Anesthesia Management in Severe Prematurity

15

Marinella Astuto and Concetta Gullo

15.1 Introduction

Over the last 30 years, greater numbers of premature infants of decreasing gestational age and extremely low birth weight (ELBW) have survived thanks to advances in neonatal intensive care and obstetrics. The increased survival of premature neonates has produced a population of infants who are susceptible to many unique diseases and a host of potential anesthetic challenges. With this increased survival rate, the need for infants to undergo surgery is not infrequent. It may be performed for surgical ligation of a patent ductus arteriosus (PDA), which is causing severe heart failure not controlled by medical therapy, or a laparotomy for the consequences of necrotizing enterocolitis (NEC).

These infants are also at risk of developing retinopathy of prematurity (ROP), which often coexists with chronic lung disease and may require laser or cryosurgery. Many develop inguinal hernias, which occur with increased frequency in those born before a gestational age of 32 weeks and a birth weight of less than1,250 g [1]. Inguinal hernia repair remains the most common surgical procedure carried out in pre-term infants. For the purpose of this chapter, we will focus on the very low and ELBW infant, or severe prematurity, and discuss the associated developmental physiology and its impact on anesthetic care.

15.2 Defining the Levels of Prematurity

Prematurity is defined as birth before 37 weeks of gestation, which is based on the last menstrual period and ultrasound scan. Unfortunately, ultrasonographic assess-

M. Astuto (✉)
Anesthesia and Intensive Care, Pediatric Anesthesia and Intensive Care Section, and Postgraduate School, University of Catania, AOU Policlinico-Vittorio Emanuele Catania, Italy

M. Astuto (ed.) *Pediatric Anesthesia, Intensive Care and Pain: Standardization in Clinical Practice*. Anesthesia, Intensive Care and Pain in Neonates and Children
DOI: 10.1007/978-88-470-2685-8_15, © Springer-Verlag Italia 2013

ment of gestational age in the second trimester is not always accurate. An error of 1.2 weeks can have a significant impact on management decisions, because survival rate improves significantly with each incremental week of intrauterine life beyond 23 weeks of gestation [2]. Premature babies may be further divided into borderline prematurity (36–37 weeks of gestation), moderate prematurity (31–36 weeks of gestation), and severe prematurity (24–30 weeks of gestation) [3]. Low birth weight (LBW) infants are defined as infants born with a birth weight of less than 2,500 g; very low birth weight (VLBW) infants are those with a birth weight of less than 1,500 g; and ELBW infants are infants with a birth weight of less than 1,000 g. Birth weight may therefore be a more accurate measure of prematurity. In fact, comparisons between gestational age and birth weight have found them to be independent predictors of survival [4].

15.3 Problems Associated with Severely Premature and Extremely Low Birth Weight Infants

Morbidity and mortality for the smallest infants remains high with one study estimating a mortality rate of 89% for infants weighing 401–500 g. Almost all of the survivors in this ELBW group suffered from considerable morbidity [5].

The premature infant presents a unique physiology, anatomy, and pathology and requires focused strategies for presurgical management and for the administration of anesthesia. Most of the important organs in these babies are still in the process of development and maturation. There is inadequate production of efficient surfactant, a susceptibility of retinal blood vessels to oxygen toxicity, and a susceptibility to hemorrhagic and ischemic brain damage. These factors lead to the development of diseases exclusively found in these babies, e.g., respiratory distress syndrome (RDS), intraventricular hemorrhage, ROP, PDA, and NEC. Other factors include hypoglycemia, apnea (especially during the postoperative period), and hypothermia.

15.3.1 Pulmonary Disease

Premature infants of less than 32 weeks gestation are at increased risk of developing RDS. This is characterized by increasing atelectasis secondary to the inadequate production of surfactant. This low level of surfactant leads to alveolar collapse, a reduction in functional residual capacity, intrapulmonary shunting, and hyaline membrane formation. Atelectasis, hyaline membrane formation, and interstitial edema combine to reduce pulmonary compliance and necessitate the use of supplemental oxygen and positive pressure ventilation. The incidence and severity of RDS is inversely proportional to gestational age. Bronchopulmonary dysplasia (BPD) is defined as the need for supplemental oxygen before 30 days of life. BPD is a combination of pulmonary parenchymal and interstitial changes secondary to the ef-

fects of oxygen therapy and positive pressure ventilation on the premature lung. A severity index for BPD based on the need for supplemental oxygen and/or positive pressure ventilation or nasal continuous positive airway pressure has been developed, and shown to identify a spectrum of risk for adverse pulmonary and neurodevelopmental outcomes in prematurely born infants [6]. Anesthetic goals include minimizing the inspired oxygen concentration and peak inspiratory pressures while maintaining oxygenation and ventilation. The introduction of maternal steroid administration and artificial surfactant replacement therapy in the infant with less than 28 weeks gestational age has dramatically improved the prognosis of these infants.

15.3.2 Apnea and Respiratory Control

Severely premature infants possess a biphasic ventilatory response to hypoxia. Initially, ventilation increases during hypoxia, but after several minutes, ventilation decreases and apnea may ensue [7]. Apneic episodes occur commonly in the severely premature but decrease with advancing postconceptional age [8].

Apneic spells are a common neonatal problem occurring in approximately 25% of premature infants and ex pre-term infants during recovery from general anesthesia [9]. The apnea of prematurity and apnea following general anesthesia appear to have a similar distribution of central (70%), obstructive (10%), and mixed (20%) origins [10].

Pre-term infants with a history of periodic breathing often become apneic in response to airway obstruction; this effect declines with increasing postnatal age. As upper airway obstruction appears to be important in the development of apnea, it seems reasonable to assume that general anesthesia, which can decrease upper airway muscle tone, may contribute to the development of apnea after general anesthesia, even in infants without a history of apnea. Prolonged apnea is often accompanied by hypoxia, hypercarbia, and bradycardia. Apnea is usually defined as absent respiratory airflow of 15 s or longer. Postoperative apnea occurs as a cluster of episodes over several minutes, with minutes of normal breathing in between the clusters, accompanied by bradycardia. The incidence of postoperative apnea depends on postconceptional and gestational age, hematocrit, and the type of surgical procedure. The most significant risk factor is postconceptional age; the lower the postconceptional age, the greater the risk. Hypothermia and hypoglycemia are known to induce apnea. Anemia (hematocrit < 30%) and younger gestational age increase the risk of apnea for a given postconceptional age [11,12].

15.3.3 Brain Injury

Brain injury in premature infants includes intraventricular hemorrhage (IVH), cerebral ischemia [periventricular leukomalacia (PVL)], and posthemorrhagic hydrocephalus. IVH is the most common cause of intracranial hemorrhage in VLBW infants.

The incidence and severity of IVH is directly proportional to the degree of prematurity. An early onset of IVH appears during the first day of life. Risk factors include fetal distress, vaginal delivery, low Apgar (appearance, pulse, grimace, activity, respiration) scores, metabolic acidosis, hypercapnia, and the need for mechanical ventilation [13,14].

Hypercapnia, hypoglycemia, and anemia are associated with a rise in cerebral blood flow which may induce the onset of IVH. Factors that may decrease the incidence and severity of IVH include the administration of sedation with opioids, antenatal glucocorticoids, or indometacin. The outcome for infants with IVH depends, to a large extent, on the degree of associated parenchymal injury.

PVL is due to the impairment of the blood supply to the cerebral white matter. Severe hypotension, marked hypocarbia, and impairment of cerebral autoregulation in these infants are some of the risk factors leading to insufficient cerebral blood flow and ischemia.

15.3.4 Retinopathy of Prematurity

The pathophysiology of ROP is thought to be due to retinal artery constriction leading to retinal ischemia resulting in neovascularization. ROP occurs in approximately 50% of ELBW infants, with the incidence and severity being inversely proportional to birth weight and gestational age [15–17]. Although the pathogenesis of ROP is not completely understood, variations in arterial oxygenation (hypoxia or hyperoxia) and exposure to bright light appear to play a role.

One theory suggests that the combination of the hyperoxic vasoconstriction of retinal vessels, the induction of vascular endothelial growth factors, and free oxygen radicals damage the spindle cells in the retina. Other contributing factors include the use of supplemental oxygen, fluctuations in oxygen saturation, mechanical ventilation, total parenteral nutrition (TPN), and blood transfusion [18].

During anesthesia, the lowest inspired oxygen concentration that provides oxygen saturations between 92% and 96% is used and all attempts are made to avoid significant fluctuations in oxygen saturation.

15.3.5 Gastrointestinal Disease

NEC is an intestinal disease more common in premature infants and occurs in about 5% of ELBW infants; birth weight less than 1000 g that is the most important risk factor for NEC [19]. The prognosis for ELBW infants with NEC is poor. The pathogenesis of NEC has a multifactorial etiology, including hypoperfusion of the gut due to systemic hypoxia or hypotension, infection due to bacterial translocation across an immature gut wall, and enteric feeding, typically coincide with the onset of enteral feeding. Other factors include exposure to antenatal glucocorticoids, vaginal delivery, the need for mechanical ventilator support, PDA, exposure to postnatal indometacin, and a low Apgar score at 5 min [20].

The initial signs of NEC are feeding intolerance, increased work breathing, temperature instability, and lethargy; later signs include abdominal distension, bile-stained vomiting, bloody and frothy stools, gastric residuals of previous feeds, and periumbilical discoloration. There may be signs of systemic sepsis—circulatory collapse, hypotension, apnea, low blood glucose levels—and occasionally signs of gut perforation. Thrombocytopenia is common and may require correction. Initial management includes resuscitation, cardiopulmonary support, and antibiotics. Large volumes of colloids may be required together with blood and blood components. Surgical intervention may be required when there is perforation and when there is continuing deterioration despite full support.

15.3.6 Temperature Regulation

Premature and ELBW infants are susceptible to hypothermia during surgery. At birth, body temperature tends to decrease and this is due to heat loss from physical contact with cold surfaces or cold clothing as the temperature control system of premature infants is not yet developed. Moreover, the neonate depends on nonshivering thermogenesis for heat production. Nonshivering thermogenesis uses brown adipose tissue and requires oxygen consumption. It is believed that in small premature infants, brown adipose tissue is not sufficiently developed, and this, combined with the larger surface/volume ratio, makes infants more susceptible to hypothermia. In fact, brown fat cells begin to differentiate from reticular cells at 20 to 30 weeks of gestation and increase in size and number about 3–6 weeks after birth [3]. Volatile anesthetics are potent inhibitors of brown adipose tissue thermogenesis [21,22], while nitrous oxide and intravenous anesthetics such as sodium thiopental and propofol do not have this inhibitory property [23]. Hypothermia significantly increases metabolic activity and oxygen consumption, and this leads to serious clinical consequences such as hypoxemia, metabolic acidosis, periodic breathing or apnea, respiratory distress, bradycardia, hyperglycemia, and pulmonary aspiration of gastric contents, all factors that may seriously threaten the infant's life [3].

A premature infant's flaccid, open posture tends to increase heat loss rather than conserve heat, whereas the flexed, curled-up position of full-term neonates tends to conserve heat. We have to then add to this the risk in patients with central nervous system damage or suffering from hypoglycemia, who have more difficulty maintaining body temperature. After exposure to low temperatures, infants appear agitated because they increase their muscle activity in an attempt at compensation. This also produces an increase in the secretion of catecholamines in the serum as an attempt to increase heat production and safeguard the noble organs from the effects of hypothermia.

Both before arrival in the operating room and during any operation, heat loss must be minimized; therefore, any transport of the infant has to be in a thermo-heated incubator and an adequate temperature has to be maintained through the use of heat exchangers connected to special thermal blankets. It is of great importance

to carefully cover the body of the infant, and in particular the head, which in this subject is a large surface for heat loss [3,24].

15.3.7 Patent Ductus Arteriosus

The PDA connects the main pulmonary artery with the aorta. It is essential during intrauterine life and its persistent patency is common in prematurity [25].

The small dimensions of the ducts result in a minimum left–right shunt without major hemodynamic consequences, while in the larger volume ducts overload will affect pulmonary circulation and the left sections over time, with the appearance of cyanosis and pulmonary hypertension.

In many cases, the duct closes spontaneously; where this does not happen, pharmacological intervention or surgery is necessary. The initial medical treatment includes fluid restriction [26–28], diuretics, and the administration of cyclooxygenase inhibitors, indometacin, and ibuprofen [28–30]. Indometacin therapy is less likely to close the PDA in ELBW infants compared with pre-term infants and is more likely to produce complications, including thrombocytopenia, renal failure, hyponatremia, and intestinal perforation [31].

Surgery consists of ligation through a left thoracotomy [32], with retraction of the left lung with decreased lung compliance. One of the most feared complications is severe bleeding [33]. When surgery is performed by experienced teams, the incidence of major complications is small [34].However, substantial late morbidity and mortality have been reported from the long-term complications of prematurity.

Anesthesia includes the use of fentanyl (20–50 g/kg) and pancuronium bromide (0.2 mg/kg). Although this procedure does not usually cause hypotension or bradycardia, a reduction in arterial pressure after anesthetic induction does occur because of loss of sympathetic tone, especially in the setting of hypovolemia due to diuretic therapy. This condition can be prevented by administering albumin (10 mL/kg) before induction [33].

15.3.8 Infection

Pneumonia, sepsis, and meningitis are the most common infections in *premature and ELBW infants*. The presence of catheters and respirators can, in fact, become a vehicle for bacteria. The main reason is that infants do not have a fully developed immune system, which is adapted to respond appropriately to external pathogens. The signs of sepsis are nonspecific and immediate; however, the following should be considered as possible signs of an infection: the presence of hypo- or hyperthermia, lethargy, apnea, or an increase of serum glucose levels. Sepsis can develop without changes in white blood cell count (WBC), fever, or signs of positive blood cell cultures. However, a 15% increase in WBC may be suggestive of an infection [35]. On occasions, traces of WBC in the cerebral spinal fluid and urine can be found [36].

Treatment with antibiotics appears to be the most appropriate therapy, even if aminoglycosides can cause muscle weakness and paralysis. Recent studies have shown that early treatment of sepsis is very important to prevent neurological damage from developing even several years after the original infection [37].

15.3.9 Anemia

Anemia is defined as a reduction of the total quantity of circulating hemoglobin in the peripheral blood and within erythrocytes. Premature infants are particularly subject to anemia because red blood cells in the neonatal period have a shorter life span and during the first weeks of life, their production is limited, being body growth relatively faster. At birth, the concentration of hematocrits (50–55%) is greater in infants than in older children and adults. This concentration tends to decrease normally in about in 2 or 3 months [3].

Normally, fetal hemoglobin is replaced by the adult variety which has lower affinity with oxygen (the affinity of hemoglobin for oxygen is a reduced P50 of 19 mmHg in the newborn vs. 30 mmHg in the infant vs. 27 mmHg in the adult). Consequently, in pre-term infants with the same hematocrit, less oxygen is delivered to the tissues. The situation can be aggravated by poor nutrition of the newborn with low vitamin E, folic acid, and iron, and by lung disorders [3,38].

In these premature infants, elective surgery should not take place when the hemoglobin concentration is lower than 10 g/dL. Thrombocytopenia occurs in about 70% of premature infants and the cause is not always very clear, although sepsis, coagulation intravascular disease, and NEC are among the most common causes. In the preoperative evaluation, a recent platelet count must be obtained and platelet availability must be evaluated [33]. The hematology values at different ages are shown in Table 15.1.

15.3.10 Hyperbilirubinemia

Almost all pre-term infants less than 35 weeks old have elevated levels of total bilirubin in serum or plasma and this condition is called prenatal jaundice. The

Table 15.1 Hematology values at different ages [68–70]

	Pre-term 28–32 weeks	Pre-term 32–36 weeks	Full-term infant
Hemoglobin (g/dL)	12.9	13.6	16.8
Hematocrit (%)	40.9	43.6	55
White blood cell count(/mm^3)	5,160	7,710	18,000
Platelet count (/mm^3)	255,000	260,000	300,000
Prothrombin time (s)	15.4	13	13
Activated partial thromboplastin time (s)	108	53.6	42.9
Fibrinogen (mg/dL)	256	243	283
Bleeding time (min)		3.5	3.5

yellowish discoloration of the skin and/or sclerae is caused by bilirubin deposition because pre-term infants have a reduced ability to conjugate this substance. The major complication produced by bilirubin is a neurological dysfunction (bilirubin-induced neurological dysfunction), which occurs when the circulating bilirubin crosses the blood–brain barrier and binds to brain tissue. A bilirubin concentration of 10–15 mg/dL causes kernicterus if the infant is in a state of acidosis and hypoxemia [39–41]. Additionally, certain substances such as sulfonamides, furosemide, and benzyl alcohol, having high affinity for proteins, displace bilirubin thereby increasing the risk of kernicterus [33]. Therefore, a two-volume exchange transfusion should be performed before surgery if the infant has elevated indirect bilirubin, because intraoperative hypoxemia and acidosis may prove disastrous.

15.3.11 Electrolyte Disorders

In the infant in a critical condition, the relationship between energy expenditure and water loss is affected by functional immaturity, environmental stress, and redistribution of body water at birth. The premature infant has a relative excess of the total volume of water and extracellular fluid than the full-term infant. Changes in the concentration of electrolytes in the premature infant can be very frequent, but one should never rely on the first sample [42]. An increase of sodium in the blood may be caused either by excessive dehydration or by the excessive administration of sodium [3]. Renal blood flow and glomerular filtration rate (GFR) increase with gestational age; in full-term newborns, these parameters improve rapidly after birth, while they remain altered in premature infants, resulting in intolerance to excessive fluid and electrolytes [42]. Hypokalemia is common (< 3 mEq/L), especially in pre-term infants who received diuretics. The serum chloride concentration is normally higher (105–115 mEq/L) and the total calcium concentration is usually lower than that of full-term infants. Hyperventilation may further reduce serum potassium levels and ionized calcium concentration.

Most neonatologists tend to maintain the total serum calcium concentration above 8 mg/dL, although many neonates do perfectly well with concentrations below this level [3]. The serum calcium concentration in premature and ELBW infants is normally lower than that of full-term infants because pre-term infants have a diminished concentration of serum proteins [3].

15.3.12 Hypoglycemia

Premature and LBW infants are susceptible to hypoglycemia. This is attributed to immature gluconeogenic and glycogenolytic enzyme systems. A plasma glucose concentration of less than 25 mg/dL in these infants is taken as a sign of hypoglycemia. Infants who use glucose at an increased rate are prone to hypo-

glycemia, e.g., infants experiencing perinatal asphyxia, neonatal sepsis, and a cold environment [43].

Glucose levels in infants at increased risk of hypoglycemia should be checked intraoperatively. Intravenous infusions should contain glucose to maintain a glucose infusion rate of between 6 and 8 mg/kg/min.

15.4 Anesthetic Management

Anesthesia provides insensitivity to pain during surgical procedures. The most commonly used technique in severely premature infants is general anesthesia. Over the last 25 years, general anesthesia has been delivered using both inhaled and intravenous drugs in very premature infants for a variety of surgical procedures. The most frequent diseases for which surgery is required in VLBW infants are inguinal hernia, NEC, PDA, ROP, and ventriculoperitoneal shunt.

15.5 Drug Pharmacokinetics and Pharmacodynamics

The pharmacokinetics and pharmacodynamics of drugs for severe premature infants are different from those of full-term neonates, children, or adults.

The main factors affecting drug pharmacokinetics in severely premature infants are higher body water than body fat content, which results in higher volume distribution, and hence a need for a higher loading dose, and a decrease in albumin and α1-acid glycoprotein binding leading to an increase in free drug concentration. In these infants, the biotransformation of drugs by hepatic enzyme systems may be slower due to the immaturity of the systems. Renal excretion of drugs may be slow or impaired due to low renal blood flow, low GFR, and poor tubular secretion. The minimum alveolar concentration of inhaled anesthetics is lower in pre-term infants compared with full-term neonates [44].

15.6 Effects of Anesthesia and Sedation on Brain Development

Recent findings in neonatal animals have revealed that all commonly used anesthetics and sedatives induce neuronal cell death in several regions of the developing brain [45,46].

Whether the observed degenerating neurons were destined to die by physiologically programmed cell death, called apoptosis, or whether exposure to the anesthetic induced apoptotic cell death in neurons otherwise not destined to die remains controversial [47]. Nonetheless, these disturbing findings in animals have raised significant safety concerns regarding anesthetic exposure in immature neonates [48].

Emerging findings from epidemiological studies in humans remain conflicting; while some studies have suggested an association between anesthetic exposure early in life and subsequent learning or behavioral abnormalities [49,50], other studies have failed to find this association [51,52]. The mechanism for neurotoxicity appears to be attributed to the neurotransmitters glutamate and γ-aminobutyric acid, which act as trophic factors in the developing brain [53]. In the immature brain, these trophic factors promote synaptic growth and plasticity and are necessary for neuronal survival.

The inhaled anesthetics ketamine, nitrous oxide, and midazolam exert their anesthetic effects by altering synaptic transmission through the blockade of glutamate and γ-aminobutyric acid receptors. In the immature brain, this blockade also precipitates neuronal cell death by apoptosis [54]. Moreover, pre-term infants who receive anesthesia and sedation for painful procedures experience less morbidity and mortality than those who do not [55,56]. Based on animal models, the severe premature infant exposed to several hours of high concentrations of the inhaled anesthetics ketamine, nitrous oxide, and midazolam is potentially at risk, as is the premature infant exposed to surgery with insufficient anesthesia. We often anesthetize babies with low concentrations of the inhaled agent, but with large doses of opioids and regional anesthesia whenever possible.

15.7 Choice of Operation Site

Which is the best place to perform surgery in severe premature infants, the operating room or the neonatal intensive care unit (NICU)?

Anesthesiologists and surgeons are more comfortable performing surgery in an operating room which allows them to work in a familiar place with access to the assistance of colleagues and nursing staff, and a variety of surgical and anesthetic equipment nearby. On the other hand, performing surgery in the NICU avoids transportation of the infant which may be accompanied by a significant amount of risk.

In the past, some surgeons chose to perform surgery at the bedside in the NICU without an anesthesiologist present because it was deemed unsafe to transport the infant, or if there was no operating room or anesthesiologist to perform the surgery in a timely manner, or because it was believed that the severely premature did not need anesthesia. In the authors' opinion, this model of care does not provide the highest level of patient care; there is ample evidence that premature neonates require anesthesia for surgery.

There is clearly no answer as to which is the best place. The decision should be made based on the setting and conditions in each individual case and institution, minimizing the period of transportation and providing optimal surgical conditions (optimal lighting, sterile conditions, and controlled room temperature).

15.8 Preoperative Evaluation

Preoperative preparation focuses on the optimization of cardiac and respiratory status and on the treatment of anemia, electrolyte abnormalities, metabolic acidosis, and coagulopathy. For nonemergency procedures such as inguinal hernia repair, preoperative evaluation occurs well in advance of surgery to optimize medical status before the administration of anesthesia. Communication between the anesthesiologist, surgeon, and neonatologist before and after surgery is vital for safe care. For almost all surgeries, packed red blood cells should be available in the operating room.

The NPO (nil by mouth) status should be determined. In our institution, babies less than 6 months are required to be NPO for formula for 4 h or longer, breast milk for 3 h or longer, and clear liquids for 2 h or longer (Table 15.2)

15.9 General Anesthesia

Anesthesia may be induced using either an inhalational agent or an intravenous agent; usually this depends on whether the infant has an intravenous catheter in place and whether there is a risk of pulmonary aspiration. For elective procedures, inhalation induction of anesthesia is common because access may be difficult after a long neonatal NICU stay. Saphenous, external jugular, and scalp veins often yield the greatest success when it is impossible to insert a hand or foot intravenous cannula. The size of the endotracheal tube (ETT) chosen should be based on the age of the infant and whether they require prolonged tracheal intubation (> 1 months) in the NICU. If the infant has to undergo a prolonged period of tracheal intubation, the ETT used should have an internal diameter that is 0.5 mm smaller than the tube usually chosen for a child of this age. The anesthesiologist should ensure that there is an adequate air leak around the ETT during positive pressure ventilation to prevent an excessively tight tube from contributing to postoperative tracheal edema and airway obstruction.

Particular intraoperative concerns for severely premature infants include maintenance of normal body temperature, balanced use of intravenous fluids, and effective humidification of inhaled gases to promote effective pulmonary hygiene and help maintain a normal body temperature. Premature infants have large surface area/volume ratios and lose body heat easily through their skin. For infants less than 6 months of age, the operating room should be pre-warmed to prevent radiant heat loss during preparation and before the young patient is covered with drapes. A warming mattress, a heated and humidified breathing circuit, and warmed intravenous fluids further help prevent heat loss. A reduction of body temperature contributes

Table 15.2 Preoperative fasting recommendations in infants and children

Age	Formula	Breast milk	Clear liquids
< 6 months	4 h	3 h	2 h

to an increase in the expenditure of metabolic energy postoperatively and may contribute to apnea in infants of less than 60 weeks postconceptional age.

Intravenous fluids consist primarily of a balanced salt solution (such as lactated Ringer's solution) for the replacement of intraoperative fluid losses. The compositions of commonly used intravenous solutions are shown in Table 15.3.

Maintenance fluids need not contain dextrose routinely, but should be used for patients receiving continuous infusion via TPN or those with documented hypoglycemia. For the smallest premature infants (< 3 months of age) who have inadequate glycogen stores, the routine administration of a 5–10% dextrose solution at maintenance rates will usually maintain normal blood glucose concentrations. Maintenance fluid rate can be calculate as 4 mL/kg/h for the first 10 kg of body weight plus 2 mL/kg/h for the next 10 kg of body weight plus 1 mL/kg/h for each kg thereafter (Table 15.4).

Positioning of the patient must be done in a way that prevents hyperextension of contracted joints. Placing a roll under the infant's upper back will align the airway of infants with large heads relative to their chest size.

The hemodynamic state should be maintained in as stable a level as possible to avoid an abrupt increase or decrease in cerebral blood flow, which may lead to intracerebral hemorrhage or cerebral ischemia. An estimate of the circulating blood volume is shown in Table 15.5.

Table 15.3 Composition of extracellular fluid and commonly used intravenous solutions

	Na^+	K^+	Ca^{2+}	Mg^{2+}	NH_4^+	Cl^-	HCO_3-	HPO_4^-
Extracellular fluid	142	4	5	3	0.3	103	27	3
Lactated Ringer's solution	130	4	3	–	–	109	28	–
0.45% NaCl	77	–	–	–	–	77	–	–
0.9% NaCl (normal saline)	154	–	–	–	–	154	–	–
3% NaCl	590	–	–	–	–	590	–	–

Table 15.4 Maintenance fluid requirements in children

Weight (kg)	Hour	Day
< 10	4 mL/kg	100 mL/kg
10–20	40 mL + 2 mL/kg for every kg > 10 kg	1,000 mL + 50 mL/kg for every kg > 10 kg
> 20	60 mL + 1 mL/kg for every kg > 20 kg	1,500 mL + 20 mL/kg for every kg > 20 kg

Table 15.5 Estimate of circulating blood volume

Age	Estimated blood volume (mL/kg)
Pre-term infant	100
Full-term neonate	90
Infant	80
School age	75

Basic monitoring includes electrocardiogram, blood pressure, pulse oximetry, end-tidal carbon dioxide and temperature. For major surgery, invasive blood pressure monitoring, central venous pressure, and urine output may be needed. An intra-arterial cannula may be sited at the umbilical artery, radial artery, or posterior tibial artery.

15.10 Regional Anesthesia

There is increasing evidence that regional anesthesia is beneficial when used alone or in combination with general anesthesia in VLBW infants. Epidural anesthesia has been shown to decrease the need for postoperative ventilatory support in infants undergoing major surgery [57]. Huang and Hirshberg [58] showed that regional anesthesia decreased the need for postoperative mechanical ventilation in infants with a mean gestational age of 26 weeks and a mean postconceptional age at surgery of 38 weeks, when undergoing hernia repair. Good success rates and low complication rates have also been reported [59]. The incidence of postoperative apnea following general anesthesia has been reported to be 11–37%, whereas the risk of postoperative apnea following spinal anesthesia without sedative supplementation is close to 0% [60,61]. The risk of apnea, oxygen desaturation, and bradycardia is not completely abolished by the use of regional anesthesia because there is occasional need to supplement regional anesthesia with intravenous or inhaled agents.

Inguinal hernia repair is the most common surgical indication for regional anesthesia in severely premature infants. Inguinal hernia repair under spinal [62] or caudal [63,64] anesthesia is reported to have fewer episodes of apnea, hypoxemia, and bradycardia than in infants who receive general anesthesia [65]. The jury is out, though, because recent publications using newer inhalational agents (desflurane, sevoflurane) suggest little difference [66,67]. The main limitation of spinal anesthesia is the limited duration of action of local anesthetics, even when relatively large doses per kg of body weight are administered. The duration of action is up to 80% shorter in the youngest children compared with adults. The maximum duration of spinal anesthesia is about 90 min, even when long-acting local anesthetics are administered in relatively large doses. The short duration of action of intrathecal drugs in these infants has prompted interest in continuous regional anesthesia techniques so that the duration of anesthesia may be extended while drug toxicity is minimized. Successful regional anesthesia techniques offer many advantage in this high-risk population.

15.11 Emergence from Anesthesia

Extremely premature and VLBW infants who were mechanically ventilated before surgery should remain ventilated during the return journey to the NICU. The trachea need not be extubated in the operating room immediately after the surgical

procedure even if the infant was not on a ventilator before surgery. The trachea can be extubated later in the NICU when full recovery from the remaining effects of the anesthetic is obtained.

15.12 Postoperative Management

Pre-term infants tend to have apneic spells postoperatively. The generally accepted limit of such a risk in infants is a 44–46 weeks postconceptional age. Monitors should be applied to detect apnea, desaturation, and bradycardia in these infants for at least 48 h postoperatively.

15.13 Conclusions

Severely premature and VLBW infants present significant challenges to the anesthesiologist. They are susceptible to prematurity-related diseases. When providing anesthesia for these infants, precautions should be taken to deliver safe anesthesia. Attention should be paid to the inspired oxygen concentration to avoid hyperoxia, which is a major contributing factor to the development of ROP. Hemodynamic parameters should be kept stable to avoid IVH and cerebral ischemia. Prevention of hypothermia and hypoglycemia is also essential. These infants handle drugs in a less predictable fashion and therefore there is a need to titrate drug dosages. These very young patients will benefit from adequate anesthesia and analgesia.

References

1. Peevy KJ, FA Speed, CJ Hoff (1986) Epidemiology of inguinal hernia in preterm neonates. Pediatrics, 77(2):246-247
2. Boat AC et al (2011) Outcome for the extremely premature neonate: how far do we push the edge? Paediatr Anaesth, 21(7):765-770
3. Gregory, ed. Pediatric Anestesia
4. El-Metwally D, B Vohr, R Tucker, (2000) Survival and neonatal morbidity at the limits of viability in the mid 1990s: 22 to 25 weeks. J Pediatr, 137(5):616-622
5. Lemons JA et al (2001) Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 107(1):E1
6. Kurth CD et al (1987) Postoperative apnea in preterm infants. Anesthesiology 66(4):483-488
7. Rigatto H, JP Brady (1972)Periodic breathing and apnea in preterm infants. II. Hypoxia as a primary event. Pediatrics 50(2):219-228
8. Daily WJ, M Klaus, HB Meyer (1969) Apnea in premature infants: monitoring, incidence, heart rate changes, and an effect of environmental temperature. Pediatrics, 43(4):510-518

9. Gallagher, TM and PM Crean, (1989) Spinal anaesthesia in infants born prematurely. Anaesthesia 44(5):434-436
10. Kurth CD, SE LeBard (1991) Association of postoperative apnea, airway obstruction, and hypoxemia in former premature infants. Anesthesiology 75(1):22-26
11. Cote CJ et al (1995) Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. Anesthesiology 82(4):809-822
12. Welborn LG et al (1991) Anemia and postoperative apnea in former preterm infants. Anesthesiology 74(6):1003-1006
13. Wells JT, LR Ment, (1995).Prevention of intraventricular hemorrhage in preterm infants. Early Hum Dev 42(3):209-233
14. Kaiser JR et al (2006) Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. J Perinatol 26(5):279-285
15. Lermann VL, JB Fortes Filho, RS Procianoy (2006) The prevalence of retinopathy of prematurity in very low birth weight newborn infants. J Pediatr (Rio J), 82(1):27-32
16. Whitfill CR, AV Drack (2000) Avoidance and treatment of retinopathy of prematurity. Semin Pediatr Surg 9(2):103-105
17. Nair PM et al (2003) Retinopathy of prematurity in VLBW and extreme LBW babies. Indian J Pediatr 70(4):303-306
18. Cunningham S et al (1995) Transcutaneous oxygen levels in retinopathy of prematurity. Lancet 346(8988):1464-1465
19. Snyder CL et al (1997) Survival after necrotizing enterocolitis in infants weighing less than 1,000 g: 25 years' experience at a single institution. J Pediatr Surg 32(3):434-437
20. Guthrie SO et al (2003) Necrotizing enterocolitis among neonates in the United States. J Perinatol 23(4):278-285
21. Ohlson K.B et al (1994) Thermogenesis in brown adipocytes is inhibited by volatile anesthetic agents. A factor contributing to hypothermia in infants? Anesthesiology 81(1):176-183
22. Dicker A et al (1995) Halothane selectively inhibits nonshivering thermogenesis. Possible implications for thermoregulation during anesthesia of infants. Anesthesiology 82(2):491-501
23. Ohlson KB et al (2003) Thermogenesis inhibition in brown adipocytes is a specific property of volatile anesthetics. Anesthesiology 98(2):437-448
24. Jahnukainen T et al (1993) Dynamics of vasomotor thermoregulation of the skin in term and preterm neonates. Early Hum Dev 33(2):133-143
25. Trus T et al (1993) Optimal management of patent ductus arteriosus in the neonate weighing less than 800 g. J Pediatr Surg 28(9):1137-1379
26. Radtke WA, (1998)Current therapy of the patent ductus arteriosus. Curr Opin Cardiol 13(1):59-65
27. Stevenson JG (1977) Fluid administration in the association of patent ductus arteriosus complicating respiratory distress syndrome. J Pediatr 90(2):257-261
28. Heymann MA, AM Rudolph, NH Silverman (1976) Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N Engl J Med 295(10):530-533
29. Merritt TA et al (1978) Closure of the patent ductus arteriosus with ligation and indomethacin: a consecutive experience. J Pediatr 93(4):639-646
30. Ohlsson A, R Walia, S Shah (2008) Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev (1):CD003481
31. Little DC et al (2009) Patent ductus arteriosus in micropreemies and full-term infants: the relative merits of surgical ligation versus indomethacin treatment. J Pediatr Surg 2003. 38(3):492-496
32. Benjacholmas V et al (2009) Short-term outcome of PDA ligation in the preterm infants at King Chulalongkorn Memorial Hospital, Thailand. J Med Assoc Thai 92(7):909-913
33. Cotè-Lerman-Todres (2003) Practice of Anesthesia in Infants and Children IV edition
34. Gould DS et al (2003) A comparison of on-site and off-site patent ductus arteriosus ligation in premature infants. Pediatrics 112(6 Pt 1):1298-1301

35. Spector SA, W Ticknor, M Grossman (1981) Study of the usefulness of clinical and hematologic findings in the diagnosis of neonatal bacterial infections. Clin Pediatr (Phila) 20(6):385-392
36. Avery GB (1988) Neonatology in the NICU: three new techniques, three continuing problems. Pediatr Ann 17(8):503
37. Schlapbach LJ et al (2011) Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. Pediatrics 128(2):e348-357
38. Jilani T, MP Iqb al (2011) Does vitamin E have a role in treatment and prevention of anemia? Pak J Pharm Sci 24(2):237-242
39. Watchko JF, FA Oski (1992) Kernicterus in preterm newborns: past, present, and future. Pediatrics 90(5):707-715
40. Gartner LM et al (1970) Kernicterus: high incidence in premature infants with low serum bilirubin concentrations. Pediatrics 45(6):906-917
41. Okumura A et al (2009) Kernicterus in preterm infants. Pediatrics 123(6):e1052-1058
42. Parigi GB, chirurgia pediatrica Masson
43. Lorenz JM (2001) The outcome of extreme prematurity. Semin Perinatol 25(5):348-359
44. LeDez K.M, J Lerman (1987) The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology 67(3):301-307
45. Loepke AW, FX McGowan Jr, SG Soriano (2008) CON: The toxic effects of anesthetics in the developing brain: the clinical perspective. Anesth Analg 106(6):1664-1669
46. Loepke AW (2010) Developmental neurotoxicity of sedatives and anesthetics: a concern for neonatal and pediatric critical care medicine? Pediatr Crit Care Med 11(2):217-226
47. Loepke AW et al (2009).The effects of neonatal isoflurane exposure in mice on brain cell viability, adult behavior, learning, and memory. Anesth Analg, 108(1):90-104
48. Jevtovic-Todorovic V, JW Olney (2008) PRO: Anesthesia-induced developmental neuroapoptosis: status of the evidence. Anesth Analg 106(6):1659-1663
49. DiMaggio C et al (2009) A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. J Neurosurg Anesthesiol 21(4):286-291
50. Wilder RT et al (2009) Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 110(4):796-804
51. Sprung J et al (2009) Anesthesia for cesarean delivery and learning disabilities in a population-based birth cohort. Anesthesiology 111(2):302-310
52. Bartels M, RR Althoff, DI Boomsma (2009) Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet 12(3):246-253
53. Ikonomidou C et al (2001) Neurotransmitters and apoptosis in the developing brain. Biochem Pharmacol 62(4):401-405
54. Ikonomidou C et al (1999) Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 283(5398):70-74
55. Anand KJ (2000) Pain, plasticity, and premature birth: a prescription for permanent suffering? Nat Med 6(9):971-973
56. Anand K.S (1993) Relationships between stress responses and clinical outcome in newborns, infants, and children. Crit Care Med 21(9 Suppl):S358-S359
57. Bosenberg AT (1998) Epidural analgesia for major neonatal surgery. Paediatr Anaesth 8(6):479-483
58. Huang JJ, G Hirshberg (2001) Regional anaesthesia decreases the need for postoperative mechanical ventilation in very low birth weight infants undergoing herniorrhaphy. Paediatr Anaesth 11(6):705-709
59. Webster AC et al (1993) Lumbar epidural anaesthesia for inguinal hernia repair in low birth weight infants. Can J Anaesth 40(7):670-675
60. Welborn LG et al (1990) Postoperative apnoea in former preterm infants: does anaemia increase the risk? Can J Anaesth 37(4 Pt 2):S92

61. Veverka TJ et al (1991) Spi nal anesthesia reduces the hazard of apnea in high-risk infants. Am Surg 57(8):531-534; discussion 534-535
62. Krane EJ, CM Haberkern, LE Jacobson (1995) Postoperative apnea, bradycardia, and oxygen desaturation in formerly premature infants: prospective comparison of spinal and general anesthesia. Anesth Analg 80(1):7-13
63. Hoelzle M et al (2010) Comparison of awake spinal with awake caudal anesthesia in preterm and ex-preterm infants for herniotomy. Paediatr Anaesth 20(7):620-624
64. Walther-Larsen S, LS Rasmussen (2006) The former preterm infant and risk of post-operative apnoea: recommendations for management. Acta Anaesthesiol Scand 50(7):888-893
65. Steward DJ (1982) Preterm infants are more prone to complications following minor surgery than are term infants. Anesthesiology, 56(4):304-306
66. Somri M et al (1998) Postoperative outcome in high-risk infants undergoing herniorrhaphy: comparison between spinal and general anaesthesia. Anaesthesia 53(8):762-766
67. Sale SM et al (2006) Prospective comparison of sevoflurane and desflurane in formerly premature infants undergoing inguinal herniotomy. Br J Anaesth 96(6):774-778
68. Andrew M (1997) The relevance of developmental hemostasis to hemorrhagic disorders of newborns. Semin Perinatol 21:70–85
69. Andrew M, Vegh P, Johnston M, et al (1992) Maturation of the hemostatic system during childhood. Blood 80:1998–2005
70. Goodnight SH, Hathaway WE (2001) Disorders of Hemostasis and Thrombosis, A Clinical Guide, 2nd ed. New York, McGraw-Hill, pp 31-38