Perioperative Care of the Pediatric Neurosurgical Patient

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Abstract

The management of infants and children with conditions of the brain and spinal cord can be challenging, and optimal management requires a thorough understanding of the developmental stages, age related physiological changes, and the pathophysiological processes that occur with these conditions. Patients with neurological conditions often undergo neurosurgical procedures and encounter clinicians from a variety of specialties. The perioperative period, is therefore, an important therapeutic window and clinicians who manage these patients during this period can provide patients with the opportunity to achieve full neurological recovery before, during, and after neurosurgery. For the preoperative period, pediatricians and emergency physicians are able to diagnose urgent/emergent neurosurgical conditions, prepare patients neurosurgery and prevent clinical deterioration from neurological conditions until definitive therapy such as neurosurgery can be provided. During surgery, anesthesiologists aim to provide optimal brain physiological conditions and optimal anesthetic and hemodynamic care during complex neurosurgical procedures. During the postoperative period, intensivists are responsible for anticipating and preventing postoperative consequences, and for helping patients achieve full neurological recovery. This chapter provides information on the neurological issues that should be considered during the perioperative period in the care of children undergoing neurosurgery.

Keywords

Neurosurgery • Brain • Perioperative • Critical care

Abbreviations

ADH	Antidiuretic hormone
ATLS	Advanced Trauma Life Support
ATP	Adenosine triphosphate
AVM	Arteriovenous malformations
BBB	Blood brain barrier
CBF	Cerebral Blood Flow
CBFV	Cerebral blood flow velocity\
cCAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CMR	Cerebral metabolic rate
CMRglu	Cerebral metabolic rate for glucose
$CMRO_2$	Cerebral metabolic rate of oxygen
CNS	Central Nervous System

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CO_2	Carbon dioxide
CO_2R	Reactivity to Carbon dioxide
CPP	Cerebral perfusion pressure
CS	Cortical stimulation
CSF	Cerebro-spinal fluid
CSW	Cerebral salt wasting
CT	Computed tomography
CVR	Cerebrovascular resistance
DI	Diabetes insipidus
ECoG	Electrocorticography
EEG	Electroencephalogram
EMG	Electromyography
ET-1	Endothelin-1
GCS	Glasgow Coma Scale
HR	Hoffman reflex
ICP	Intracranial Pressure
ICPm	Intracranial Pressure monitoring
IHAST	International Hypothermia in Aneurysm Surgery Trial \
IM	Intramuscular
iTBI	Involving Traumatic Brain Injury
IV	Intravenous
LLA	Lower Limit of Autoregulation
MAC	Minimum alveolar concentration
MAP	Mean Arterial Pressure
MEP	Motor evoked potentials
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
NIRS	Near infrared spectroscopy
NO	Nitric oxide
NOS	Nitric oxide synthase
O_2	Oxygen
$PaCO_2$	Partial pressure of arterial carbon dioxide
PALS	Pediatric Advanced Life Support
PaO_2	Partial pressure of oxygen in arterial blood
PG	Prostaglandin
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SBP	Systolic blood pressure
SCI	Spinal cord injury
SCIWORA	Spinal cord injury without radiological abnormalities
SDR	Selective dorsal rhizotomy
$SjvO_2$	Jugular venous oxygen saturation
SSEP	Somatosensory evoked potentials
TBI	Traumatic Brain Injury
TCD	Transcranial Doppler
TIVA	Total intravenous anesthesia
VAE	Venous air embolus (or emboli)
V_{BAS}	Basilar artery flow velocity
V_{MCA}	Middle cerebral artery flow velocity

Introduction

The perioperative management of pediatric neurosurgical patients presents challenges to physicians from many disciplines including pediatricians, emergency medicine physicians, neurosurgeons, anesthesiologists, and intensivists. A basic understanding of age-dependent variables and the interaction between preoperative, anesthetic, and surgical conditions and needs are essential to minimizing perioperative morbidity and mortality and to optimizing outcomes after neurosurgery. This chapter will highlight these age-dependent physiological and pathophysiological changes relevant to the perioperative (preoperative, intraoperative and postoperative) management of the pediatric neurosurgical patient.

Developmental Physiology of the Nervous System

Intracranial Pressure (ICP)

Under normal physiological conditions, ICP is 2–6 mmHg in full term infants and higher in children and adults (0–15 mmHg). Intracranial compliance is defined as the change in intracranial pressure relative to the intracranial volume. As intracranial volume acutely rises, the ability to compensate due to lack of compliance reduces and ICP increases. Acute increases in cranial volume due to massive hemorrhage or obstructed cerebro-spinal fluid (CSF) flow cannot be attenuated by expansion of the cranial vault and frequently result in life-threatening intracranial hypertension in infants [1]. Once the fontanelles and sutures have closed, children have a relatively smaller cranial volume and lower intracranial compliance than adults. Contributory factors to increases in ICP include a higher ratio of brain water content, less CSF volume, and a higher ratio of brain content to intracranial capacity [2]. Intracranial hemorrhage, inflammation/infection, tumors or congenital malformations can lead to decreased CSF absorption with possible elevations in ICP. Pediatric neurosurgical patients may have elevated ICP during the perioperative period due to any of these processes described above from preoperative or post surgical hemorrhage of any space occupying lesion.

Cerebral Blood Flow (CBF)

Complex homeostatic mechanisms regulate the cerebral circulation during the perioperative period and these must be considered when managing systemic and cerebral hemodynamics. Factors influencing CBF are: (1) cerebral

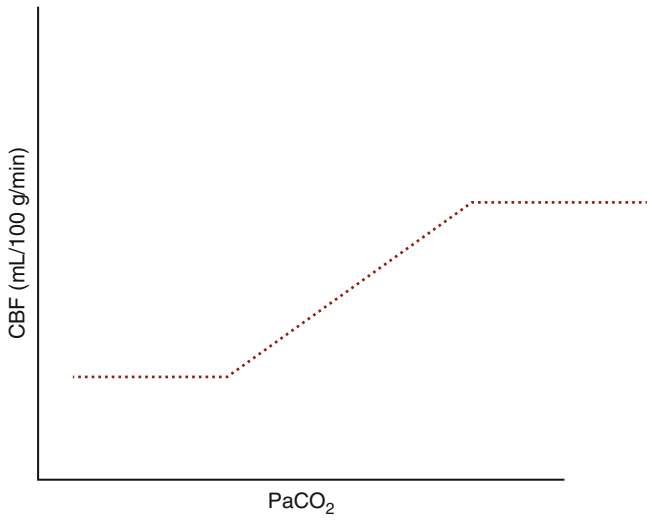

Fig. 10.1 Relationship between $PaCO_2$ and cerebral blood flow

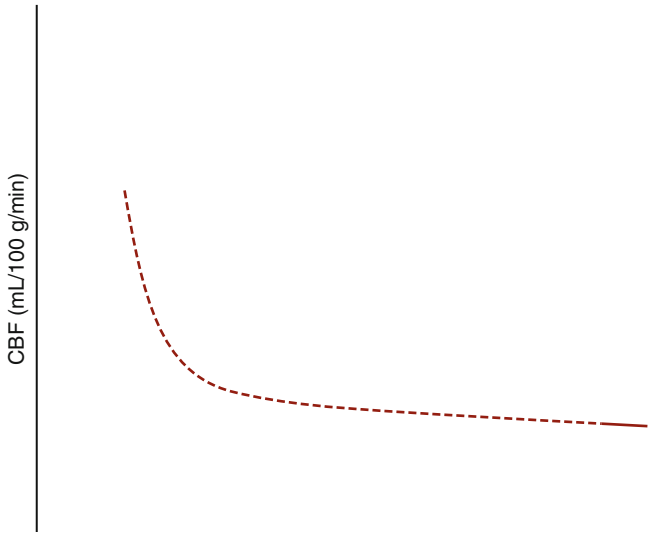

Fig. 10.2 Relationship between PaO_2 and cerebral blood flow

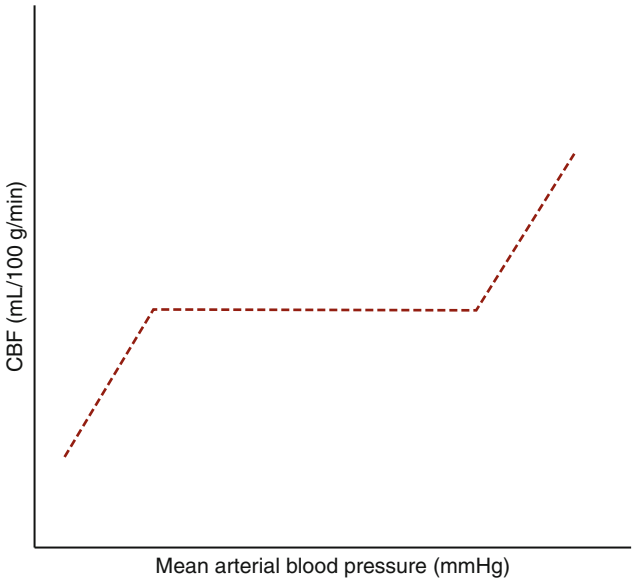

Fig. 10.3 Relationship between mean arterial pressure and cerebral blood flow (normal cerebral autoregulation)

metabolism, (2) partial pressure of arterial carbon dioxide ($PaCO_2$) (Fig. 10.1) (3) partial pressure of oxygen in arterial blood (PaO_2) (Fig. 10.2) (4) blood viscosity and (5) cerebral autoregulation (Fig. 10.3). Flow-metabolism coupling is the most significant regulator of the cerebral circulation and is typically preserved [3–5]. However, during periods of central nervous system (CNS) activation, CBF increases more than $CMRO_2$, resulting in a decrease in the cerebral oxygen extraction fraction [6] During development, CBF changes with age, mirroring changes in neural development and synaptogenesis. The healthy brain receives about 15 % of cardiac output and normal adult CBF is approximately 50 mL/100 g/min. There are relatively few data on CBF available from healthy children. In one older study, Kennedy and Sokoloff found CBF to be much higher, on the order of 100 mL/100 g/min, in conscious healthy children [7]. A recent study using arterial spin labeling found similar values in young children [8], which then decrease and approach adult values during the adolescent years, suggesting that CBF increases during early childhood, peaks during early-mid childhood and plateaus during late childhood at approximately 7–8 years [9].

Compared to $PaCO_2$, the influence of PaO_2 on the cerebral circulation is of much less clinical significance. There are minimal changes in CBF with changes in PaO_2 above 50 mmHg below a threshold of PaO_2 of 50 mmHg, CBF increases to maintain adequate cerebral oxygen delivery. Cerebral blood flow may be excessive (hyperemia) or inadequate (ischemia) relative to cerebral metabolism during the perioperative period, these changes may be focal, regional and or global, and advanced neuromonitoring techniques may aid in increasing our understanding of the pathophysiological processes involved.

Cerebral Metabolic Rate (CMR)

Global CMR for oxygen and glucose is generally higher in children than in adults (oxygen 5.8 vs. 3.5 mL/100 g brain tissue/min and glucose 6.8 vs. 5.5 mL/100 g brain tissue/min respectively [7]). Similar to age related changes in CBF, studies of healthy anesthetized children also suggest age-related increases in $CMRO_2$, which are 104 μmol/100 g/min in infants and 135 μmol/100 g/min in children ages 3 weeks–14 years [8]. Similar to $CMRO_2$, cerebral metabolic rate for

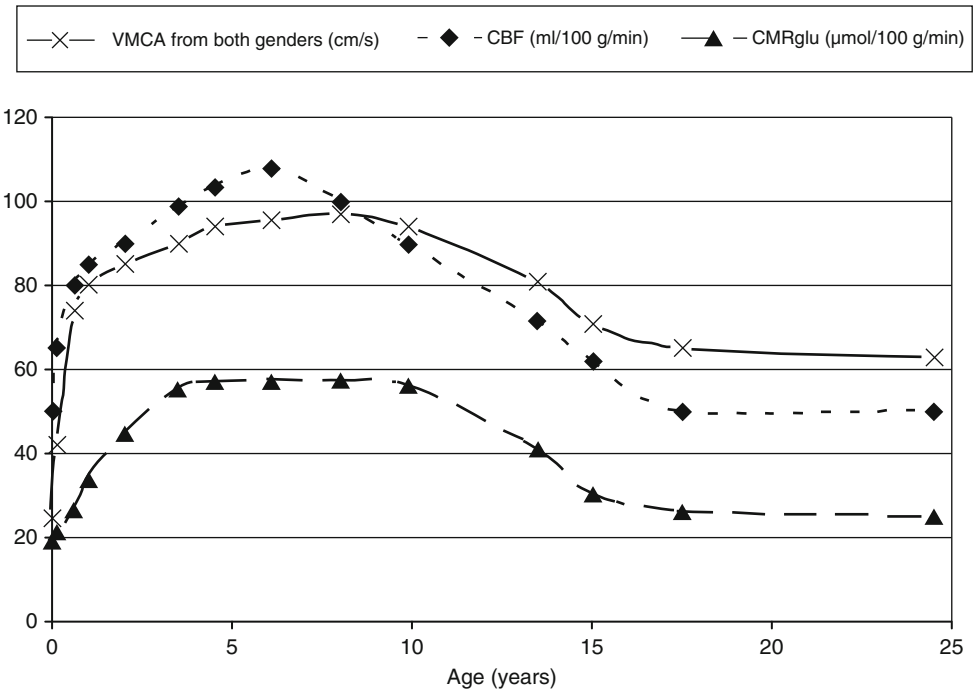

Fig. 10.4 Age-related changes in mean flow Velocity of Middle Cerebral Artery (*VMCA*) in both sexes, Cerebral Blood Flow (*CBF*), and Cerebral Metabolic Rate of Glucose (*CMRglu*). Corresponding Adult Values: VMCA 50 cm/s, CBF 50 mL/100 g/min, CMRglu 19–33 mol/100 g/min

glucose (CMRglu) is lower at birth (13–25 µmol/100 g/min), increases during childhood, peaks by 3–4 years (49–65 µmol/100 g/min), and remains high until 9 years of age. Thereafter CMRglu decreases, and approaches adult rates (19–33 µmol/100 g/min) [10]; changes in $CRMO_2$ and CRMGlu mirror age-related changes in CBF (Fig. 10.4). Cerebral metabolic rate of oxygen and glucose may be altered in children with neurosurgical conditions during the perioperative period, especially while receiving sedation, and or while recovering from general anesthesia.

CO_2 Reactivity

$PaCO_2$ is the most powerful modulator of the cerebral circulation and the cerebral circulation is exquisitely sensitive to changes in $PaCO_2$ [11, 12]. Yet, much of our therapy aimed to modulate changes in CBF via changes in $PaCO_2$ is empiric, and without knowledge of individual patients CO_2 reactivity or CBF response to the intervention made. Similar to CBF and metabolism, carbon dioxide (CO_2) reactivity may be higher in healthy children than in adults [13–15]. Studies suggest that reactivity to CO_2 is well developed even in healthy preterm infants [16] and that CO_2 reactivity in newborns correlates with the lowest pH and may reflect the severity of perinatal asphyxia [17]. One recent study suggests that CO_2 reactivity and cerebral autoregulation may be altered in patients undergoing tumor resections (Fig. 10.5). While these data are from adults, it is possible that the same pathophysiological processes occur in children.

Viscosity and CBF

Compared to $PaCO_2$, the influence of viscosity on the cerebral circulation is less. There are minimal changes in CBF with changes in PaO_2 above 50 mmHg below a threshold of PaO_2 of 50 mmHg, CBF increases to maintain adequate cerebral oxygen delivery. Unlike CO_2R, the equilibration of CBF is longer and takes approximately 6 min after the establishment of hypoxemia [18]. The influence of oxygen, on the cerebral circulation is less so than exerted by $PaCO_2$. Variability in Hct in children undergoing neurosurgery may lead to variability in CBF, CBV and ICP.

Cerebral Autoregulation

Cerebral autoregulation is an important homeostatfic regulator of CBF where arterioles dilate and constrict to maintain CBF nearly constant over a range of blood pressures. In healthy adults, changes in mean arterial pressure (MAP) between 60 and 160 mmHg results in little or no change in CBF [19, 20]. This adaptive mechanism maintains constant (adequate) CBF by vasodilation or decreasing cerebrovascular resistance. Under normal conditions, beyond these limits of autoregulation, hypotension may result in cerebral ischemia, and hypertension may cause cerebral hyperemia.

Healthy infants appear to autoregulate CBF as well as older children, but the long held assumption that the lower limit of autoregulation (LLA) is lower in younger compared to older children may not be valid (same LLA range for

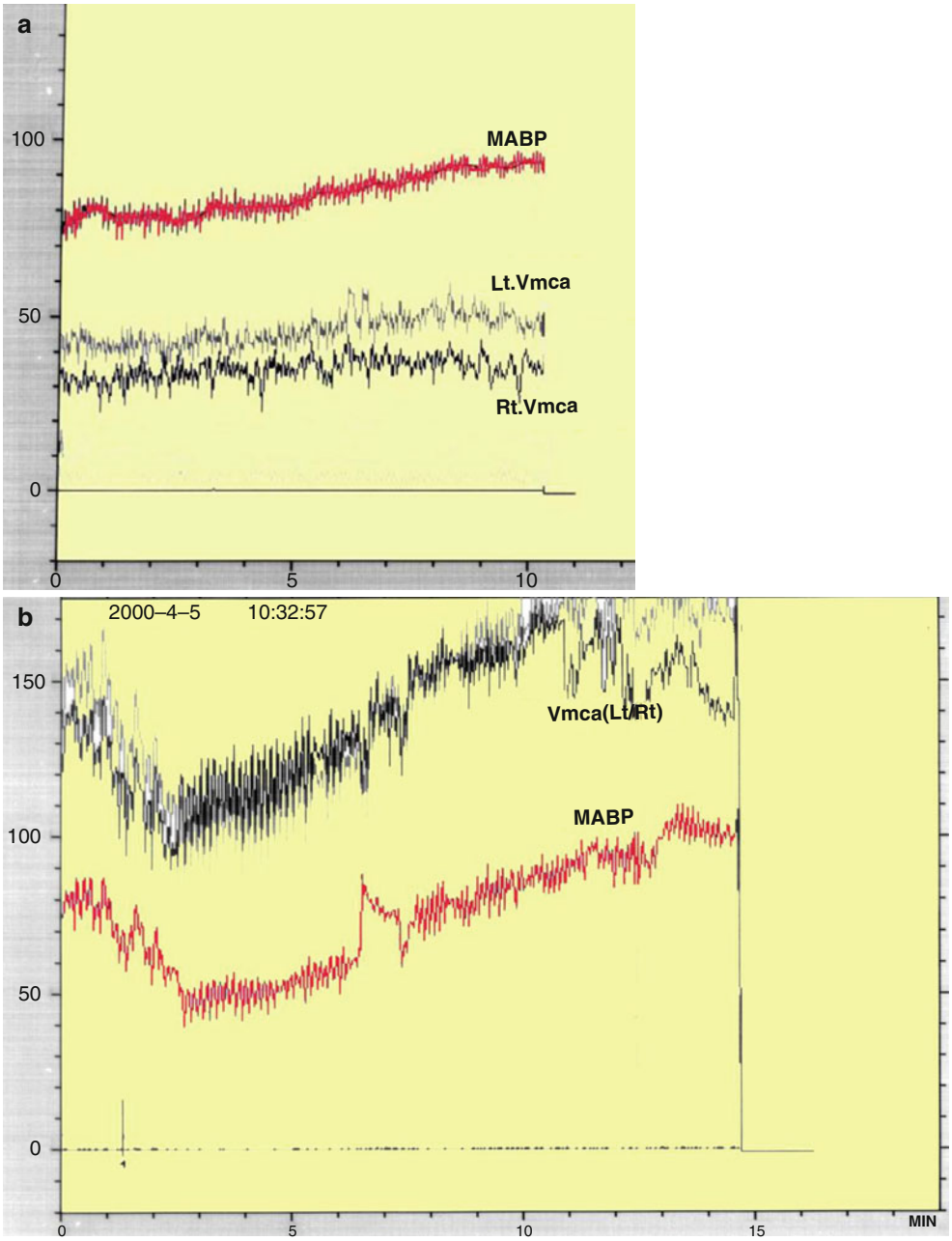

Fig. 10.5 Intact (**a**) and impaired (**b**) Cerebral autoregulation

younger and older children 46–76 mmHg) [21]. There are no data on the LLA in healthy neonates. However, estimates of the lower limit of autoregulation derived from the cerebral oximetry index in pediatric patients undergoing cardiopulmonary bypass were at 42 ± 7 mmHg [22]. Since blood pressure increases with age, neonates and young children may be at increased risk of cerebral ischemia due to lower blood pressure reserve (mean arterial pressure – LLA) and narrow autoregulatory range [23] and during critical illness, CBF may be completely pressure passive [24]. Therefore, tight blood pressure control is essential in the management of neonates to minimize both cerebral ischemia during hypotension and intraventricular hemorrhage with increased blood pressure. There may also be age-related differences in the time to return of normal autoregulation in young children [25] but there are no data on this in neonates. Animal data suggest that while CBF pressure autoregulation and reactivity to CO_2 operate in the newborn rat, hypercapnia abolishes cerebral autoregulation [23] and that abolished autoregulation is associated with cerebral damage in asphyxiated infants. Moreover, the combination of isoelectric electroencephalograms and cerebral hyperperfusion is an early indicator of very severe brain damage [16]. Despite these clinical observations, mechanisms of normal cerebral autoregulation in healthy children and adaptations in acute disease are not completely understood and like changes in CBF, both

anatomic and physiological maturation might play a role in the development of a fully developed autoregulatory response. Children with neurosurgical conditions such as traumatic brain injury (TBI) or tumors may have impaired cerebral autoregulation during the peri-operative period, requiring clinicians to actively provide tight control of systemic and cerebral hemodynamics [26].

Pharmacology of the Nervous System

Intravenous sedative and anesthetic drugs affect cerebral hemodynamics and have varying cerebral hemodynamic profiles. Different classes of sedatives differentially impact cerebrovascular resistance, cerebral autoregulation, CBF, and CMR. Preoperative sedation and analgesia choice may impact intraoperative cerebral hemodynamics, and intraoperative use of volatile anesthetic agents may affect post operative recovery and outcomes. Post operative choice of sedation and analgesia may influence the clinician's ability to perform an adequate neurological examination and prevent timely tracheal extubation.

Propofol

It has been reported that propofol maintains cerebral autoregulation and cerebrovascular reactivity to carbon dioxide above 30 mmHg end-tidal carbon dioxide levels in children [27]. Furthermore, propofol, at high doses, lowers CBF and mean arterial pressure values in children, which may be mediated by its cerebral vasoconstrictive properties [28]. Propofol may depress systemic blood pressure but both potently decrease $CMRO_2$, CBF, and ICP [29]. Propofol has been purported to have neuroprotective properties, especially in preclinical studies, but its clinical efficacy in neurologically compromised pediatric patients has not been tested. Etomidate and ketamine are less likely to cause hypotension than propofol. However, CNS excitation and increased ICP have been associated with these drugs respectively, and they may not be appropriate for many neurosurgical patients. Finally, propofol infusion syndrome which characterized by the lactic acidosis, rhabdomyolysis, and circulatory collapse after prolonged administration of propofol, in children, precludes its use for sedation beyond 48 h in the PICU setting [30].

Barbiturates

Barbiturates decrease CBF, CBV, and $CMRO_2$ in a dose dependent manner [31–33] and therefore reduce ICP. Neither CBF nor cerebral metabolism is significantly altered by subanesthetic doses of barbiturates. When the electroencephalogram (EEG) becomes isoelectric, CBF and $CMRO_2$ decrease to about 50 % of normal, and additional doses of barbiturates have little further effect. Barbiturates may also be used to prevent increases in ICP that can occur with laryngoscopy and tracheal intubation. Autoregulation and the cerebrovascular response to changes in $PaCO_2$ remain intact during barbiturate anesthesia. The rate of CSF formation and the resistance to reabsorption of CSF are not altered by barbiturates [34]. In doses that suppress the EEG, barbiturates reduce cerebral damage in animal and human models of focal cerebral ischemia [35, 36]. In animals, barbiturates also reduce the extent of cerebral edema after a cortical freeze injury. This decrease in edema is in contrast to the response observed with the volatile anesthetics [37].

Opioids

Opioids are commonly used as a part of a sedation plan during the perioperative period in neurosurgical patients. In general, opioids have little effect on CBF, CBV, or ICP unless respiration is depressed and $PaCO_2$ is increased [38–41]. Fentanyl, for example, is generally considered safe in pediatric neurosurgical patients and does not alter the rate of CSF formation, though it does reduce the resistance to CSF reabsorption by 50 % [42, 43]. The neonatal cerebral circulation is unaffected by fentanyl [44]. At conventional doses, sufentanil [45, 46] and alfentanil [47] do not appear to have adverse effects on the cerebral vasculature or upon ICP in most patients. In a subset of patients with severe head injuries and very poor intracranial compliance, sufentanil may cause a small (e.g., 10 mmHg) and transient increase in ICP that may be clinically significant in some settings [48–50]. Remifentanil is an ultra–short-acting opioid that is rapidly metabolized by plasma cholinesterases and has gained in popularity for use as part of the general anesthetic technique. The very short clinical duration of effect of remifentanil and its context-sensitive half life that is independent of the duration of infusion [51, 52] make it an appealing opioid for lengthy neurosurgical procedures, after which rapid return of consciousness is desirable. As is the case with other opioids that have been studied, remifentanil does not increase CBF or ICP [53, 54]. Remifentanil, like other opioids, preserves cerebral autoregulation and CO_2 reactivity [55–58]. Return of consciousness is very rapid after remifentanil is discontinued, and the frequency of administration of naloxone to permit neurologic assessment is decreased [59]. However, because remifentanil analgesia is very brief after its discontinuation, a long-acting opioid analgesic must be administered to prevent severe pain and rebound hypertension before or soon after remifentanil is discontinued [60, 61].

Etomidate

Etomidate reduces ICP by decreasing CBF and $CMRO_2$ by 34 and 45 %, respectively. It, too, preserves the CO_2 responsiveness of the cerebral circulation [62, 63]. A side effect of etomidate administration is myoclonus. Myoclonus has been reported after prolonged continuous infusion of etomidate [64].

Lidocaine

Lidocaine in clinical doses decreases CBF and reduces the increase in ICP associated with endotracheal intubation [65, 66]. The *benzodiazepines* (diazepam, lorazepam, and midazolam) decrease CBF and $CMRO_2$ approximately 25 % [67–72]. Adrenal suppression remains a concern.

Ketamine

In contrast to the other intravenous anesthetic agents, ketamine is a potent cerebrovasodilator. Ketamine increases CBF by 60 % with little change in $CMRO_2$ [73–75]. The cerebrovascular response to administration of ketamine is thought to be the result of regional cerebral activation induced by the drug [76]. Ketamine produces a marked increase in ICP, which can be reduced, but not prevented, by hyperventilation [74, 77, 78]. The increase in CBF, and presumably in ICP, can be blocked by previous administration of thiopental [73]. Ketamine has been associated with sudden elevation of ICP and clinical deterioration when used in patients with hydrocephalus and other intracranial pathology [78–80]. While ketamine is currently not routinely used as a general anesthetic in patients with reduced intracranial compliance, one recent study in critically ill children reported decreases in ICP following ketamine [81], thereby questioning the notion that ketamine increases ICP.

Dexmedetomidine

Dexmedetomidine is a selective alpha 2 agonist sedative hypnotic agent with a short half life that reduces sympathetic tone and is associated with decreasing opioid needs, benzodiazepines, propofol, and other sedative medication needs. Short-term sedation has been shown to be safe in studies, although hypotension and bradycardia are the most significant side effects with rebound hypertension occurring after abrupt cessation [82–86]. These side effects can be ameliorated by a low dose infusion without bolus (generally $\leq$0.5 μg/kg/h). In adults, dexmedetomidine decreases CBF in a dose related manner, decreases CMR, and preserves flow metabolism coupling, though it may decrease dynamic autoregulation [87, 88]. One small series found no adverse effect on brain PbO_2 with dexmedetomidine. Dexmedetomidine has been used as a sedative to facilitate awake craniotomy [89]. Overall, dexmedetomidine is emerging as an effective therapeutic agent in the management with a favorable cerebrovascular profile [90].

Neuromuscular Blocking Agents

Succinylcholine is a depolarizing neuromuscular blocking agent and is associated with life-threatening hyperkalemia and cardiac arrest in children with undiagnosed myopathies and has a U.S. Food and Drug Administration "black box warning". Life-threatening hyperkalemia has been associated with succinylcholine administration in many types of central nervous system disorders, including TBI [90–93], near-drowning [94] subarachnoid hemorrhage [95], encephalitis [96], cerebrovascular accidents [97], and paraplegia [98, 99]. The onset of the period of vulnerability may begin as early as 24–48 h after injury and may last up to 1–2 years after injury [98]. Because the period of risk for succinylcholine-induced hyperkalemia after cerebral injury is undefined, succinylcholine should be avoided in these patients, except in the period immediately after injury. Succinylcholine can increase CBF and ICP in patients with reduced intracranial compliance [100–103] probably because of cerebral stimulation from succinylcholine-induced increases in afferent muscle spindle activity [104]. In contrast, most nondepolarizing relaxants have little effect on CBV and ICP [105–108] unless associated with histamine release (*d*-tubocurarine, atracurium), which causes transient cerebrovasodilation and increased ICP [109]. Succinylcholine use in critically ill children, especially in those who have not been ambulatory for 48 h is not recommended. Hemiplegia from an upper motor neuron lesion (such as a stroke or a brain tumor) is associated with resistance to nondepolarizing relaxants on the paretic side [110–112] Excessive doses of muscle relaxants may be given if dosage is guided by a nerve stimulator monitoring a hemiplegic extremity. In contrast, an increased response to nondepolarizing muscle relaxants is observed in paretic muscle lower motor neuron lesions (e.g., paraplegia and quadriplegia) [113]. Acute administration of several anticonvulsants, including phenytoin and phenobarbital, enhances nondepolarizing neuromuscular blockade or delays its reversal [114, 115]. Importantly, many patients who have been receiving chronic phenytoin or carbamazepine therapy are relatively resistant to the effects of nondepolarizing relaxants [116–119], including rocuronium [115, 120], due to enhanced metabolism [121, 122].

Cerebral Vasodilators

Direct-acting vasodilators, including sodium nitroprusside, adenosine, nitroglycerin, diazoxide, and hydralazine, which may be used intraoperatively and into the postoperative period, impact cerebral physiology. These agents are cerebrovasodilators and may increase CBF and ICP [123–126]. The calcium channel blockers also raise CBF and ICP [127, 128]. These drugs should therefore be avoided in patients with reduced intracranial compliance, unless the dura is open or ICP is being monitored. Sodium nitroprusside lowers the range of cerebral autoregulation. Brain-surface oxygen tension is greater [129] and metabolic disturbances in brain biochemistry (e.g., lactate, pyruvate, and phosphocreatine levels) are less during nitroprusside-induced hypotension than with trimethaphan-induced or hemorrhage-induced hypotension [130].

Fluids, Blood Products, and Electrolytes

Meticulous fluid management is critical in the care of neurosurgical patients in children. Small patient size and immature renal function result in fluid and electrolyte imbalances. Water freely diffuses through the blood brain barrier and disruptions in tight junctions, and inequality of pressure gradients in osmolality, hydrostatic pressure, and colloid oncotic pressure facilitate the net movement of fluid across the blood brain barrier into the brain, resulting in increased ICP. Osmolar gradients are maintained only when the blood brain barrier is intact, otherwise large molecules that are typically excluded such as albumin enter the brain and can worsen edema.

There is no definitive formula for volume replacement for the pediatric neurosurgical patient. Hemodynamic stability during the perioperative period requires careful maintenance of intravascular volume where pre-operative fluid restriction and/or diuretic therapy may lead to blood pressure instability and even cardiovascular collapse if sudden blood loss occurs during surgery. Therefore, normovolemia should be maintained throughout the perioperative period. Estimation of the patient's blood volume is essential in determining the amount of allowable blood loss and when to transfuse blood.

Isotonic crystalloid solutions (Plasmalyte) are commonly used during general anesthetic and for cerebral resuscitation. Rapid infusion of large quantities of normal saline (>60 mL/kg) can be associated with hyperchloremic acidosis [131]. The calculated maintenance rate of fluid administration depends on the weight of the patient [132]. These rates are based on normal physiologic conditions. Increases in insensible losses, blood loss, or other conditions such as diabetes insipidus or the syndrome of inappropriate anti-diuretic hormone excretion, as noted below should be considered when determining the proper amount of fluid administration. Depending on the extent and length of the surgical procedure and exposure of vascular beds, additional fluid administration 3–10 mL/kg/h may be necessary during the intraoperative period. Unlike adults, children can become hypovolemic from scalp injuries and isolated TBI. Hypotonic crystalloids should be avoided during the perioperative period. The role of colloids is controversial. In 2007, the SAFE study reported that adult patients with TBI who received fluid resuscitation with albumin had higher mortality rates compared to those who received fluids with crystalloids [133]. The use of hydroxyethyl starch is discouraged during the perioperative period for resuscitation because of its role in exacerbating coagulopathy. Hypertonic saline 0.1–1.0 mL/kg may be used to increase CPP, but in this setting, studies show that there is no advantage to hypertonic saline compared to conventional pre-hospital fluid protocols [134].

Since the potential for significant blood loss is likely in most craniotomies in infants and children, the maximum allowable blood loss should be determined in advance and a type and cross should be available prior to surgery and during the postoperative period. There are no guidelines regarding an appropriate threshold for transfusing blood in the neurosurgical patient since it is unclear what hematocrit is needed for optimum oxygen delivery for the pediatric brain and in different disease states. Thus, the decision to transfuse should be dictated by the type of surgery, underlying medical condition of the patient, and potential for additional blood loss both intra- and postoperatively. In general, hematocrits of 17–25 % may warrant blood transfusion. Packed red blood cells (10 mL/kg) will raise the hematocrit by 10 %. Blood losses during surgery may be replaced with 3 mL of normal saline for 1 mL of estimated blood loss or a colloid solution such as 5 % albumin of an equal volume to the blood loss. It can be difficult to accurately estimate blood loss during intracranial procedures as the anesthesiologist may have a compromised view of the surgical field as well as having "hidden" blood loss in the drapes or elsewhere.

Infants are at particular risk for perioperative hypoglycemia. Small premature neonates, with limited reserves of glycogen and limited gluconeogenesis, require continuous infusions of glucose at 5–6 mg/kg/min in order to maintain serum levels. At the same time, the stress of critical illness and resulting insulin resistance can produce hyperglycemia that, in turn, is associated with neurologic injury [135, 136] and poor outcomes in adults [137]. However, it is unclear if tight glycemic control offers significant benefits to children [138, 139]. Limited evidence now suggests that tight control may carry undue risk of hypoglycemia and newer data are less supportive of very tight glycemic control [140]. Retrospective studies from children suggest that both hyperglycemia (glucose 200–250 mg/100 mL) and hypoglycemia occur after TBI [141] and that hyperglycemia is associated with poor outcome.

Cerebral edema can be occur during the perioperative period and may result in devastating consequences. Aggressive hyperventilation should be reserved for situations where herniation is impending and immediate life-saving maneuvers are required and data from patients with TBI suggest that even mild hyperventilation leads to hypoperfusion [142]. Elevation of the head above the heart and the use of hyperosmolar therapy (i.e., mannitol/hypertonic saline) are also methods to reduce ICP. Mannitol may be used in doses of 0.25–0.5 g/kg intravenously. This will transiently alter cerebral hemodynamics and raise serum osmolality by 10–20 mOsm/kg [143]. However, repeated dosing can lead to extreme hyperosmolality, renal failure and further brain edema. Hypertonic saline increases serum sodium, decreases ICP and increases CPP titrated to a serum sodium rate change and brain edema [144]. Standard administration at our institution is typically 3 mL/kg as a 3 % via a central line (to avoid phlebitis and tissue necrosis) targeted to a serum sodium rate change of 0.05 meq/h with endpoints depending on initial serum sodium and degree of brain edema (typically 155–160 meq/L). Hypertonic saline concentrations of 2 % may be administrated peripherally. Theoretical risks include central pontine myelinolysis and renal failure. Furosemide is a useful adjunct to mannitol, can reduce CSF formation, and decrease acute cerebral edema as well as preventing rebound swelling due to mannitol [145, 146].

Electrolyte Disorders

Non-osmotic secretion of antidiuretic hormone (ADH) makes hyponatremia common after neurosurgery. Elevated ADH levels can result from a variety of stimuli ranging from pain and nausea to fluid shifts and intravascular hypovolemia. Acute hyponatremia can provoke seizures and may be treated with hypertonic saline, fluid restriction, and administration of diuretics [147]. Cerebral salt wasting (CSW) occurs in approximately 11.3/1,000 procedures [148] with a duration of 6 days [149] in children and can be seen following TBI and other neurosurgical procedures and disease states such as meningitis [150], calvarial remodeling [151, 152], tumor resection [149], and even hydrocephalus [153]. Cerebral salt wasting, the result of excessively high atrial or brain natriuretic peptide levels [154], is marked by hyponatremia, hypovolemia, and excessive urinary excretion of sodium. Although the classic treatment involves saline administration, more rapid resolution has been achieved with fludocortisone [155].

Diabetes insipidus (DI) is a well-known complication of neurosurgical procedures involving or adjacent to the pituitary and hypothalamus, in association with craniopharyngioma, where it can be a presenting symptom in 40 % of cases. Diabetes insipidus is recognized by a rising serum sodium (>145 mg/dL) accompanied by copious (>4 mL/kg/h) output of dilute urine. Severe dehydration and hypovolemia may develop. One effective protocol employs maximal antidiuresis with intravenous vasopressin and strict limitation of intravenous fluids [156]. This strategy avoids the pitfalls of titrating drug to urine output and recognizes that renal blood flow remains normal in the normovolemic, but maximally antidiurese, child. Since urine output can be minimal (0.5 mL/kg/min), other clinical markers of volume status must be assessed.

Preoperative Evaluation and Preparation

Given the urgent nature of many pediatric neurosurgical procedures, a thorough preoperative evaluation may be difficult. However, it is important to obtain a relevant patient history which can reveal conditions that may increase the risk of adverse reactions to anesthesia and perioperative morbidity and identify patients who need more extensive evaluation or whose medical condition needs to be optimized before surgery. The chronicity and severity of the patient's neurological condition will vary greatly and should dictate perioperative management. Special attention should be given to symptoms of allergy to latex products (e.g., meningomyeloceles) [157]. Severe dehydration and electrolyte abnormalities can be the result of protracted vomiting from intracranial hypertension. Patients with diabetes insipidus can develop hypovolemia due to polyuria. During the perioperative period, steroids are frequently initiated to palliate cerebral swelling in patients with intracranial tumors and therapeutic levels of anticonvulsants should be verified preoperatively and maintained. Patients on long-term anticonvulsants may develop toxicity, especially if seizures are difficult to control. This reaction frequently manifests with abnormalities in either the hematologic, hepatic function, or both.

Physical Examination

The preoperative physical examination should, at a minimum, include a brief but serial neurologic evaluation, that includes; (1) level of consciousness, (2) motor and sensory function, (3) normal and pathologic reflexes, (4) integrity of the cranial nerves, and (5) signs and symptoms of intracranial hypertension. Preoperative diagnoses predispose patients to complications such as those listed in Table 10.1. The modified Glasgow Coma Scale for infants and children is useful for assessing the mental status of the patient (Table 10.2). Lesions of the brainstem can manifest with cranial nerve dysfunction such as respiratory distress, impaired gag and swallowing, and pulmonary aspiration. Evidence of muscle atrophy and weakness should be noted, particularly if the

patient is hemiparetic, hemiplegic or bedridden, since up-regulation of acetylcholine receptors may precipitate sudden hyperkalemia following succinylcholine administration and induce resistance to nondepolarizing muscle relaxants in the affected limbs. Body weight should be accurately measured to guide the administration of drugs, fluids, and blood products. Physical signs of dehydration should be noted, especially in patients who have been chronically ill or received osmotic or diuretic agents.

Table 10.1 Perioperative clinical implications for infants and children with neurological conditions

Condition	Clinical implications
Denervation injuries	Hyperkalemia after succinylcholine,
	Resistance to non-depolarizing muscle relaxants, abnormal response to nerve stimulation
Chronic anticonvulsant therapy	Hepatic and hematological abnormalities
	Increased metabolism of anesthetic and sedative agents
Arteriovenous malformation	Potential congestive heart failure
	Seizures
	Increased intracranial pressure
Neuromuscular disease	Malignant hyperthermia
	Respiratory failure
	Sudden cardiac death
Chiari malformation	Apnea
	Aspiration pneumonia
	Stridor
Hypothalamic/pituitary lesions	Diabetes insipidus/SIADH
	Hypothyroidism/hyperthyroidism
	Adrenal insufficiency/adrenal excess

Radiologic and Laboratory Evaluation

Most neurosurgical patients will have a brain magnetic resonance imaging (MRI) or CT scan as part of the preoperative assessment regardless of whether the preoperative period includes the emergency department or the ICU. These scans should be reviewed with the neurosurgeon in order to confirm the primary lesion and the presence of evolving neurological conditions (hydrocephalus, compressed cisterns, and midline shifts). For elective patients undergoing neurosurgery and who otherwise have no reason to have anemia, coagulopathy or electrolyte disturbances, no preoperative laboratory data may be required, as blood samples can be frequently obtained after induction of general anesthesia. In emergent cases, critically ill children, and trauma, the risk of significant blood loss associated with neurosurgery makes it desirable to have a preoperative hematocrit, electrolytes, and coagulation studies (e.g., prothrombin time and partial thromboplastin time). Patients with suprasellar pathology who undergo elective or semi-elective neurosurgery should have a preoperative endocrinology evaluation for ensuring optimized endocrine status (i.e., thyroid function). Type and cross matched blood should be order prior to all craniotomies and this may be facilitated either preoperatively or immediately after induction of anesthesia depending on local blood availability.

Premedication

Patients are typically admitted to the operating room for neurosurgery from the emergency department or ICU. Perioperative anxiety plays a significant role in the care of the pediatric neurosurgical patient for patients, providers and

Table 10.2 Modification of the Glasgow Coma Scale Score for young children

Glasgow Coma Scale	Pediatric Coma Scale	Infant Coma Scale	Score
Eyes	*Eyes*	*Eyes*	
Open spontaneously	Open spontaneously	Open spontaneously	4
Verbal command	React to speech	React to speech	3
Pain	React to pain	React to pain	2
No response	No response	No response	1
Best verbal response	*Best verbal response*	*Best verbal response*	
Oriented and converses	Smiles, oriented, interacts	Coos, babbles, interacts	5
Disoriented and converses	Interacts inappropriately	Irritable	4
Inappropriate words	Moaning	Cries to pain	3
Incomprehensible sounds	Irritable, inconsolable	Moans to pain	2
No response	No response	No Response	1
Best motor response	*Best motor response*	*Best motor response*	
Obeys verbal command	Spontaneous or obeys verbal command	Normal spontaneous movements	6
Localizes pain	Localizes pain	Withdraws to touch	5
Withdraws to pain	Withdraws to pain	Withdraws to pain	4
Abnormal flexion	Abnormal flexion	Abnormal flexion	3
Extension posturing	Extension posturing	Extension posturing	2
No response	No response	No response	1

parents, often related to the cognitive development and age of the child. Preoperative sedatives given prior to the induction of anesthesia can ease the transition from the preoperative holding or ICU area to the operating room [158]. Sedatives are administered in the parents' presence to facilitate a smooth separation and induction whether patients are coming to the OR from the ED or ICU. Midazolam (0.5–1.0 mg/kg) may be given orally or intravenously with adequate nurse supervision and in the absence of respiratory symptoms. Heavy premedication may be warranted to avoid agitation in patients with Moyamoya Syndrome or an intracranial aneurysm/arteriovenous malformation that has recently hemorrhaged. Opioids may be withheld preoperatively, since they may cause nausea or respiratory depression, especially in patients with increased ICP. Any administration of sedatives or analgesics that depress mental status merits close clinical observation and pulse oximetry in the child who will undergo neurosurgery.

General Principles of Intraoperative Management

General anesthesia is typically described to have three phases: induction, maintenance, and emergence. Typically, the patient's preoperative status will dictate the appropriate technique and medication choices for all phases of general anesthesia.

Induction Phase of Anesthesia

In the presence of intracranial hypertension, the primary goal during induction is to minimize severe increases in ICP. In general, most intravenous drugs decrease CBF and metabolism and ICP. Thiopental (4–8 mg/kg) or propofol (2–5 mg/kg) have similar effects on cerebral hemodynamics and maintain tight coupling of CBF and CMR. Patients at risk for aspiration pneumonitis (including certain patients with high ICP) should have a rapid-sequence induction of anesthesia using cricoid pressure. An intravenous hypnotic drug such as thiopental or propofol is given and then immediately followed by a rapid acting muscle relaxant. Rocuronium can be used when succinylcholine is contraindicated, such as for patients with spinal cord injuries or paretic extremities. In instances of pre-existing neurologic injury such as a patient with a history of a stroke resulting in a weak extremity, succinylcholine can result in sudden, catastrophic hyperkalemia. Etomidate and ketamine are frequently used to induce anesthesia in hemodynamically compromised patients, since these drugs are less likely to cause hypotension than thiopental or propofol. However, CNS excitation and increased ICP have been associated with these drugs respectively, and they may not be appropriate for many neurosurgical patients. Ketamine may be avoided because of its known ability to increase cerebral metabolism, CBF, and ICP in patients with increased ICP. Mask induction can be induced in certain situations when patients are neurologically stable. ICP can be lowered during induction with controlled hyperventilation and administration of an opioid and/or barbiturates before laryngoscopy and intubation. A non-depolarizing muscle relaxant may then be administered after intravenous (IV) access has been established to facilitate intubation of the trachea. As discussed above, succinylcholine should be avoided in patients with denervating processes such stroke, or spinal cord injury, since it can result in life-threatening hyperkalemia.

Airway Management

Developmental changes and the presence of genetic disorders/syndromes in airway anatomy have a significant impact on management of the pediatric airway. Nasotracheal tubes may be preferred for situations when there is no concern for basilar skull fractures and when the patient will be prone since orotracheal tubes can kink at the base of the tongue when the head is a flexed and result in airway obstruction. The timing of tracheal extubation may be challenging following neurosurgical procedures. Infants, particularly those with the Chiari malformation [158] or myelomeningocoele [159] or children after procedures in the posterior fossa [160] may exhibit intermittent apnea, vocal cord paralysis, or other irregularities before resuming a stable respiratory pattern. Significant airway edema and postoperative obstruction can complicate prone procedures or those involving significant blood losses and large volume replacement. Lingual or supraglottic swelling may require direct laryngoscopy to assess the airway. Head-up positioning and gentle forced diuresis usually improves airway edema within 24 h. The presence of airway edema post operatively may be impacted by intraoperative patient positioning (e.g., prone positioning for posterior fossa and spinal cord surgery). In addition to the physiological sequelae of the sitting position, a whole spectrum of neurovascular compression and stretch injuries can occur. . Postoperative visual loss has been linked to spine surgery. The etiology is unclear but, in adults, may be linked to prone positioning, surgical duration, surgical blood loss, anemia or hypotension. Challenges with intraoperative positioning include prevention of excessive neck rotation to prevent venous flow, and prevention of venous air emboli (VAE) [161, 162].

Vascular Access

The routine use of central venous catheters in pediatric neurosurgical patients is controversial. At a minimum, the anesthesiologist will use two large peripheral venous cannulae for most craniotomies. Should peripheral intravenous be difficult to secure, central venous access may be needed.

Since significant blood loss and hemodynamic instability can occur during craniotomies, an arterial catheter provides direct blood pressure monitoring and sampling for blood gas analysis.

Maintenance Phase of Anesthesia

Specific drugs utilized for the maintenance of anesthesia have not been shown to affect the outcome of neurosurgical procedures when properly administered [163]. The most frequently utilized technique during neurosurgery consists of an opioid (i.e., fentanyl, sufentanil or remifentanil) and low dose (0.2–0.5 %) isoflurane or sevofurane (<1 MAC). Administration of a preoperative benzodiazepine such as midazolam (0.5 mg/kg p.o., 0.1 mg/kg I.V.) in select patients should provide some degree of amnesia of perioperative events as well as minimize anxiety.

Chronic administration of anticonvulsant drugs, such as phenytoin and carbamazepine induces rapid metabolism and clearance of neuromuscular blockers and opioids, due to enhance activity of the hepatic P450 enzymes [122]. Patients receiving chronic anticonvulsant therapy will require larger doses of muscle relaxants and opioids because of induced enzymatic metabolism of these agents [164]. Muscle relaxants should be withheld or permitted to wear off when assessment of motor function during neurosurgery is planned, either intraoperatively or post operatively.

Monitoring

Intraoperatively, patients undergoing major craniotomies are at risk of sudden hemodynamic instability due to hemorrhage, venous air emboli (VAE), herniation syndromes, and/or manipulation of cranial nerves. Postoperative opening of central venous line ports may also place patients at risk for VAE. In addition to standard monitoring of electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring, the potential massive blood loss warrants placement of an arterial cannula for continuous invasive blood pressure monitoring as well as for sampling serial blood gases, electrolytes, glucose levels and hematocrit, in both the operating room and ICU. The utility of central venous catheterization remains controversial and there is no clear cut evidence suggesting the superiority of one location over the other. Concerns over the lack of adequate venous drainage with indwelling internal jugular lines sometimes leads clinicians to place lines in either the subclavian and or femoral vein, but these alternate sites are associated with complications such as pneumothorax and infection, respectively. Moreover, the diameter of the internal jugular vein is large enough to typically accommodate a central line and facilitate adequate venous drainage [165].

Advanced Neurophysiological Monitoring

Neurophysiological monitoring is commonly used in the intraoperative setting but is an emerging area of investigation in the ICU setting for diagnosis and prognostication. Recent advances in neurophysiological monitoring have enhanced the ability to safely perform neurosurgical procedures in functional areas of the brain and spinal cord. In general, electrocorticography (ECoG), electroencephalography (EEG), and somatosensory evoked potentials (SSEP) can be utilized with low levels of volatile anesthetics or ICU sedation. An anesthetic technique using high dose opioids and minimal inhaled agents (<1 MAC) is the most appropriate agent for this type of monitoring in the OR. Moreover, the use of sedatives should not be prohibitive to neuromonitoring in the ICU setting. Spinal cord and peripheral nerve surgery may require electromyography (EMG) and detection of muscle movement as an end-point, but muscle relaxation should be avoided or discontinued after tracheal intubation to facilitate monitoring. Motor evoked potentials (MEP) monitors the integrity of the motor tracts of the spinal cord by stimulating the motor cortex and detecting the action potentials in the corresponding muscle groups. Volatile anesthetic agents, including nitrous oxide, have a dose-dependent depressant effect on the MEPs, while intravenous anesthetic drugs (propofol, opioids, ketamine, and dexmedetomidine) typically preserve MEPs.

Somatosensory evoked potentials, electroencephalograms, and bispectral index are examples of neurophysiological monitors which have been used in the OR and ICU in critically ill children [166]. Of these, EEG is the most commonly used monitor for seizures and cerebral ischemia and has been intensively investigated. Electroencephalographic waveforms are the summation of excitatory and inhibitory postsynaptic potentials from the superficial layers of the cerebral cortex. Both regional and global ischemia results in profound depression of EEG activity, characterized by an attenuation of high-frequency activity and appearance of slow waves in the corresponding area. This feature makes EEG monitoring the most reliable intraoperative monitor for focal cerebral ischemia. Direct analysis of the raw EEG by an electrophysiologist remains the gold standard for monitoring cerebral ischemia. Conditions in which cerebral perfusion may be compromised can be monitored with scalp EEG electrodes or direct ECoG with subdural strip electrodes. Cerebrovascular disease is rare in infants and children, but two conditions in which EEG monitoring may be beneficial are temporary clipping of cerebral aneurysms and moyamoya disease. Cerebral aneurysm clipping can result in ischemia in the cerebral regions supplied by adjacent arteries. Direct electrocorticography in the region at risk can detect cerebral ischemic during test occlusion of the aneurysm and can serve as a guide for proper positioning of the aneurysm

clip and institution of pharmacological interventions of improved cerebral perfusion.

Cerebral Oxygenation Monitors

The primary cause of cerebral ischemia in infants and children is cerebral hypoperfusion secondary to systemic arterial hypotension or sustained intracranial hypertension. The major perioperative modalities for monitoring cerebral ischemia are: (1) jugular venous oximetry, (2) cerebral oximetry and, (3) brain tissue oxygenation.

Jugular Oximetry

Jugular bulb catheters may be inserted retrograde into the internal jugular using angiocaths for intermittent sampling or fiberoptic catheters for continuous readings and are a useful tool for determining cerebral oxygenation (jugular venous oxygen saturation, $SjvO_2$). Normal $SjVO_2$ ranges from 50–75 %; values at either extreme reflect global ischemia or hyperemia, respectively. $SjvO_2$ monitoring can provide early diagnosis of global ischemia and is useful to guide decisions for guiding and optimizing hyperventilation therapy, perfusion pressure, fluid management, and oxygenation in head injured patients [167, 168]. While $SjvO_2$ monitoring is not ubiquitous during craniotomies, it is routinely performed for most craniotomies at some institutions. Matta et al. [169] have demonstrated in adults that $SjvO_2$ monitoring detects critical intraoperative cerebral desaturation that would otherwise have been untreated, and Moss et al. [170] have used $SjvO_2$ monitoring to determine the minimum blood pressure that should be maintained to avoid hypoperfusion during aneurysm surgery [171].

Cerebral Oximetry

Near infrared spectroscopy (NIRS) provides a noninvasive assessment of cerebral intravascular oxyhemoglobin and deoxyhemoglobin (oxy-Hb and deoxy-Hb) and mitochondrial cytochrome oxygenation by measuring the abilities of these two chromophores to absorb near infrared light. Quantitative measurement of changes in cerebral chromophore oxygen concentration is related to the overall optical attenuation of NIR light, and has been used to assess oxygen delivery and extraction, cerebral blood volume, CBF (indicator dye technique), and the redox state of the brain. The NIRS correlated with mean arterial pressure and is effective in identifying premature infants with impaired cerebrovascular autoregulation [172]. The equipment used in these studies is primarily research prototype and is not commercially produced. Therefore, this technique has yet to find a niche in routine intraoperative monitoring. Regional cerebral oximetry (rSO~INVOS, Somanetics Corporation, Troy, MI) is a simpler NIRS modality that measures relative changes in oxygen extraction in the total blood volume of a small brain area. This technique uses two wavelengths to determine oxy-Hb and total cerebral hemoglobin concentration. Because approximately 75 % of the blood volume within the brain is venous, the cerebral oximeter measurement reflects venous oxy-Hb saturation and has been reported to correlate with jugular bulb saturation.

Brain Tissue Oxygenation (PbO_2)

Brain tissue oxygenation is best studied in children in the TBI population. Measuring oxygen tension in the brain, it provides a measure of brain ischemia. A PbO_2 <10 mmHg in severe pediatric TBI reflects cerebral ischemia and this technology has been used to guide blood transfusion and prognosticate outcome in pediatric TBI [173]. Increasing normobaric oxygenation increases PbO_2 values in children with severe TBI but the response is variable. Currently, PbO_2 monitoring is an emerging advanced neruomonitor.

Anatomic Imaging and Cerebral Perfusion

Computed tomography (CT) is the mainstay of imaging during the preoperative and immediate postoperative periods. Indications for CT scans include timely diagnosis of lesions that cause increased ICP, detection of blood and the need for neurosurgery. Postoperative head CT scans are typically performed to exclude new onset hemorrhage post procedure. Intraoperative CT scans are available in some centers which obviates the need for transporting neurosurgical patient during the immediate postoperative period. Neurosurgical patients may be exposed to a large number of head CT scans during the perioperative period, which causes unwanted exposure to radiation. Concerns over the lifetime attributable risk of cancer from medical imaging, especially in the developing brain, from head CT scans have been raised by individual investigators [174] as well as national organizations which have campaigned to reduce unnecessary radiation exposure to children [175]. Early MRI scanning has been suggested as an alternative to head CT scans, especially in cases of suspected inflicted injury [176]. Advanced CT based techniques to examine cerebral perfusion are available but at present are constrained by radiation dose concerns. Arterial spin labeling and advanced MRI techniques provide estimates of changes in CBF and CBV and bedside transcranial Doppler technology measures cerebral blood flow velocity and is an appealing modality of evaluating cerebrovascular hemodynamics at the patient's bedside and with no radiation risk.

Emergence Phase of Anesthesia

In critically ill children, when patients are taken from the operating room to the ICU with residual anesthesia or sedation and an indwelling tracheal tube, there is no emergence phase of anesthesia.

Special Considerations for Perioperative Management of Select Neurosurgical Diseases

Congenital Anomalies

Congenital anomalies of the central nervous system generally occur as midline defects. This dysraphism may occur anywhere along the neural axis, involving the head (encephalocele) or spine (meningomyelocele). The defect may be relatively minor and affect only superficial bony and membranous structures or may include a large segment of malformed neural tissue.

Encephalocele

Encephaloceles are neural tube defects that present as protrusions of brain and CSF arising from the occiput to the frontal area. They can even appear as nasal "polyps" if they protrude through the cribriform plate. Large defects may present challenges to tracheal intubation. Significant blood loss can develop during surgical excision of these anomalies, especially if venous sinuses are entered. Adequate intravenous access should be ensured and blood products should be available.

Myelodysplasia and Spinal Cord Defects

Defects in the spine are known as spina bifida. If a bulge containing CSF without spinal tissue exists, it is called a meningocele. When neural tissue is also present within the lesion, the defect is called a meningomyelocele. Open neural tissue is known as rachischisis. Hydrocephalus is usually present when paralysis occurs below the lesion and is usually associated with an Arnold-Chiari malformation. Airway management, mask fit, and intubation may be difficult in infants with massive hydrocephalus or very large defects. Blood loss may be considerable during repair of a meningomyelocele when large amounts of skin are to be undermined to cover the defect. Patients with myelodysplasia are at high risk of developing allergic reactions to latex [157]. Postoperatively, respiratory status should be carefully assessed. Pulse oximetry is valuable during recovery from anesthesia because of difficulty with breathing after a tight closure, and because ventilatory responses to hypoxia are often diminished or absent in these patients when a Chiari malformation co-exists [177].

Spinal dysraphism is the primary indication for laminectomies in pediatric patients. Patients with myelomeningocele suffer from multisystem diseases that result from a severe injury to the developing CNS early in gestation. The systems involved may include the musculoskeletal system, genitourinary system and immune system in addition to the central nervous system. As mentioned above, these patients are at high risk of latex allergy. Insertion of an epidural catheter by the surgeon under direct vision can provide a conduit for the administration of local anesthetics and opioids for the management of postoperative pain. Other spinal anomalies (lipomeningoceles, lipomyelomeningoceles, diastematomyelias, and dermoid tracts) may manifest themselves as tethered cords. Children who have had a meningomyelocele repaired after birth may also develop an ascending neurologic deficit from a tethered spinal cord as growth occurs. EMG monitoring can be helpful for identifying functional nerve roots as described above.

Cerebral Palsy results in spasticity and severe spasticity can be surgically alleviated by a selective dorsal rhizotomy (SDR). SDR reduces spasticity by surgically dividing dorsal rootlets to diminish the afferent input to motor neurons in the spinal cord, thus decreasing the hyperactive active reflexes associated with spastic diplegia. Pathologic rootlets are identified by direct stimulation and noting the corresponding muscle action potential with EMG. Exaggerated action potentials can be elicited in innervated as well as other distal muscle groups. These abnormal rootlets are partially sectioned in order to decrease afferent nerve conduction. However, these rootlets can potentially contain sensory and proprioceptive fibers. Spinal cord reflexes can be quantified by measuring the Hoffman reflex as noted above. The postoperative care of these patients is completed by severe somatic incisional pain, dysasthesia and hyperesthesia of the affected limb and muscle spasms. A variety of post operative pain management techniques have been advocated in these patients. These include intravenous morphine and midazolam/diazepam infusions and epidural opioids [178].

Chiari Malformations

Chiari malformations are generally defined as an anatomical abnormality of the posterior fossa leading to cephalad displacement of the cerebellar vermis through the foramen magnum. There are four types of Chiari malformations. Type I occur in healthy children without myelodysplasia. These patients generally have much milder symptoms, sometimes presenting only with headache or neck pain, usually during adolescence. The Arnold-Chiari malformation (type II) almost always co-exists in children with myelodysplasia. This defect consists of a bony abnormality in the posterior fossa and upper cervical spine with caudal displacement of the cerebellar vermis and lower brainstem below the plane of the foramen magnum. Medullary cervical cord compression can occur. Vocal cord paralysis with stridor and respiratory distress, apnea, abnormal swallowing and pulmonary aspiration, opisthotonos, and cranial nerve deficits may be associated with the Arnold-Chiari malformation and usually present during infancy. Patients of any age may have abnormal responses to hypoxia and hypercarbia because of cranial nerve and brainstem dysfunction [179]. Extreme head flexion may cause brainstem compression in otherwise

asymptomatic patients. Type III Chiari malformations are associated with encephaloceles and have the most severe symptoms and long term disability. Type IV Chiari malformations are associated with absent cerebellum, and large posterior fossa cerebrospinal fluid spaces.

Tumors

Since the majority of intracranial tumors in children occur in the posterior fossa, CSF flow is often obstructed and intracranial hypertension and hydrocephalus is often present. The intraoperative period includes elevation of the bone flap which can result in sinus tears, massive blood loss, and/or VAE. Surgical resection of tumors in the posterior fossa can also lead to brainstem and/or cranial nerve damage. Damage to the respiratory centers and cranial nerves can lead to apnea and airway obstruction after extubation of the patient's trachea.

Brain tumors are the most common solid tumors in children [180]. Supratentorial tumors account for about 25–40 % of brain tumors in children, and supratentorial resection usually requires invasive monitoring and techniques to control elevated ICP. The majority of brain tumors in children are infratentorial, and include medulloblastomas, cerebellar astrocytomas, brainstem gliomas, and ependymomas of the fourth ventricle. Because posterior fossa tumors usually obstruct CSF flow, increased ICP occurs early. Presenting signs and symptoms include early morning vomiting and irritability or lethargy. Cranial nerve palsies and ataxia are also common findings with respiratory and cardiac irregularities, usually occurring late. Sedation or general anesthesia may be required for radiologic evaluation or radiation therapy and surgical resection poses a number of anesthetic challenges including positioning, arrhythmias and acute blood pressure changes, depressed respiration, as well as VAE and increased ICP.

Tumors in the midbrain include craniopharyngiomas, optic gliomas, pituitary adenomas, and hypothalamic tumors and account for approximately 15 % of all intracranial tumors. Hypothalamic tumors (hamartomas, gliomas, and teratomas) frequently present with precocious puberty in children who are large for their chronological age. Craniopharyngiomas are the most common perisellar tumors in children and adolescents and may be associated with hypothalamic and pituitary dysfunction. Symptoms often include growth failure, visual impairment, and endocrine abnormalities. Signs and symptoms of hypothyroidism should be sought and thyroid function tests measured. Steroid replacement (dexamethasone or hydrocortisone) is generally administered since the integrity of the hypothalamic-pituitary-adrenal axis may be uncertain. In addition, diabetes insipidus occurs preoperatively in some patients and is a common postoperative problem. A careful history usually reveals this condition preoperatively, especially if attention is focused on nocturnal drinking and enuresis. Evaluation of serum electrolytes and osmolality, urine-specific gravity, and urine output is helpful since hypernatremia and hyperosmolality, along with dilute urine, are typical findings. If diabetes insipidus does not exist preoperatively, it usually does not develop until the postoperative period. This occurs due to the adequate reserve of antidiuretic hormone in the posterior pituitary gland capable of functioning for many hours even when the hypothalamic-pituitary stalk is damaged intraoperatively. Postoperative diabetes insipidus is marked by a sudden large increase in dilute urine output associated with a rising serum sodium concentration and osmolality. Treatment can initially be with dilute crystalloid solutions to replace the urine output with careful attention to electrolyte measurements. However, urine output is usually so prodigious (up to 1 L/h in an adult) that an infusion of aqueous vasopressin (1–10 mU/kg/h) is best utilized with fluid input then carefully restricted to match urine replacement and estimates of insensible losses. If diabetes insipidus persists, intranasal desmopressin can be used to replace intravenous pitressin, since desmopressin generally needs to be administered only twice daily. Return of antidiuretic hormone activity a few days postoperatively may cause a marked decrease in urinary output, water intoxication, seizures, and cerebral edema if desmopressin is not discontinued and fluid administration not adjusted appropriately. Transsphenoidal surgery is generally only performed in adolescents and older children with pituitary adenomas. Since nasal packs are inserted at the end of surgery, patients should be fully awake prior to tracheal extubation and transported to the recovery room.

Approximately 25 % of intracranial tumors in children involve the cerebral hemispheres. These are primarily astrocytomas, oligodendrogliomas, ependymomas, and glioblastomas. Neurologic symptoms are more likely to include a seizure disorder or focal deficits. Succinylcholine should be avoided if motor weakness is present since it can cause sudden massive hyperkalemia. Nondepolarizing muscle relaxants and narcotics may be metabolized more rapidly than usual in patients receiving chronic anticonvulsants. Choroid plexus papillomas are rare but occur most often in children younger than 3 years of age. They usually arise from the choroid plexus of the lateral ventricle and produce early hydrocephalus as a result of increased production of CSF and obstruction of CSF flow. Hydrocephalus usually resolves with surgical resection. When lesions lie near the motor or sensory strip, a special type of somatosensory evoked potential monitoring called "phase reversal" may also be used to delineate these locations [181]. If cortical stimulation is planned to help identify motor areas, muscle relaxants must be permitted to wear off. Nitrous oxide and narcotics are usually sufficient to prevent patient movement during these periods.

Hydrocephalus

Hydrocephalus is the most common pediatric neurosurgical condition. It is a condition involving a mismatch of CSF production and absorption leading to increased intracranial CSF volume. The majority of cases of hydrocephalus are due to obstruction of CSF flow or inability to absorb CSF appropriately. Hemorrhage (neonatal intraventricular or subarachnoid), congenital problems (aqueductal stenosis) trauma, infection, or tumors (especially in the posterior fossa) can cause hydrocephalus. Hydrocephalus is classified as nonobstructive/communicating or obstructive/noncommunicating based on the ability of CSF to flow around the spinal cord in its usual manner. Unless the etiology of the hydrocephalus can be definitively treated, treatment entails surgical placement of a ventricular drain or ventriculoperitoneal shunt.

Intracranial hypertension or a decrease in intracranial compliance almost always accompanies untreated hydrocephalus in children. How much intracranial compliance exists and how acutely hydrocephalus develops are both instrumental in how severe the signs and symptoms of hydrocephalus will be. In the young infant, if hydrocephalus develops slowly, the skull will insidiously expand and the cerebral vault will expand. However in older children the cranial bones are fused or the cranium cannot expand fast enough and signs of impending herniation rapidly become apparent. The patient may become progressively more lethargic and develop vomiting, cranial nerve dysfunction, bradycardia, and ultimately death.

The approach to patients with symptomatic hydrocephalus should be directed at controlling ICP and rapidly relieving the obstruction. These patients may be vomiting and at risk for pulmonary aspiration. A rapid sequence induction of anesthesia with thiopental or propofol followed by succinylcholine or rocuronium is indicated in these situations. Hyperventilation should be instituted as soon as the trachea is intubated. Unless the etiology of the hydrocephalus can be definitively treated, treatment entails surgical placement of a ventricular shunt. Most shunts transport CSF from the lateral ventricles to the peritoneal cavity (ventriculoperitoneal shunts). Occasionally the distal end of the shunt must be placed in the right atrium or pleural cavity, usually due to problems with the ability of the peritoneal cavity to absorb CSF as in peritonitis. VAE can occur during placement of the distal end of a ventriculoatrial shunt.

Endoscopic third ventriculoscopy by way of a percutaneous flexible neuroendoscope is an alternative to extracranial shunt placement [182]. During these procedures, a ventriculostomy may be made to bypass an obstruction (such as aqueductal stenosis) by forming a communicating hole from one area of CSF flow to another using a blunt probe inserted through the neuroendoscope. Common locations for a ventriculostomy are through the septum pellucidum (so the lateral ventricles can communicate) or through the floor of the third ventricle into the adjacent CSF cisterns. Complications such as damage to the basilar artery or its branches or neural injuries can be life threatening when they occur, and the anesthesiologist should be prepared for an emergency craniotomy during these procedures. Bradycardia and other arrhythmias have been also reported in conjunction with irrigation fluids and/or manipulation of the floor of the third ventricle [183].

There are a few special situations involving shunts that critical care physicians and anesthesiologists should be familiar with. Children who develop a shunt infection usually have their entire shunt system removed and external ventricular drainage established. They return to the operating room for placement of a new system several days later after their infection has been treated with antibiotics. While an external drain is in place, one must be careful not to dislodge the ventricular tubing. In addition, the height of the drainage bag should not be changed in relationship to the patient's head to avoid sudden changes in ICP. For example, suddenly lowering an open drainage bag can siphon CSF rapidly from the patient, resulting in collapse of the ventricles and rupture of cortical veins. When transporting patients with CSF drainage, it is best to temporarily close the ventriculostomy tubing during these brief periods.

Slit ventricle syndrome develops in approximately 5–10 % of patients with CSF shunts and is associated with overdrainage of CSF and small, "slit-like" lateral ventricular spaces. Patients with this condition do not have the usual amount of intracranial CSF to compensate for alterations in brain or intracranial blood volume. Administration of excess or hypotonic intravenous solutions should be avoided in order to minimize brain swelling, because postoperative cerebral herniation have been reported after uneventful surgical procedures in these children [184]. Postoperatively, the patient's mental status should be monitored because of the possibility of the reobstruction of the shunt leading to life threatening hydrocephalus.

Craniosynostosis

Craniosynostosis is a congenital anomaly in which one or more cranial sutures close prematurely. It occurs in approximately one of every 2,000 births, with males affected more frequently than females. The craniosynostosis can involve one suture, or it may be very complex and be associated with a variety of syndromes. If left uncorrected, the deformed cranium can result in increased ICP and compression of brain, with potential neurologic sequelae [185]. Surgical correction is usually performed within the first months of life to achieve the best cosmetic results. This is because brain growth is very rapid during infancy, "pushing" the skull into a normal shape. Repair of cranio-synostosis may involve removal of one small strip of bone from the skull, or it may entail a

complete reconstruction of the calvarium. Although these operations are extradural procedures, significant blood loss from the scalp and cranium make these challenging anesthetic procedures. It is essential that adequate venous access for rapid blood administration is secured, especially if multiple sutures are involved during surgery and postoperatively. Antifibrinolytic drugs (tranexemic acid) may have some utility in these procedures [186]. However, seizures have been reported after the use of high doses in cardiac surgery, which may be due to the intrinsic ability of TXA to inhibit glycine receptors [187]. The incidence of VAE is also significant during these procedures [188]. Endoscopic strip craniectomies are associated with decreased blood loss, decreased surgical time, and improved postoperative recovery time during endoscopic strip craniectomy in neonates and infants [189, 190]. Tobias and colleagues reported a significant decrease in the incidence of VAE during this procedure [191].

Epilepsy

Epilepsy remains one of the most common neurologic disorders in children. Although a number of new pharmacologic interventions have shown promise in the medical management of childhood epilepsy, a large number of children continue to have intractable seizures and resort to surgical interventions in such situations. Chronic administration of anticonvulsant drugs, such as phenytoin and carbamazepine induces rapid metabolism and clearance of neuromuscular blockers and opioids by upregulating hepatic P450 enzymes [122]. Intraoperative neurophysiologic monitors can be used to guide the actual resection of the epileptogenic focus and general anesthetics can compromise the sensitivity of these devices [192]. If cortical stimulation is utilized to mimic the seizure pattern or identify areas on the motor strip, neuromuscular blockade should be antagonized.

A variety of techniques are utilized during the entire perioperative period to aid in localization of seizure foci. A major part of preoperative planning should include a through discussion of the modality and type of neurophysiological monitoring to be used during the surgical procedure. In patients with generalized seizures, precise localization of the seizure focus is essential to minimize postoperative functional deficits. This involves serial craniotomies. The first is insertion of intracranial grid and strip electrodes. EEG grids and/or strips and placed on the exposed cortical surface in order to accurately create a map that will to localize the seizure focus. The patient is then observed in an electrophysiology unit in order to map the location of the seizure foci and provide a "road map" for the neurosurgeon for the resection. In some cases, the patient is monitored over several days. Once a seizure map is generated, the patient returns to the operating room for definitive resection. Depending on the location of seizure foci, age, and development of the patient, the resection is performed under general anesthesia or via an awake craniotomy technique. It is imperative that candidates for an awake craniotomy be mature and psychologically prepared to participate in this procedure. Therefore, patients who are developmentally delayed or have a history of severe anxiety or psychiatric disorders should not be considered appropriate for an awake craniotomy.

Intraoperative and postoperative seizures are an uncommon but devastating complication. Prophylaxis in the perioperative period and aggressive treatment of new convulsions are well-recognized mainstays of care. While phenytoin is the agent used most commonly for prophylaxis, maintaining therapeutic serum levels can be challenging [193]. Levetiracetam is becoming increasingly common and in many instances supplanting phenytoin as the choice for postoperative seizure prophylaxis. Both drugs can administered intravenously but unlike phenytoin, administration of levetiracetam does not require following serum drug levels to monitor for toxicity. Alternative agents frequently used in pediatrics include phenobarbital, carbamazepine, and valproic acid. Status epilepticus can be treated with, lorezepam 0.1 mg/kg IV push over 2 min or diazepam 0.5 mg/kg PR are effective agents. Lorezapam may be repeated after 10 min and accompanied by fosphenytoin 20 mg/kg IV or IM if initial doses are ineffective. Phenobarbital 20 mg/kg is also an effective first line antiepileptic drug.

Vascular Malformations

Vascular anomalies are rare in infants and children. Most of these conditions are congenital lesions that present early in life. Large arteriovenous malformations (AVM) in neonates may be associated with high output congestive heart failure and require vasoactive support. Initial treatment of large AVMs often consists of several treatments involving intravascular embolization in the interventional radiology suite [194]. Operative management is commonly associated with massive blood loss. Ligation of an AVM can lead to sudden hypertension with hyperemic cerebral edema [195] and should be treated with vasodilators such as labetalol or nitroprusside. Postoperative angiography may be indicated in order to rule out any residual AVMs or vascular leaks. Since re-hemorrhage or stroke can occur during the postoperative period, strict blood pressure parameters should be set to avoid hypo- and hypertension.

Moyamoya syndrome is a rare chronic vaso-occlusive disorder of the internal carotid arteries that presents as transient ischemic attacks and/or recurrent strokes in childhood. The etiology is unknown, but the syndrome can be associated with prior intracranial radiation, neurofibromatosis, Down's syndrome, and a variety of hematological disorders including sickle cell disease. Medical management consists of antiplatelet medications, e.g., aspirin or

calcium channel blockers. Surgical management is aimed at improving blood flow to the ischemic area. The operation involves suturing a scalp artery onto the pial surface of the brain (pial synangiosis). The anesthetic management of these patients is directed at optimizing cerebral perfusion [196]. This includes assuring generous preoperative hydration and maintaining the blood pressure within the patient's preoperative levels. Maintenance of normocapnia is essential as well because both hyper- and hypocapnia can lead to steal phenomenon from the ischemic region and further aggravate cerebral ischemia [197]. Once the patient emerges from anesthesia, the same maneuvers that optimize cerebral perfusion should be extended into the postoperative period. Postoperative agitiation and pain should be aggressively treated to minimize hyperventilation and increases in cerebral metabolic demand.

Neurotrauma

The fundamentals of pediatric neurotrauma, including TBI, spinal cord injury, multiple trauma and inflicted injury are discussed elsewhere in this textbook. In brief, the perioperative management of pediatric neurotrauma consists of adhereing to published national guidelines. For severe TBI, recommendations of care are well described in the recently published 2012 Guidelines for Acute Care Management of Infants and Children with Severe TBI [198]. Neurotrauma and prevention of secondary insults after neurotrauma remains the mainstay of anesthetic and intensive care medicine except for when surgical decompression is needed. There are documented changes in cerebral hemodynamics that occur after TBI where systemic hypotension, cerebral hypoperfusion, impaired cerebral autoregulation may ensue. These secondary insults may lead to cerebral ischemia, cerebral hyperemia and poor outcomes [7, 26, 123, 167, 199–210]. It is important to note that the Pediatric Guidelines for Severe TBI do not contain data from the intraoperative period and hence the specific hemodynamic thresholds for treatment may or may not apply. However, at present, given the paucity of data, a target cerebral perfusion pressure of at least 40 mmHg should be targeted [211–214]. The choice of vasopressors to increase blood pressure and CPP may vary. One single center study suggests that norepinephrine might lead to a higher increase in CPP than phenylephrine or dopamine in children with severe TBI [215]. The management of increased ICP, including hyperventilation for severe TBI in children is also described elsewhere in this text and in the Pediatric Guidelines [198, 211, 216, 217]. Patients who have refractory high ICP may undergo decompressive craniectomy and or receive hypothermia. It is important to note, however, that hypothermia is associated with increased mortality in these patients [218].

Additional Considerations

Neuroendoscopy

Technological advances in minimally invasive endoscopic surgery have entered the neurosurgical arena. Since neuroendoscopic techniques are designed to minimize surgical incision, dissection, and blood loss, less aggressive fluid replacement and invasive hemodynamic monitoring is becoming the norm. Endoscopic strip craniectomies are associated with decreased blood loss, decreased surgical time, and improved postoperative recovery time during endoscopic strip craniectomy in neonates and infants [189, 190, 219]. Tobias and colleagues reported a significant decrease in the incidence of VAE during this procedure [191]. Endoscopic third ventriculostomy is another approach for the treatment of obstructive hydrocephalus in infants and children [220]. A flexible fiberoptic scope is inserted through a trocar and provides a working channel that allows the neurosurgeon to insert a ventricular catheter or make frenestrations. Despite the relative safety of this procedure, bradycardia and other arrhythmias have been reported in conjunction with lack of egress of irrigation fluids and/or manipulation of the floor of the third ventricle [183, 221]. Neurogenic pulmonary edema due to acute intracranial hypertension has also been reported with this procedure [222].

Pain Management

Physicians are typically taught that the brain feels no pain and that this is due to the fact that only the dura has pain receptors. Traditionally, concerns over opioid related respiratory depression have resulted in conservative pain control strategies, such as avoiding opioids and or the use of suboccipital nerve blockers or as needed opioids. The use of sedation may also decrease the ability to assess and accurately record pain and patients with extracranial disease states or conditions might have pain from those conditions. Yet, pain after craniotomy may be more common that previously recognized. Optimal perioperative pain control in neurosurgical patients may aid with lowering ICP, assure a favorable neurovascular milieu, and facilitate timely diagnosis of the neurological problem. In one meta analysis of RCTs data from a total of 519 adults, who received four treatment strategies (scalp infiltration [five RCTs], nerve scalp block [two RCTs], parecoxib [one RCT] and patient-controlled analgesia with morphine [one RCT]), the authors reported that scalp infiltration with local anaesthetic may provide adequate analgesia in the first few postoperative hours, and nerve scalp block may provide longer lasting analgesia for 6 h. Morphine was found to reduce total analgesic rescue doses with no significant effect on nausea and no other side-effects and there was no significant evidence

was found to support the use of parecoxib in the treatment of postcraniotomy pain [223]. In the only pediatric study on postcraniotomy pain in children, Teo et al. reported that while most patients do not have pain during the first 72 h after surgery, many patients have at least one episode of a pain score ≥3 and predicted by duration of procedure. Perioperative pain regimens vary and include parenteral morphine, paracetamol, oxycodone, codeine, tramadol and ibuprofen [224]. No firm recommendations on analgesic therapy following craniotomy can be made because the number of well performed RCTs is limited and the study populations are very small. However, evidence on scalp infiltration suggests an analgesic effect in the first few postoperative hours.

OR to ICU Handoffs and ICU Handoffs to OR

Communication between the preoperative, intraoperative, and postoperative teams is essential for optimizing outcomes of pediatric neurosurgical patients. Creating specified checklists that facilitate transfer of critical and anticipatory events between members of the health care team including nurses and physicians is essential to preventing adverse events and to capturing near misses in these patients. One study by Brannen and colleagues showed that three-fourths of the handoffs had agreement about the severity of the patient's illness but that there was low agreement about the most severe problem and the total problem lists between residents involved in the handoff communication. Attending physicians were able to identify more patient problems [225].

Conclusion

The perioperative management of the neurosurgical patient is complex and challenging, requiring a solid understanding of the patient, preoperative conditions, surgical procedure, anesthetic events and potential postoperative complications. Developmental age and gender related differences between patients add to the complexity and may impact the course and outcome of neurosurgical patients. Finally, tremendous coordination between the clinical care teams is critical to preventing adverse events in this vulnerable patient population.

References

1. Shapiro K, Marmarou A, Shulman K. Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. Ann Neurol. 1980;7:508.
2. Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. BMJ. 1992;304:1218–22.
3. Madsen PL, Vorstrup S. Cerebral blood flow and metabolism during sleep. Cerebrovasc Brain Metab Rev. 1991;3(4):281–96.
4. Lenzi P, Zoccoli G, Walker AM, Franzini CLenzi P, Zoccoli G, Walker AM, Franzini C. Cerebral circulation in REM sleep: is oxygen a main regulating factor? Sleep Res Online. 2000;3(2):77–85.
5. Lam AM, Matta BF, Mayberg TS, Strebel S. Change in cerebral blood flow velocity with onset of EEG silence during inhalation anesthesia in humans: evidence of flow-metabolism coupling? J Cereb Blood Flow Metab. 1995;15(4):714–7.
6. Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci U S A. 1986;83(4):1140–4.
7. Kennedy C, Sokoloff L. An adaptation of the nitrous oxide method to the study of the cerebral circulation in children; normal values for cerebral blood flow and cerebral metabolic rate in childhood. J Clin Invest. 1957;36(7):1130–7.
8. Biagi L, Abbruzzese A, Bianchi MC, Alsop DC, Del Guerra A, Tosetti M. Age dependence of cerebral perfusion assessed by magnetic resonance continuous arterial spin labeling. J Magn Reson Imaging. 2007;25(4):696–702.
9. Wintermark M, Lepori D, Cotting J, et al. Brain perfusion in children: evolution with age assessed by quantitative perfusion computed tomography. Pediatrics. 2004;113:1642.
10. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann Neurol. 1987;22(4):487–97.
11. Harper AM, Glass HI. Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. J Neurol Neurosurg Psychiatry. 1965;28(5):449–52.
12. Padayachee TS, Kirkham FJ, Lewis RR, Gillard J, Hutchinson MC, Gosling RG. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: a method of assessing the Circle of Willis. Ultrasound Med Biol. 1986;12(1):5–14.
13. Karsli C, Luginbuehl I, Farrar M, Bissonnette B. Cerebrovascular carbon dioxide reactivity in children anaesthetized with propofol. Paediatr Anaesth. 2003;13(1):26–31.
14. Leon JE, Bissonnette B. Cerebrovascular responses to carbon dioxide in children anaesthetized with halothane and isoflurane. Can J Anaesth. 1991;38(7):817–25.
15. Rowney DA, Fairgrieve R, Bissonnette B. Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane. Br J Anaesth. 2002;88:357.
16. Pryds O, Andersen GE, Friis-Hansen B. Cerebral blood flow reactivity in spontaneously breathing, preterm infants shortly after birth. Acta Paediatr Scand. 1990;79(4):391–6.
17. Baenziger O, Moenkhoff M, Morales CG, Waldvogel K, Wolf M, Bucher H, Fanconi S. Impaired chemical coupling of cerebral blood flow is compatible with intact neurological outcome in neonates with perinatal risk factors. Biol Neonate. 1999;75(1):9–17.
18. Ellingsen I, Hauge A, Nicolaysen G, Thoresen M, Walløe L. Changes in human cerebral blood flow due to step changes in PAO2 and PACO2. Acta Physiol Scand. 1987;129(2):157–63.
19. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev. 1990;2:161–91.
20. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev. 1959;39:183–238.
21. Vavilala MS, Lee LA, Lam AM. The lower limit of cerebral autoregulation in children during sevoflurane anesthesia. J Neurosurg Anesthesiol. 2003;15:307.
22. Brady KM, Mytar JO, Lee JK, Cameron DE, Vricella LA, Thompson WR, Hogue CW, Easley RB. Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. Stroke. 2010;41(9):1957–62.
23. Pryds A, Tønnesen J, Pryds O, Knudsen GM, Greisen G. Cerebral pressure autoregulation and vasoreactivity in the newborn rat. Pediatr Res. 2005;57(2):294–8. Epub 2004 Dec 7.

24. Boylan GB, Young K, Panerai RB, Rennie JM, Evans DH. Dynamic cerebral autoregulation in sick newborn infants. Pediatr Res. 2000;48(1):12–7.
25. Vavilala MS, Newell DW, Junger E, et al. Dynamic cerebral autoregulation in healthy adolescents. Acta Anaesthesiol Scand. 2002;46:393.
26. Vavilala MS, Tontisirin N, Udomphorn Y, et al. Hemispheric differences in cerebral autoregulation in children with moderate and severe traumatic brain injury. Neurocrit Care. 2008;9(1):45–54.
27. Karsli C, Luginbuehl I, Bissonnette B. The cerebrovascular response to hypocapnia in children receiving propofol. Anesth Analg. 2004;99(4):1049–52.
28. Karsli C, Luginbuehl I, Farrar M, Bissonnette B. Propofol decreases cerebral blood flow velocity in anesthetized children. Can J Anaesth. 2002;49(8):830–4.
29. Van Hemelrijck J, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T. Effect of propofol on cerebral circulation and autoregulation in the baboon. Anesth Analg. 1990;71(1):49–54.
30. Cremer OL. The propofol infusion syndrome: more puzzling evidence on a complex and poorly characterized disorder. Crit Care. 2009;13(6):1012.
31. Pierce Jr EC, Lambertsen CJ, Deutsch S, Chase PE, Linde HW, Dripps RD, Price HL. Cerebral circulation and metabolism during thiopental anesthesia and hyper-ventilation in man. J Clin Invest. 1962;41:1664–71.
32. Michenfelder JD. The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. Anesthesiology. 1974;41(3):231–6.
33. Albrecht RF, Miletich DJ, Rosenberg R, Zahed B. Cerebral blood flow and metabolic changes from induction to onset of anesthesia with halothane or pentobarbital. Anesthesiology. 1977;47(3):252–6.
34. Mann JD, Butler AB, Johnson RN, Bass NH. Clearance of macromolecular and particulate substances from the cerebrospinal fluid system of the rat. J Neurosurg. 1979;50(3):343–8.
35. Smith AL, Hoff JT, Nielsen SL, Larson CP. Barbiturate protection in acute focal cerebral ischemia. Stroke. 1974;5(1):1–7.
36. Nehls DG, Todd MM, Spetzler RF, Drummond JC, Thompson RA, Johnson PC. A comparison of the cerebral protective effects of isoflurane and barbiturates during temporary focal ischemia in primates. Anesthesiology. 1987;66(4):453–64.
37. Smith AL, Marque JJ. Anesthetics and cerebral edema. Anesthesiology. 1976;45(1):64–72.
38. Miller R, Tausk HC, Stark DC. Effect of innovar, fentanyl and droperidol on the cerebrospinal fluid pressure in neurosurgical patients. Can Anaesth Soc J. 1975;22(4):502–8.
39. Misfeldt BB, Jörgensen PB, Spotoft H, Ronde F. The effects of droperidol and fentanyl on intracranial pressure and cerebral perfusion pressure in neurosurgical patients. Br J Anaesth. 1976;48(10):963–8.
40. Jobes DR, Kennell EM, Bush GL, Mull TD, Lecky JH, Behar MG, Wollman H. Cerebral blood flow and metabolism during morphine–nitrous oxide anesthesia in man. Anesthesiology. 1977;47(1):16–8.
41. Moss E, Powell D, Gibson RM, McDowall DG. Effects of fentanyl on intracranial pressure and cerebral perfusion pressure during hypocapnia. Br J Anaesth. 1978;50(8):779–84.
42. Artru AA. Effects of halothane and fentanyl on the rate of CSF production in dogs. Anesth Analg. 1983;62(6):581–5.
43. Artru AA. Isoflurane does not increase the rate of CSF production in the dog. Anesthesiology. 1984;60(3):193–7.
44. Yaster M, Koehler RC, Traystman RJ. Effects of fentanyl on peripheral and cerebral hemodynamics in neonatal lambs. Anesthesiology. 1987;66(4):524–30.
45. Herrick IA, Gelb AW, Manninen PH, Reichman H, Lownie S. Effects of fentanyl, sufentanil, and alfentanil on brain retractor pressure. Anesth Analg. 1991;72(3):359–63.
46. Weinstabl C, Mayer N, Richling B, Czech T, Spiss CK. Effect of sufentanil on intracranial pressure in neurosurgical patients. Anaesthesia. 1991;46(10):837–40.
47. Mayberg TS, Lam AM, Eng CC, Laohaprasit V, Winn HR. The effect of alfentanil on cerebral blood flow velocity and intracranial pressure during isoflurane-nitrous oxide anesthesia in humans. Anesthesiology. 1993;78(2):288–94.
48. Sperry RJ, Bailey PL, Reichman MV, Peterson JC, Petersen PB, Pace NL. Fentanyl and sufentanil increase intracranial pressure in head trauma patients. Anesthesiology. 1992;77(3):416–20.
49. Weinstabl C, Mayer N, Spiss CK. Sufentanil decreases cerebral blood flow velocity in patients with elevated intracranial pressure. Eur J Anaesthesiol. 1992;9(6):481–4.
50. Albanese J, Durbec O, Viviand X, Potie F, Alliez B, Martin C. Sufentanil increases intracranial pressure in patients with head trauma. Anesthesiology. 1993;79(3):493–7.
51. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil II. Model application. Anesthesiology. 1997;86(1):24–33.
52. Mertens MJ, Engbers FH, Burm AG, Vuyk J. Predictive performance of computer-controlled infusion of remifentanil during propofol/remifentanil anaesthesia. Br J Anaesth. 2003;90(2):132–41.
53. Hoffman WE, Cunningham F, James MK, Baughman VL, Albrecht RF. Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide. Anesthesiology. 1993;79(1):107–13; discussion 26A.
54. Lagace A, Karsli C, Luginbuehl I, Bissonnette B. The effect of remifentanil on cerebral blood flow velocity in children anesthetized with propofol. Paediatr Anaesth. 2004;14(10):861–5.
55. Baker KZ, Ostapkovich N, Sisti MB, Warner DS, Young WL. Intact cerebral blood flow reactivity during remifentanil/nitrous oxide anesthesia. J Neurosurg Anesthesiol. 1997;9(2):134–40.
56. Ostapkovich ND, Baker KZ, Fogarty-Mack P, Sisti MB, Young WL. Cerebral blood flow and CO2 reactivity is similar during remifentanil/N2O and fentanyl/N2O anesthesia. Anesthesiology. 1998;89(2):358–63.
57. Klimscha W, Ullrich R, Nasel C, Dietrich W, Illievich UM, Wildling E, Tschernko E, Weidekamm C, Adler L, Heikenwälder G, Horvath G, Sladen RN. High-dose remifentanil does not impair cerebrovascular carbon dioxide reactivity in healthy male volunteers. Anesthesiology. 2003;99(4):834–40.
58. Engelhard K, Reeker W, Kochs E, Werner C. Effect of remifentanil on intracranial pressure and cerebral blood flow velocity in patients with head trauma. Acta Anaesthesiol Scand. 2004;48(4):396–9.
59. Guy J, Hindman BJ, Baker KZ, Borel CO, Maktabi M, Ostapkovich N, Kirchner J, Todd MM, Fogarty-Mack P, Yancy V, Sokoll MD, McAllister A, Roland C, Young WL, Warner DS. Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions. Anesthesiology. 1997;86(3):514–24.
60. Gerlach K, Uhlig T, Hppe M, Khirt T, Saager L, Schmucker P. Postoperative analgesia after preincisional administration of remifentanil. Minerva Anestesiol. 2003;69(6):563–9, 569–73.
61. Cafiero T, Di Minno RM, Sivolella G, Di Iorio C. Immediate postoperative pain management in patients undergoing major abdominal surgery after remifentanil-based anesthesia: sufentanil vs tramadol. Minerva Anestesiol. 2004;70(9):661–9.
62. Renou AM, Vernhiet J, Macrez P, Constant P, Billerey J, Khadaroo MY, Caillé JM. Cerebral blood flow and metabolism during etomidate anaesthesia in man. Br J Anaesth. 1978;50(10):1047–51.
63. Moss E, Powell D, Gibson RM, McDowall DG. Effect of etomidate on intracranial pressure and cerebral perfusion pressure. Br J Anaesth. 1979;51(4):347–52.
64. Laughlin TP, Newberg LA. Prolonged myoclonus after etomidate anesthesia. Anesth Analg. 1985;64(1):80–2.

65. Sakabe T, Maekawa T, Ishikawa T, Takeshita H. The effects of lidocaine on canine cerebral metabolism and circulation related to the electroencephalogram. Anesthesiology. 1974;40(5):433–41.
66. Donegan MF, Bedford RF. Intravenously administered lidocaine prevents intracranial hypertension during endotracheal suctioning. Anesthesiology. 1980;52(6):516–8.
67. Cotev S, Shalit MN. Effects on diazepam on cerebral blood flow and oxygen uptake after head injury. Anesthesiology. 1975;43(1): 117–22.
68. Rockoff MA, Naughton KV, Shapiro HM, Ingvar M, Ray KF, Gagnon RL, Marshall LF. Cerebral circulatory and metabolic responses to intravenously administered lorazepam. Anesthesiology. 1980;53(3):215–8.
69. Forster A, Juge O, Morel D. Effects of midazolam on cerebral blood flow in human volunteers. Anesthesiology. 1982;56(6):453–5.
70. Nugent M, Artru AA, Michenfelder JD. Cerebral metabolic, vascular and protective effects of midazolam maleate: comparison to diazepam. Anesthesiology. 1982;56(3):172–6.
71. Nakahashi K, Yomosa H, Matsuzawa N, Yamagishi N, Ueda Y, Yan S, Hiraki N. Effect on cerebral blood flow of midazolam during modified neurolept-anesthesia. Masui. 1991;40(12):1787–92.
72. Tateishi A, Maekawa T, Takeshita H, Wakuta K. Clinical doses of midazolam and diazepam do not alter ICP Diazepam and intracranial pressure. Anesthesiology. 1981;54(4):335–7.
73. Dawson B, Michenfelder JD, Theye RA. Effects of ketamine on canine cerebral blood flow and metabolism: modification by prior administration of thiopental. Anesth Analg. 1971;50(3):443–7.
74. Takeshita H, Okuda Y, Sari A. The effects of ketamine on cerebral circulation and metabolism in man. Anesthesiology. 1972;36(1): 69–75.
75. Schwedler M, Miletich DJ, Albrecht RF. Cerebral blood flow and metabolism following ketamine administration. Can Anaesth Soc J. 1982;29(3):222–6.
76. Hougaard K, Hansen A, Brodersen P. The effect of ketamine on regional cerebral blood flow in man. Anesthesiology. 1974;41(6):562–7.
77. Gardner AE, Dannemiller FJ, Dean D. Intracranial cerebrospinal fluid pressure in man during ketamine anesthesia. Anesth Analg. 1972;51(5):741–5.
78. Wyte SR, Shapiro HM, Turner P, Harris AB. Ketamine-induced intracranial hypertension. Anesthesiology. 1972;36(2):174–6.
79. Lockhart CH, Jenkins JJ. Ketamine-induced apnea in patients with increased intracranial pressure. Anesthesiology. 1972;37(1):92–3.
80. List WF, Crumrine RS, Cascorbi HF, Weiss MH. Increased cerebrospinal fluid pressure after ketamine. Anesthesiology. 1972;36(1):98–9.
81. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. J Neurosurg Pediatr. 2009;4(1):40–6.
82. Aantaa R, Kallio A, Virtanen R. Dexmedetomidine, a novel [alpha]2-adrenergic agonist: a review of its pharmacodynamic characteristics. Drugs Future. 1993;18:49–56.
83. Frangoulidou E, Kuhlen R, Marenghi C. Sedative agents and respiratory depression: a unique profile of dexmedetomidine. In: Maze M, Morrison P, editors. Redefining sedation. London: The Royal Society of Medicine Press Ltd.; 1998. p. 40–50.
84. Precedex™ (dexmedetomidine) [package insert]. North Chicago: Abbott Laboratories.
85. Hassan E. Dexmedetomidine: a viewpoint by Dr Erkan Hassan. Drugs. 2000;59:269–70.
86. Shehabi Y, Ruettimann U, Adamson H, et al. Dexmedetomidine infusion for more than 24 h in critically ill patients: sedative and cardiovascular effects. Intensive Care Med. 2004;30:2188–96.
87. Drummond JC, Dao AV, Roth DM, Cheng CR, Atwater BI, Minokadeh A, Pasco LC, Patel PM. Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. Anesthesiology. 2008;108(2):225–32.
88. Ogawa Y, Iwasaki K, Aoki K, Kojima W, Kato J, Ogawa S. Dexmedetomidine weakens dynamic cerebral autoregulation as assessed by transfer function analysis and the thigh cuff method. Anesthesiology. 2008;109(4):642–50.
89. Drummond JC, Sturaitis MK. Brain tissue oxygenation during dexmedetomidine administration in surgical patients with neurovascular injuries. J Neurosurg Anesthesiol. 2010;22(4): 336–41.
90. Everett LL, van Rooyen IF, Warner MH, Shurtleff HA, Saneto RP, Ojemann JG. Use of dexmedetomidine in awake craniotomy in adolescents: report of two cases. Paediatr Anaesth. 2006;16(3):338–42.
91. Mazze RI, Escue HM, Houston JB. Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. Anesthesiology. 1969;31(6):540–7.
92. Thomas ET. Circulatory collapse following succinylcholine: report of a case. Anesth Analg. 1969;48(3):333–7.
93. Smith RB, Grenvik A. Cardiac arrest following succinylcholine in patients with central nervous system injuries. Anesthesiology. 1970;33(5):558–60.
94. Tong TK. Succinylcholine-induced hyperkalemia in near-drowning. Anesthesiology. 1987;66(5):720.
95. Iwatsuki N, Kuroda N, Amaha K, Iwatsuki K. Succinylcholine-induced hyperkalemia in patients with ruptured cerebral aneurysms. Anesthesiology. 1980;53(1):64–7.
96. Cowgill DB, Mostello LA, Shapiro HM. Encephalitis and a hyperkalemic response to succinycholine. Anesthesiology. 1974;40(4): 409–11.
97. Cooperman LH, Strobel Jr GE, Kennell EM. Massive hyperkalemia after administration of succinylcholine. Anesthesiology. 1970;32(2):161–4.
98. Cooperman LH. Succinylcholine-induced hyperkalemia in neuromuscular disease. JAMA. 1970;213(11):1867–71.
99. Tobey RE. Paraplegia, succinylcholine and cardiac arrest. Anesthesiology. 1970;32(4):359–64.
100. Cottrell JE, Hartung J, Giffin JP, Shwiry B. Intracranial and hemodynamic changes after succinylcholine administration in cats. Anesth Analg. 1983;62(11):1006–9.
101. Thiagarajah S, Sophie S, Lear E, Azar I, Frost EA. Effect of suxamethonium on the ICP of cats with and without thiopentone pretreatment. Br J Anaesth. 1988;60(2):157–60.
102. Minton MD, Grosslight K, Stirt JA, Bedford RF. Increases in intracranial pressure from succinylcholine: prevention by prior nondepolarizing blockade. Anesthesiology. 1986;65(2):165–9.
103. Stirt JA, Grosslight KR, Bedford RF, Vollmer D. "Defasciculation" with metocurine prevents succinylcholine-induced increases in intracranial pressure. Anesthesiology. 1987;67(1):50–3.
104. Lanier WL, Milde JH, Michenfelder JD. Cerebral stimulation following succinylcholine in dogs. Anesthesiology. 1986;64(5): 551–9.
105. Lanier WL, Milde JH, Michenfelder JD. The cerebral effects of pancuronium and atracurium in halothane-anesthetized dogs. Anesthesiology. 1985;63(6):589–97.
106. Minton MD, Stirt JA, Bedford RF, Haworth C. Intracranial pressure after atracurium in neurosurgical patients. Anesth Analg. 1985;64(11):1113–6.
107. Rosa G, Sanfilippo M, Orfei P, Di Giugno G, Vilardi V, Oppido PA, Gasparetto A. The effects of pipecuronium bromide on intracranial pressure and cerebral perfusion pressure. J Neurosurg Anesthesiol. 1991;3(4):253–7.
108. Stirt JA, Maggio W, Haworth C, Minton MD, Bedford RF. Vecuronium: effect on intracranial pressure and hemodynamics in neurosurgical patients. Anesthesiology. 1987;67(4):570–3.
109. Tarkkanen L, Laitinen L, Johansson G. Effects of d-tubocurarine on intracranial pressure and thalamic electrical impedance. Anesthesiology. 1974;40(3):247–51.

110. Graham DH. Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron lesions. Anesthesiology. 1980;52(1):74–5.
111. Moorthy SS, Hilgenberg JC. Resistance to non-depolarizing muscle relaxants in paretic upper extremities of patients with residual hemiplegia. Anesth Analg. 1980;59(8):624–7.
112. Shayevitz JR, Matteo RS. Decreased sensitivity to metocurine in patients with upper motoneuron disease. Anesth Analg. 1985;64(8):767–72.
113. Brown JC, Charlton JE, White DJ. A regional technique for the study of sensitivity to curare in human muscle. J Neurol Neurosurg Psychiatry. 1975;38(1):18–26.
114. Gandhi IC, Jindal MN, Patel VK. Mechanism of neuromuscular blockade with some antiepileptic drugs. Arzneimittelforschung. 1976;26(2):258–61.
115. Spacek A, Nickl S, Neiger FX, Nigrovic V, Ullrich OW, Weindmayr-Goettel M, Schwall B, Taeger K, Kress HG. Augmentation of the rocuronium-induced neuromuscular block by the acutely administered phenytoin. Anesthesiology. 1999;90(6):1551–5.
116. Roth S, Ebrahim ZY. Resistance to pancuronium in patients receiving carbamazepine. Anesthesiology. 1987;66(5):691–3.
117. Ornstein E, Matteo RS, Young WL, Diaz J. Resistance to metocurine-induced neuromuscular blockade in patients receiving phenytoin. Anesthesiology. 1985;63(3):294–8.
118. Ornstein E, Matteo RS, Schwartz AE, Silverberg PA, Young WL, Diaz J. The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. Anesthesiology. 1987;67(2):191–6.
119. Alloul K, Whalley DG, Shutway F, Ebrahim Z, Varin F. Pharmacokinetic origin of carbamazepine-induced resistance to vecuronium neuromuscular blockade in anesthetized patients. Anesthesiology. 1996;84(2):330–9.
120. Hernández-Palazón J, Tortosa JA, Martínez-Lage JF, Pérez-Ayala M. Rocuronium-induced neuromuscular blockade is affected by chronic phenytoin therapy. J Neurosurg Anesthesiol. 2001;13(2):79–82.
121. Soriano SG, Kaus SJ, Sullivan LJ, Martyn JA. Onset and duration of action of rocuronium in children receiving chronic anticonvulsant therapy. Paediatr Anaesth. 2000;10:133–6.
122. Soriano SG, Martyn JA. Antiepileptic-induced resistance to neuromuscular blockers: mechanisms and clinical significance. Clin Pharmacokinet. 2004;43:71.
123. Stoyka WW, Schutz HH. The cerebral response to sodium nitroprusside and trimethaphan controlled hypotension. Can Anesth Soc J. 1975;22:275.
124. Turner JM, Powell D, Gibson RM, McDowall DG. Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. Br J Anaesth. 1977;49(5):419–25.
125. Marsh ML, Aidinis SJ, Naughton KV, Marshall LF, Shapiro HM. The technique of nitroprusside administration modifies the intracranial pressure response. Anesthesiology. 1979;51(6):538–41.
126. McDowall DG. Induced hypotension and brain ischaemia. Br J Anaesth. 1985;57(1):110–9.
127. Griffin JP, Cottrell JE, Hartung J, Shwiry B. Intracranial pressure during nifedipine-induced hypotension. Anesth Analg. 1983;62(12):1078–80.
128. Mazzoni P, Giffin JP, Cottrell JE, Hartung J, Capuano C, Epstein JM. Intracranial pressure during diltiazem-induced hypotension in anesthetized dogs. Anesth Analg. 1985;64(10):1001–4.
129. Maekawa T, McDowall DG, Okuda Y. Oxygen tension on the brain surface during hypotension induced by haemorrhage, trimetaphan or sodium nitroprusside. Acta Neurol Scand Suppl. 1977;64:504–5.
130. Michenfelder JD, Theye RA. Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimethaphan, halothane, or nitroprusside. Anesthesiology. 1977;46(3):188–95.
131. Scheingraber S, Rehm M, Sehmisch C, et al. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology. 1999;90:1265.
132. Bailey AG, McNaull PP, Jooste E, Tuchman JB. Perioperative crystalloid and colloid fluid management in children: where are we and how did we get here? Anesth Analg. 2010;110(2):375–90. Epub 2009 Dec 2.
133. Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health. N Engl J Med. 2007;357(9):874–84.
134. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, Tremayne AB, Bernard SS, Ponsford J, HTS Study Investigators. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA. 2004;291(11):1350–7.
135. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. J Trauma. 2005;58:47–50.
136. Van den BG, Schoonheydt K, Becx P, et al. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005;64:1348.
137. Van den BG, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359.
138. Branco RG, Tasker RC. Glycemic level in mechanically ventilated children with bronchiolitis. Pediatr Crit Care Med. 2007;8:546–50.
139. Klein GW, Hojsak JM, Rapaport R. Hyperglycemia in the pediatric intensive care unit. Curr Opin Clin Nutr Metab Care. 2007;10:187–92.
140. Van den BG, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes. 2006;55:3151.
141. Sharma D, Jelacic J, Chennuri R, et al. Incidence and risk factors for perioperative hyperglycemia in children with traumatic brain injury. Anesth Analg. 2009;108:81.
142. Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, Downey SP, Williams G, Chatfield D, Matthews JC, Gupta AK, Carpenter TA, Clark JC, Pickard JD, Menon DK. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med. 2002;30:1950–9.
143. Soriano SG, McManus ML, Sullivan LJ, et al. Cerebral blood flow velocity after mannitol infusion in children. Can J Anaesth. 1996;43:461.
144. Khanna S, Davis D, Peterson B, Fisher B, Tung H, O'Quigley J, Deutsch R. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. Crit Care Med. 2000;28:1144–51.
145. McManus ML, Soriano SG. Rebound swelling of astroglial cells exposed to hypertonic mannitol. Anesthesiology. 1998;88:1586–91.
146. Thenuwara K, Todd MM, Brian Jr JE. Effect of mannitol and furosemide on plasma osmolality and brain water. Anesthesiology. 2002;96:416.
147. Porzio P, Halberthal M, Bohn D, Halperin ML. Treatment of acute hyponatremia: ensuring the excretion of a predictable amount of electrolyte-free water. Crit Care Med. 2000;28:1905–10.
148. Singh S, Bohn D, Carlotti AP, et al. Cerebral salt wasting: truths, fallacies, theories, and challenges. Crit Care Med. 2002;30:2575.
149. Jimenez R, Casado-Flores J, Nieto M, Garcia-Teresa MA. Cerebral salt wasting syndrome in children with acute central nervous system injury. Pediatr Neurol. 2006;35:261–3.

150. Celik US, Alabaz D, Yildizdas D, Alhan E, Kocabas E, Ulutan S. Cerebral salt wasting in tuberculous meningitis: treatment with fludrocortisone. Ann Trop Paediatr. 2005;25:297–302.
151. Levine JP, Stelnicki E, Weiner HL, Bradley JP, McCarthy JG. Hyponatremia in the postoperative craniofacial pediatric patient population: a connection to cerebral salt wasting syndrome and management of the disorder. Plast Reconstr Surg. 2001;108: 1501–8.
152. Byeon JH, Yoo G. Cerebral salt wasting syndrome after calvarial remodeling in craniosynostosis. J Korean Med Sci. 2005;20: 866–9.
153. Ganong CA, Kappy MS. Cerebral salt wasting in children. The need for recognition and treatment. Am J Dis Child. 1993;147(2):167–9 [Erratum in: Am J Dis Child 1993 Apr;147(4): 369].
154. Berger TM, Kistler W, Berendes E, Raufhake C, Walter M. Hyponatremia in a pediatric stroke patient: syndrome of inappropriate antidiuretic hormone secretion or cerebral salt wasting? Crit Care Med. 2002;30(4):792–5.
155. Papadimitriou DT, Spiteri A, Pagnier A, Bayle M, Mischalowski MB, Bourdat G, Passagia JG, Plantaz D, Bost M, Garnier PE. Mineralocorticoid deficiency in post-operative cerebral salt wasting. J Pediatr Endocrinol Metab. 2007;20:1145–50.
156. Wise-Faberowski L, Soriano SG, Ferrari L, et al. Lesson of the week: hyponatremic seizures and excessive intake of hypotonic fluids in young children. J Neurosurg Anesthesiol. 2004;16:14.
157. Holzman RS. Clinical management of latex-allergic children. Anesth Analg. 1997;85(3):529–33.
158. Kain ZN, Caldwell-Andrews AA, Krivutza DM, Weinberg ME, Wang SM, Gaal D. Trends in the practice of parental presence during induction of anesthesia and the use of preoperative sedative premedication in the United States, 1995–2002: results of a follow-up national survey. Anesth Analg. 2004;98(5):1252–9, table of contents.
159. Cochrane DD, Adderley R, White CP, Norman M, Steinbok P. Apnea in patients with myelomeningocele. Pediatr Neurosurg. 1990;16:232–9.
160. Cochrane DD, Gustavsson B, Poskitt KP, Steinbok P, Kestle JR. The surgical and natural morbidity of aggressive resection for posterior fossa tumors in childhood. Pediatr Neurosurg. 1994;20: 19–29.
161. Lee LA, Roth S, Posner KL, Cheney FW, Caplan RA, Newman NJ, Domino KB. The American Society of Anesthesiologists Postoperative Visual Loss Registry: analysis of 93 spine surgery cases with postoperative visual loss. Anesthesiology. 2006;105(4): 652–9.
162. Grady MS, Bedford RF, Park TS. Changes in superior sagittal sinus pressure in children with head elevation, jugular venous compression, and PEEP. J Neurosurg. 1986;65(2):199–202.
163. Todd MM, Warner DS, Sokoll MD, et al. A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Anesthesiology. 1993;78:1005.
164. Soriano SG, Sullivan LJ, Venkatakrishnan K, et al. Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy. Br J Anaesth. 2001;86:223.
165. Breschan C, Platzer M, Jost R, Stettner H, Likar R. Size of internal jugular vs subclavian vein in small infants: an observational, anatomical evaluation with ultrasound. Br J Anaesth. 2010;105(2): 179–84.
166. Amantini A, Carrai R, Lori S, Peris A, Amadori A, Pinto F, Grippo A. Neurophysiological monitoring in adult and pediatric intensive care. Minerva Anestesiol. 2012;78(9):1067–75.
167. Skippen P, Seear M, Poskitt K, Kestle J, Cochrane D, Annich G, Handel J. Effect of hyperventilation on regional cerebral blood flow in head-injured children. Crit Care Med. 1997;25(8): 1402–9.
168. Chan KH, Miller JD, Dearden NM, Andrews PJ, Midgley S. The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain injury. J Neurosurg. 1992;77:55–61.
169. Matta BF, Lam AM, Mayberg TS, et al. A critique of the intraoperative use of jugular venous bulb catheters during neurosurgical procedures. Anesth Analg. 1994;79:745–50.
170. Moss E, Dearden NM, Berridge JC. Effects of changes in mean arterial pressure on SjO2 during cerebral aneurysm surgery. Br J Anaesth. 1995;75(5):527–30.
171. Friedmann DR, Eubig J, McGill M, Babb JS, Pramanik BK, Lalwani AK. Development of the jugular bulb: a radiologic study. Otol Neurotol. 2011;32(8):1389–95.
172. Tsuji M, Saul JP, du Plessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. Pediatrics. 2000;106:625.
173. Figaji AA, Zwane E, Graham Fieggen A, Argent AC, Le Roux PD, Peter JC. The effect of increased inspired fraction of oxygen on brain tissue oxygen tension in children with severe traumatic brain injury. Neurocrit Care. 2010;12(3):430–7.
174. Bernier MO, Rehel JL, Brisse HJ, Wu-Zhou X, Caer-Lorho S, Jacob S, Chateil JF, Aubert B, Laurier D. Radiation exposure from CT in early childhood: a French large-scale multicentre study. Br J Radiol. 2012;85(1009):53–60.
175. Image Gently. www.imagegently.org. Accessed 11 Feb 2013.
176. Ashwal S, Wycliffe ND, Holshouser BA. Advanced neuroimaging in children with nonaccidental trauma. Dev Neurosci. 2010;32(5–6):343–60.
177. Waters KA, Forbes P, Morielli A, Hum C, O'Gorman AM, Vernet O, Davis GM, Tewfik TL, Ducharme FM, Brouillette RT. Sleep-disordered breathing in children with myelomeningocele. J Pediatr. 1998;132(4):672–81.
178. Geiduschek JM, Haberkern CM, McLaughlin JF, Jacobson LE, Hays RM, Roberts TS. Pain management for children following selective dorsal rhizotomy. Can J Anaesth. 1997;41(6):492–6.
179. Ward SL, Nickerson BG, van der Hal A, Rodriguez AM, Jacobs RA, Keens TG. Absent hypoxic and hypercapneic arousal responses in children with myelomeningocele and apnea. Pediatrics. 1986;78(1):44–50.
180. Pollack IF. Brain tumors in children. N Engl J Med. 1994; 331(22):1500–7.
181. Hatipoğlu MA, Prabhu S, Weinberg J, Shah K, Sawaya R. Surgical treatment of supplementary motor area lesions. Turk Neurosurg. 2009;19(3):306–7.
182. Goumnerova LC, Frim DM. Treatment of hydrocephalus with third ventriculocisternostomy: outcome and CSF flow patterns. Pediatr Neurosurg. 1997;27(3):149–52.
183. El-Dawlatly AA, Murshid WR, Elshimy A, Magboul MA, Samarkandi A, Takrouri MS. The incidence of bradycardia during endoscopic third ventriculostomy. Anesth Analg. 2000; 91(5):1142–4.
184. Eldredge EA, Rockoff MA, Medlock MD, Scott RM, Millis MB. Postoperative cerebral edema occurring in children with slit ventricles. Pediatrics. 1997;99(4):625–30.
185. Inagaki T, Kyutoku S, Seno T, Kawaguchi T, Yamahara T, Oshige H, Yamanouchi Y, Kawamoto K. The intracranial pressure of the patients with mild form of craniosynostosis. Childs Nerv Syst. 2007;23(12):1455–9.
186. Goobie SM, Meier-Haran P, Pereira L, McGowan FX, Prescilla R, Sharp L, Rogers G, Proctor MR, Meara J, Soriano SG, Zurakowski D, Sethna NF. Efficacy of tranexamic acid in pediatric craniosynostosis surgery: a double blind placebo-controlled trial. Anesthesiology. 2011;114:862–71.
187. Lecker I, Wang DS, Romaschin AD, Peterson M, Mazer CD, Orser BA. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. J Clin Invest. 2012;122(12): 4654–66.

188. Faberowski LW, Black S, Mickle JP. Incidence of venous air embolism during craniectomy for craniosynostosis repair. Anesthesiology. 2000;92(1):20–3.
189. Jimenez DF, Barone CM, Cartwright CC, Baker L. Early management of craniosynostosis using endoscopic-assisted strip craniectomies and cranial orthotic molding therapy. Pediatrics. 2002;110(1 Pt 1):97–104.
190. Jimenez DF, Barone CM. Endoscopic craniectomy for early surgical correction of sagittal craniosynostosis. J Neurosurg. 1998;88(1):77–81.
191. Tobias JD, Johnson JO, Jimenez DF, et al. Venous air embolism during endoscopic strip craniectomy for repair of craniosynostosis in infants. Anesthesiology. 2001;95:340.
192. Eldredge A, Soriano SG, Rockoff MA. Neuroanesthesia. Neurosurg Clin N Am. 1995;6(3):505–20.
193. Wolf GK, McClain CD, Zurakowski D, et al. Total phenytoin concentrations do not accurately predict free phenytoin concentrations in critically ill children. Pediatr Crit Care Med. 2006;7:434.
194. Burrows PE, Robertson RL. Neonatal central nervous system vascular disorders. Neurosurg Clin N Am. 1998;9:155–80.
195. Morgan MK, Sekhon LH, Finfer S, Grinnell V. Delayed neurological deterioration following resection of arteriovenous malformations of the brain. J Neurosurg. 1999;90:695–701.
196. Soriano SG, Sethna NF, Scott RM. Anesthetic management of children with moyamoya syndrome. Anesth Analg. 1993;77:1066.
197. Kuwabara Y, Ichiya Y, Sasaki M, Yoshida T, Masuda K, Matsushima T, Fukui M. Response to hypercapnia in moyamoya disease. Cerebrovascular response to hypercapnia in pediatric and adult patients with moyamoya disease. Stroke. 1997;28:701–7.
198. Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, Carson S, Chesnut RM, Ghajar J, Goldstein B, Grant GA, Kissoon N, Peterson K, Selden NR, Tasker RC, Tong KA, Vavilala MS, Wainwright MS, Warden CR, American Academy of Pediatrics-Section on Neurological Surgery, American Association of Neurological Surgeons/Congress of Neurological Surgeons, Child Neurology Society, European Society of Pediatric and Neonatal Intensive Care, Neurocritical Care Society, Pediatric Neurocritical Care Research Group, Society of Critical Care Medicine, Paediatric Intensive Care Society UK, Society for Neuroscience in Anesthesiology and Critical Care, World Federation of Pediatric Intensive and Critical Care Societies. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents-second edition. Pediatr Crit Care Med. 2012;13 Suppl 1:S1–82.
199. White JRM, Farukhi Z, Bull C, et al. Predictors of outcome in severely head injured children. Crit Care Med. 2001;29:534.
200. Mandera M, Larysz D, Wojtacha M. Changes in cerebral hemodynamics assessed by transcranial Doppler ultrasonography in children after head injury. Childs Nerv Syst. 2002;18(3–4):124–8. Epub 2002 Mar 20.
201. Adelson PD, Clyde B, Kochanek PM, Wisniewski SR, Marion DW, Yonas H. Cerebrovascular response in infants and young children following severe traumatic brain injury: a preliminary report. Pediatr Neurosurg. 1997;26(4):200–7.
202. Bode H, Wais U. Age dependence of flow velocities in basal cerebral arteries. Arch Dis Child. 1988;63(6):606–11.
203. Vink R, Faden AI, McIntosh TK. Changes in cellular bioenergetic state following graded traumatic brain injury in rats: determination by phosphorus 31 magnetic resonance spectroscopy. J Neurotrauma. 1988;5:315.
204. Ogawa A, Nakamura N, Sugita K, Sakurai Y, Kayama T, Wada T, Suzuki J. Regional cerebral blood flow in children-normal value and regional distribution of cerebral blood flow in childhood. No To Shinkei. 1987;39(2):113–8.
205. Vavilala MS, Lee LA, Boddu K, et al. Cerebral autoregulation in pediatric traumatic brain injury. Pediatr Crit Care Med. 2004;5:257.
206. Bouma GJ, Muizelaar JP, Fatouros P. Pathogenesis of traumatic brain swelling: role of cerebral blood volume. Acta Neurochir Suppl. 1998;71:272–5.
207. Vavilala MS, Muangman S, Waitayawinyu P, et al. Neurointensive care; impaired cerebral autoregulation in infants and young children early after inflicted traumatic brain injury: a preliminary report. J Neurotrauma. 2007;24(1):87–96.
208. Vavilala MS, Muangman S, Tontisirin N, et al. Impaired cerebral autoregulation and 6-month outcome in children with severe traumatic brain injury: preliminary findings. Dev Neurosci. 2006;28:348.
209. Bruce DA, Alavi A, Bilaniuk L, Dolinskas C, Obrist W, Uzzell B. Diffuse cerebral swelling following head injuries in children: the syndrome of "malignant brain edema". J Neurosurg. 1981;54(2):170–8.
210. Aldrich EF, Eisenberg HM, Saydjari C, Luerssen TG, Foulkes MA, Jane JA, Marshall LF, Marmarou A, Young HF. Diffuse brain swelling in severely head-injured children. A report from the NIH Traumatic Coma Data Bank. J Neurosurg. 1992;76(3):450–4.
211. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, Kochanek PM, Miller HC, Partington MD, Selden NR, Warden CR, Wright DW, American Association for Surgery of Trauma, Child Neurology Society, International Society for Pediatric Neurosurgery, International Trauma Anesthesia and Critical Care Society, Society of Critical Care Medicine, World Federation of Pediatric Intensive and Critical Care Societies. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 8. Cerebral perfusion pressure. Pediatr Crit Care Med. 2003;4(3 Suppl):S31.
212. Chambers IR, Stobbart L, Jones PA, Kirkham FJ, Marsh M, Mendelow AD, Minns RA, Struthers S, Tasker RC. Age-related differences in intracranial pressure and cerebral perfusion pressure in the first 6 hours of monitoring after children's head injury: association with outcome. Childs Nerv Syst. 2005;21(3):195–9.
213. Chambers IR, Jones PA, Lo TY, Forsyth RJ, Fulton B, Andrews PJ, Mendelow AD, Minns RA. Critical thresholds of intracranial pressure and cerebral perfusion pressure related to age in paediatric head injury. J Neurol Neurosurg Psychiatry. 2006;77(2):234–40.
214. Philip S, Chaiwat O, Udomphorn Y, Moore A, Zimmerman JJ, Armstead W, Vavilala MS. Variation in cerebral blood flow velocity with cerebral perfusion pressure >40 mm Hg in 42 children with severe traumatic brain injury. Crit Care Med. 2009;37(11):2973–8.
215. Di Gennaro JL, Mack CD, Malakouti A, Zimmerman JJ, Armstead W, Vavilala MS. Use and effect of vasopressors after pediatric traumatic brain injury. Dev Neurosci. 2010;32(5–6):420–30.
216. Sharples PM, Stuart AG, Matthews DS, et al. Cerebral blood flow and metabolism in children with severe head injury. Part 1: relation to age, Glasgow coma score, outcome, intracranial pressure, and time after injury. J Neurol Neurosurg Psychiatry. 1995;58:145.
217. Gambardella G, Zaccone C, Cardia E, Tomasello F. Intracranial pressure monitoring in children: comparison of external ventricular device with the fiberoptic system. Childs Nerv Syst. 1993;9:470–3.
218. Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW. Hypothermia therapy after traumatic brain injury in children. N Engl J Med. 2008;358:2447–56.
219. Johnson JO, Jimenez DF, Barone CM. Blood loss after endoscopic strip craniectomy for craniosynostosis. J Neurosurg Anesthesiol. 2000;12:60.

220. Rekate HL. Selecting patients for endoscopic third ventriculostomy. Neurosurg Clin N Am. 2004;15:39–49.
221. El-Dawlatly AA, Murshid W, Alshimy A, Magboul MA, Samarkandi AH, Takrouri MS. Arrhythmias during neuroendoscopic procedures. J Neurosurg Anesthesiol. 2001;13:57–8.
222. Davidyuk G, Soriano SG, Goumnerova L, Mizrahi-Arnaud A. Acute intraoperative neurogenic pulmonary edema during endoscopic ventriculoperitoneal shunt revision. Anesth Analg. 2010;110:594–5.
223. Hansen MS, Brennum J, Moltke FB, Dahl JB. Pain treatment after craniotomy: where is the (procedure-specific) evidence? A qualitative systematic review. Eur J Anaesthesiol. 2011;28(12):821–9.
224. Teo JH, Palmer GM, Davidson AJ. Post-craniotomy pain in a paediatric population. Anaesth Intensive Care. 2011;39(1):89–94.
225. Brannen ML, Cameron KA, Adler M, Goodman D, Holl JL. Admission handoff communications: clinician's shared understanding of patient severity of illness and problems. J Patient Saf. 2009;5(4):237–42.