravenous access is also useful during surgeries with an increased risk of side effects from ophthalmic medications. For example, excessive absorption of ocular phenylephrine drops can produce profound cardiac side effects (hypertension, cardiac overload, and pulmonary edema).[24] Severe phenylephrine toxicity requires urgent treatment with intravenous vasodilators. Ophthalmic administration of local anesthetics can also lead to systemic toxicity through accidental intravascular injection or by excessive systemic absorption.[25] In the case of bupivacaine, local anesthetic toxicity typically presents with cardiac depression or arrhythmia due to the affinity of bupivacaine to bind cardiac sodium ion channels. Maximum dose recommendations for bupivacaine (up to 2.5 mg/kg) should be adhered to carefully, and special care must be taken to avoid intravascular injection.

Management of the airway during general anesthesia can be accomplished by several methods. For brief procedures, where the surgical field can be shared between surgeon and anesthesiologist, a face mask suffices. Often it is more practical to place an endotracheal tube or supraglottic device, such as the laryngeal mask airway (LMA). The use of LMAs and similar devices has become routine since their introduction in the United States in the 1990s. The device sits above the vocal cords and maintains an open conduit for gas exchange from the larynx to the anesthesia breathing circuit. LMA benefits include ease of placement and potential decrease in the incidence of complications, such as postoperative oxygen desaturation and coughing.[26] Potential disadvantages of supraglottic devices include less protection against aspiration, position dislodgement, and the risk of laryngospasm, during which the vocal cords involuntarily close, resulting in airway obstruction and hypoxia. Endotracheal intubation with paralysis remains prudent for prolonged surgeries, most intraocular surgery, and cases with a high risk of hemorrhage (eg, craniofacial/orbital procedures).

A unique concern during ophthalmologic surgery is the risk of bradycardia due to the oculocardiac reflex, which is defined as a 20% decrease in heart rate or a new arrhythmia during traction on the ocular muscles and occurs during up to 90% of strabismus surgeries.[1] Pressure on the globe or increased intraorbital pressure can also trigger the reflex, which is transmitted through the trigeminal and vagus nerves. It is more common during total IV anesthesia than with inhaled anesthetics, and it occurs more often during periods of inadequate anesthesia depth.[27] Opioids and dexmedetomidine, an alpha-2-agonist medication, can accentuate the bradycardia.[28,29] Both classes of medications alter autonomic stimulation to the heart by decreasing the sympathetic outflow and increasing the parasympathetic outflow.[30,31] Profound bradycardia or arrhythmia may require pausing surgery. The effects on heart rate will typically diminish with repeated manipulation. Some anesthesiologists prefer to prevent or blunt the phenomenon by administering an anticholinergic medication, such as glycopyrrolate or atropine, prior to surgical manipulation. However, the oculocardiac reflex can be useful to the surgeon in some rare situations, such as in the identification of a slipped or "lost" extraocular muscle.[32] In such cases, blunting the oculocardiac reflex would be disadvantageous.

Postoperative Considerations

Up to 80% of preschool and school-aged children (18 months to 8 years of age) awaken from general anesthesia with a period of postoperative excitement known as emergence delirium (ED).[33] ED manifests clinically as a state of psychomotor agitation—a constellation of involuntary restlessness, inconsolable crying, and poor eye contact that is not responsive to typical comforting and consoling measures.[34] It may be mistaken for pain or a temper tantrum. Unpleasant for parents and health care providers, ED can also lead to patient injury and prolonged postoperative care. Long-term effects on children include behavior problems, night terrors, and increased anxiety for weeks to months.[35] The pathophysiology of ED is complex and not completely understood. Its etiology is likely multifactorial, with patient temperament, pain control, and anesthetic medications being the most important contributors. Preoperative anxiety and the use of modern short-acting inhalational anesthetics (sevoflurane or desflurane) are associated with an increased chance of ED.[36] Among the many strategies to reduce the incidence or attenuate the severity of ED is the use of the relatively new intravenous anesthetic, dexmedetomidine. A highly selective alpha-2 receptor agonist, dexmedetomidine possesses anxiolytic, sedative, and analgesic properties. Dexmedetomidine has been shown to reduce ED in a number of studies.[37,38] As mentioned above, dexmedetomidine can worsen the bradycardia from the oculocardiac reflex; it should be used with caution during eye surgery.

Pain control requirements following pediatric ophthalmic surgery vary by procedure. Adequate analgesia has been shown to decrease postoperative distress and may decrease the incidence of emergence delirium. Opioids remain central to perioperative analgesia. Several points regarding opioids are worth mentioning. Opioids increase the risk of postoperative nausea in a dose-dependent mannerand should be used judiciously.[39] Likewise, it is reasonable for prescribers to minimize the quantity of opioids dispensed into the community, given the national epidemic of opioid abuse. Nonopioid analgesics, such as nonsteroidal anti-inflammatory medications (NSAIDs) and acetaminophen, should be considered for every patient, as their administration may provide sufficient analgesia without use of opioids. To control more significant postoperative pain, local anesthetics can be useful. Sub-Tenon's or subconjunctival injections of local anesthetics may provide better pain relief than topical drops alone.[40] Bupivacaine is myotoxic, however, so direct injection into the extraocular muscles should be avoided. Retrobulbar and peribulbar blocks are effective for analgesia, but they risk injury to the globe, optic nerve, or blood vessels resulting in hemorrhage.[41]

When opioids are administered for postoperative pain, clinicians must be aware of how variations in metabolism can affect the therapeutic response. The opioid codeine is uniquely problematic and should be avoided when other opioids are available. Codeine is a prodrug, requiring metabolism to the active drug, morphine, by the liver cytochrome P450 (CYP) pathway in order to be analgesic. Due to genetic variation, there exist "rapid-metabolizers" of codeine via CYP-2D6. These individuals are at increased risk of respiratory depression due to elevated serum levels of morphine when treated with codeine.[42] As a result, the Food and Drug Administration (FDA) has issued advisory warnings against the use of codeine for postoperative pain.[43,44] Conversely, codeine can be ineffective at treating pain in other individuals ("poor-metabolizers") due to low activity of CYP-2D6, resulting in less active drug morphine.[45] Hydrocodone is another commonly used opioid often formulated in combination with acetaminophen. Similar to codeine, hydrocodone is also a prodrug—it is metabolized to the active analgesic hydromorphone by CYP-2D6. As is the case with codeine, there exist "poor-metabolizers" and "rapid-metabolizers" of hydrocodone, yielding either decreased or increased serum levels of hydromorphone, respectively.[46] Given the specific issues with codeine and hydrocodone, clinicians may wish to consider opioids (such as oxycodone) that are less influenced by variation in drug metabolism.

The risk of postoperative nausea and vomiting following general anesthesia depends on the type of surgery, duration of anesthesia, and patient risk factors (eg, age and history of motion sickness). Following pediatric strabismus surgery, the rate of nausea is particularly high, occurring in 60%-70% of strabismus patients if nausea prophylaxis medication is not administered.[47] Combination therapy with dexamethasone and ondansetron has been shown in multiple studies to be more effective at reducing postoperative nausea than giving one agent alone.[1]

A theoretical concern for researchers, anesthesiologists, and surgeons for several decades has been the potential for neurotoxicity from anesthesia exposure in children. This has recently emerged as a prominent concern for parents and the public. After publication of a *Newsweek* article in 2008, public consciousness of this topic has increased greatly.[48] Toxicity concerns are rooted in in vitro and in vivo animal studies of GABA-agonist and NMDA-antagonist anesthetic agents. Animal studies, including nonhuman primate studies, have demonstrated increased neural apoptosis and corresponding clinical effects, such as impaired learning and memory, after exposure to some anesthetic agents.[49] Most of these studies exposed animals to long durations of very high doses anesthetic agents—sometimes >100 times the clinical doses used in modern anesthesia.[50,51] In contrast, human studies have been inconsistent in demonstrating harm from anesthetics. Studies that do find a link between anesthetic exposure and behavior or learning impairments are retrospective reviews and are therefore limited in their conclusions on cause and effect.[52,53] Nonetheless, the possibility of anesthetic neurotoxicity raised by existing research prompted the FDA to announce in December 2016 that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their 3rd trimester may affect the development of children's brains."[54]

Following this announcement, both the Society for Pediatric Anesthesia and the American College of Obstetrics and

Gynecology issued statements of concern regarding the potential harm in postponing or avoiding elective surgery.[55] Given that the anesthetic agents in question have been used for decades without major developmental effects noted, it is suspected that any deleterious effects would be minor cognitive impairment or subtle behavioral changes.[56-58] Prospective randomized-controlled human studies evaluating these risks are ongoing. One study (comparing general anesthesia with regional anesthesia for hernia repair) showed no detectable difference in neurodevelopment outcome at 2 years of age.[59]Subsequent neurocognitive testing at age 5 years in this same cohort also showed no significant differences in cognitive or behavioral tests.[60]

Clinicians caring for pediatric surgical patients are likely to be asked about neurotoxicity. Some pediatric anesthesiologists have altered their anesthetic management in light of these theoretical concerns. Strategies include increased use of regional anesthesia (such as local anesthetics) rather than deep general anesthesia as well as preference for agents believed to be safer for neurodevelopment. For example, dexmedetomidine has demonstrated a protective role in several animal studies, potentially reducing the neurotoxicity of general anesthesia.[61,62] Other protective agents (eg, xenon, carnitine, lithium) are under active study. For now, it is reasonable to reassure parents that although the effects of anesthesia on a child's development remain unclear, most recent human studies have been reassuring. Likewise, a short duration of anesthesia (as is common in ophthalmologic surgery) appears safer than a long-duration or repetitive exposures. At the same time, it is reasonable to wait to schedule truly elective surgeries (ie, those for which delaying surgery has no effect on potential outcome) until children are older than 3 years most.

Surgeon-anesthesiologist interactions are critical to the safe anesthesia experience for children. The surgeon should be aware of medical problems that could pose anesthesia problems and should convey these to the anesthesiologist *before* surgery. Changes in heart rate, oxygen saturation, and temperature of the patient under anesthesia should be part of the surgeon's purview as well. If the patient is "light" under anesthesia, this is often heralded by the patient showing a Bell's sign or by movement on the patient's part. Communication to the anesthesiologist that the second eye is about to be operated are helpful, because patient movement and stimulation may be generated by operating in a new area of the body. Lastly, both the surgeon and anesthesiologist should aim to create a working environment in the operating room that ensures both maximum efficiency and patient safety.

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