Anaesthetic considerations for the management of very low and extremely low birth weight infants

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The opportunities for very low birth weight infants (birth weight < 1500 g) and extremely low birth weight infants (birth weight < 1000 g) to undergo surgery are increasing. These infants are prone to prematurity-related morbidities including respiratory distress syndrome, intraventricular haemorrhage, periventricular leukomalacia, retinopathy of prematurity, patent ductus arteriosus and necrotising enterocolitis. Evidence is accumulating that preterm infants are also sensitive to pain and stress. The pharmacokinetics of drugs in preterm infants is not fully understood but smaller doses of anaesthetic drugs are usually required in preterm infants compared to term infants and older children and their effects last longer due to low clearance rates and longer elimination half-lives. Key anaesthetic considerations are (i) inspired oxygen concentration that should be adjusted to avoid hyperoxia, (ii) haemodynamic parameters that should be kept stable and (iii) prevention of hypothermia by using adequate measures to keep the infants warm. These precautions must be continuously taken during the operation and the transport to and from the operating theatre.

Key words: very low birth weight infant; extremely low birth weight infant; paediatric anaesthesia; neonate.

Low birth weight (LBW) infants are defined as infants born with a birth weight less than 2500 g, very low birth weight (VLBW) infants as those with a birth weight of less than 1500 g and extremely low birth weight (ELBW) infants as those whose birth weight is less than 1000 g. Preterm infants are defined as neonates with a gestational age of less than 37 weeks and extremely premature infants are those born after less than 28 weeks of gestation. Postconceptual age (PCA) is defined as the sum of the gestational and postnatal ages in weeks.

The survival rate of VLBW and ELBW infants has increased with the improvements in perinatal care, including the use of artificial surfactant, antenatal steroids and better...
ventilators. The increased survival rate has accompanied the increased number of very small infants with morbidity and a propensity for active treatment of the seriously ill preterm neonate. This has brought VLBW and ELBW infants more opportunities to undergo surgical procedures. Susceptibility to low blood pressure and unstable haemodynamics has hindered anaesthesiologists from providing adequate anaesthesia to these infants, along with the paucity of information on the doses necessary for the preterm infant and the pharmacokinetics and pharmacodynamics of the administered drugs. However, there is evidence that these preterm infants may benefit from adequate anaesthesia and analgesia as well as do term infants, although the required doses are lower than those for term and older infants.

In this chapter, the physiological background of the characteristic diseases, pharmacological aspects of anaesthetics, principles of anaesthesia and special anaesthetic considerations for typical surgeries in the preterm infant are described.

**PHYSIOLOGICAL BACKGROUND AND CHARACTERISTIC DISEASES OF VLBW INFANTS**

There are some peculiar features that VLBW infants possess, since most of the important organs are still in the process of development and maturation. These include inadequate production of efficient surfactant, susceptibility of retinal blood vessels to oxygen toxicity and susceptibility to haemorrhagic and ischaemic brain damage, leading to the development of diseases exclusively found in VLBW infants.

**Respiratory distress syndrome**

The introduction of artificial surfactant replacement therapy in the late 1980s dramatically improved the prognosis of VLBW and ELBW infants by resolving the respiratory distress syndrome (RDS). The survival rate of VLBW and ELBW infants significantly increased without an increase in neonatal morbidity including bronchopulmonary dysplasia, pneumothorax and intraventricular haemorrhage.\(^1,2\)

The preterm lung at risk for RDS has less surfactant than the term newborn lung and the surfactant is intrinsically defective. The surfactant has a low protein/lipid ratio and it is less effective at improving compliance than is the surfactant from the term newborn. The surfactants that are available for clinical use are not functionally equivalent to the native surfactant, but they mix with endogenous surfactant. Surfactant treatment increases both the alveolar and the tissue pools acutely because the exogenously administered saturated phosphatidylcholine is taken up into Type II cells and processed for re-secretion.\(^3\)

Surfactant is inactivated by alveolar oedema fluid, plasma, or almost any other soluble protein, which makes the preterm infant with RDS particularly susceptible to inactivation of surfactant by such proteins. Fibrinogen and fibrin split products are potent inactivators. Lipids, meconium and bilirubin can also be inhibitory.

**Chronic lung disease**

Chronic lung disease is a disease entity caused by the chronic pulmonary damage developing in infants born prematurely and undergoing prolonged mechanical ventilation for respiratory failure or apnoea. Prematurity, barotrauma, oxygen toxicity
and inflammatory reactions are the main contributing factors to chronic pulmonary damage. From a pathophysiological point of view, chronic lung disease is characterised by:

- Disturbed ventilation/perfusion ratio.
- Increased airway resistance.
- Decreased dynamic lung compliance.
- Airway hyperactivity.

Many patients require oxygen supplementation for periods ranging from a few months to a couple of years after they are weaned from ventilatory support. In the most severe cases, pulmonary hypertension and right ventricular hypertrophy will continue for years.

**Intraventricular haemorrhage**

Intraventricular haemorrhage (IVH) is the most common cause of intracranial haemorrhage in VLBW infants. The incidence of IVH in premature infants has declined in recent years in most neonatal centres. IVH, however, continues to be a major issue since the survival rate of ELBW infants continues to increase and it is known that the incidence and severity of IVH is directly correlated with the degree of prematurity.

The site of origin of IVH is typically the subependymal germinal matrix. This cellular region immediately ventrolateral to the lateral ventricle serves as the source of cerebral neuroblasts between 10 and 20 weeks of gestation and, in the third trimester, it provides glioblasts that will become cerebral oligodendrocytes and astrocytes. The many thin-walled vessels in the matrix are a ready source of bleeding. The matrix undergoes a progressive decrease in size from a width of 2.5 mm at 23–24 weeks of gestation to 1.4 mm at 32 weeks and to nearly complete involution by approximately 36 weeks of gestation.4

Hypoxia, hypercapnia, hypoglycaemia and anaemia are associated with a rise in cerebral blood flow which may induce the onset of IVH.

IVH causes the destruction of the germinal matrix, especially that of glial precursor cells, which has considerable neuropathological consequences. In effect, the destruction of these glial precursor cells may have a deleterious influence on subsequent brain development. The outcome for infants with IVH depends, to a large extent, on the degree of associated parenchymal injury. The incidence of major neurological sequelae (spastic motor deficits, major cognitive deficits) after minor degrees of haemorrhage is slightly higher than that in infants without haemorrhage. However, it increases to 30–40% in infants with severe haemorrhage and still more (up to 90%) occurs in infants with IVH complicated by either periventricular haemorrhagic infarction, periventricular leukomalacia, or both.4

**Periventricular leukomalacia**

Brain injury in the premature infant includes a variety of neuropathological lesions, including periventricular leukomalacia (PVL), germinal matrix–IVH, posthaemorrhagic hydrocephalus and several patterns of neuronal injury. The first two of these lesions are the most important and with the recently declining incidence in IVH, PVL has emerged as the principal form of brain injury in the premature infant.5

The pathogenesis of PVL is related to three major interacting factors: (i) incomplete state of development of the vascular supply to the cerebral white matter,
(ii) maturation-dependent impairment in the regulation of cerebral blood flow after ischaemic injury to the cerebral white matter and (iii) maturation-dependent vulnerability of the oligodendroglia precursor cell that represents the major cellular target in PVL. The first two of these factors underlie a propensity for the occurrence of cerebral ischaemia, while the third factor concerns the particular vulnerability of oligodendroglia precursors to ischaemia and other related insults.5

It is known that cerebral autoregulation is impaired in sick term and preterm newborn infants while term, neurologically healthy infants have a relatively intact autoregulatory response. Regarding preterm infants, there is some evidence that cerebral autoregulation may be impaired even in neurologically healthy preterm infants.6–8

Severe hypotension, marked hypocarbia, patent ductus arteriosus with retrograde cerebral diastolic flow, hypoplastic left heart syndrome and severe illness requiring extracorporeal membrane oxygenation are risk factors leading to insufficient cerebral blood flow and cerebral ischaemia and are associated with the development of PVL.5

Retinopathy of prematurity

Known risk factors for retinopathy of prematurity (ROP) are prematurity and low birth weight. Many reports have demonstrated that ROP only occurs in prematurely born infants and that the severity of ROP is inversely proportional to birth weight and gestational age.9,10 The population distribution for the occurrence of ROP in our institution is shown in Table 1. Although prematurity is the leading causal factor for ROP, iatrogenic factors are also important. Much has been described in the literature regarding the role of supplemental oxygen in the development of ROP and there is some evidence that its occurrence can be suppressed by a change of institutional treatment principle. In a prospective observational study of 568 infants of 23–27 weeks' gestation in five institutions, ROP severe enough to be treated with cryotherapy occurred in 6.2% of the babies in the first unit where target oxygen saturation was 80–90% (with the lower alarm limit set to operate at 70%) and 27.7% in the fifth unit in which target oxygen saturation was 94–98% (with the lower alarm limit set to operate at 88%). The three units employing intermediate policies for target oxygen saturation had threshold retinopathy rates in the middle of these two extremes (Figure 1).11,12

Fluctuation in oxygen saturation is another risk factor for developing ROP.

<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>No. screened (n)</th>
<th>Overall ROP n</th>
<th>Overall ROP %</th>
<th>No. treated n</th>
<th>No. treated %</th>
</tr>
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<tbody>
<tr>
<td>249–499</td>
<td>21</td>
<td>21</td>
<td>100</td>
<td>10</td>
<td>47.6</td>
</tr>
<tr>
<td>500–749</td>
<td>87</td>
<td>84</td>
<td>96.6</td>
<td>29</td>
<td>33.3</td>
</tr>
<tr>
<td>750–999</td>
<td>116</td>
<td>92</td>
<td>79.3</td>
<td>29</td>
<td>25.0</td>
</tr>
<tr>
<td>1000–1249</td>
<td>103</td>
<td>59</td>
<td>57.3</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>Total</td>
<td>327</td>
<td>256</td>
<td>78.3</td>
<td>71</td>
<td>21.7</td>
</tr>
</tbody>
</table>

Chow et al observed a significant decrease in the rate of severe ROP in VLBW infants by changing their oxygen management policy in 1998, the main objectives of which were to monitor oxygen levels more precisely and to avoid hyperoxia and repeated episodes of hypoxia–hyperoxia in VLBW infants. The incidence of ROP stage 3 to 4 decreased consistently during a 5-year period from 12.5% in 1997 to 2.5% in 2001. The need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the last 3 years. Other risk factors for ROP include mechanical ventilation, total parenteral nutrition and blood transfusion. The altered regulation of vascular endothelial growth factor has been suggested as being one of the factors involved in the pathogenesis of ROP.

Patent ductus arteriosus

The incidence of patent ductus arteriosus (PDA) is estimated to be approximately 45% in infants weighing less than 1750 g at birth and 80% in infants weighing less than 1200 g at birth. Prophylactic administration of synthetic surfactant extract to infants at risk for developing RDS may lead to an increase in the incidence of PDA and pulmonary haemorrhage, while improving the clinical outcome of RDS. Symptoms of PDA in VLBW infants usually manifest after RDS is controlled and pulmonary vascular resistance decreases. Indomethacin is used as a standard therapy to close a PDA. Although indomethacin is more useful in closing ductus arteriosus in preterm than in full term infants, some cases are refractory to pharmacological closure with indomethacin and other drugs. When the pharmacological closure fails and the haemodynamic status deteriorates, a surgical closure becomes necessary.

Left to right shunt through the ductus arteriosus causes excessive pulmonary blood flow and decreases systemic circulation leading to diminished coronary and intestinal perfusion and tissue acidosis. Excessive pulmonary blood flow may induce pulmonary haemorrhage and increases the risk of developing chronic lung disease. Pulmonary haemorrhage is thought to be due to haemorrhagic pulmonary oedema secondary to massive ductal shunting. The risk of pulmonary haemorrhage appears to occur with
both synthetic surfactant products and natural surfactant extracts. Diminished intestinal perfusion increases the risk of developing necrotising enterocolitis.

Doppler ultrasonic examinations may reveal a backflow velocity in the descending aorta often termed ‘diastolic steal’. Echoencephalograms may also demonstrate diastolic reversed flow in the cerebral arteries, indicating diminished flow to the brain. Diminished cerebral blood flow may lead to cerebral ischaemia associated with the possible development of PVL.

It is noteworthy that congenital heart diseases other than PDA in which the ductus is kept open to maintain pulmonary blood flow by using drugs such as prostaglandin A may mimic the haemodynamic status of PDA. These diseases include pulmonary artery atresia and critical pulmonary stenosis.

Necrotising enterocolitis

Necrotising enterocolitis (NEC) is more common in premature than in term newborns. It is the most frequent cause of short bowel syndrome in infancy. The prognosis for ELBW infants with NEC is poor, with a mortality rate greater than 30%. LBW is the most important risk factor for NEC. Although the pathogenesis of NEC has not been fully established, ischaemia, infection and enteric feeding have been proposed as main contributors to the development of NEC. Other factors associated with an increased risk of NEC include exposure to antenatal glucocorticoids, vaginal delivery, the need for mechanical ventilator support, PDA, exposure to postnatal indomethacin and a low Apgar score at 5 minutes. Use of indomethacin, which is the most frequently used pharmacological agent for the closure of a PDA in premature infants, is associated with reduced blood flow to the brain, kidneys and gut. Hypoperfusion of the gastrointestinal perfusion tract appears to be an important contributing factor to the development of NEC in premature infants with a haemodynamically significant ductus arteriosus.

The most common presenting sign is abdominal distension, vomiting, bloody stool and feeding intolerance. Radiological findings of dilated intestinal loops, pneumatosis intestinalis, portal vein air or free air in the peritoneal cavity are typical signs of NEC.

Apnoea

Apnoea is usually defined as an absent respiratory airflow for 20 seconds or longer. Apnoeic spells are categorised as central (no inspiratory effort), obstructive (inspiratory effort with absent airflow) and mixed (central pause greater than 2 seconds with obstructed inspiratory efforts). Mixed apnoea is the most commonly observed type of apnoea in small preterm infants. Mathew et al noted that obstruction occurred within the pharynx in 93% of mixed and obstructive apnoeic spells, and at the level of the larynx or at both the larynx and pharynx in the remaining 7%. Lee et al noted that apnoea in larger preterm and term infants weighing more than 2000 g at birth is predominantly central in nature. Prolonged apnoea is accompanied by hypoxia, hypercarbia and bradycardia. Both the frequency and duration of apnoea decrease between 1 and 20 weeks of postnatal age. Hypothermia, hypoglycaemia and anaemia are known inducing factors of apnoea. Also, apnoeic spells are frequently observed in preterm infants and ex-preterm infants during recovery from general anaesthesia.
Thermogenesis

LBW infants are susceptible to hypothermia during surgery. Neonates depend on non-shivering thermogenesis for heat production. This is required immediately after birth in contrast to shivering thermogenesis, which is the major mechanism of heat production in adults. Non-shivering thermogenesis utilises brown adipose tissue and requires oxygen consumption. When exposed to a cold environment, the sympathetic nervous system is activated and releases norepinephrine, which interacts with adrenergic receptors and leads to the release of fatty acids that are combusted in the mitochondria by the action of mitochondrial uncoupling protein (thermogenin), exclusively found in brown adipose tissue. It is believed that one of the major problems with temperature regulation in small premature infants is that the lipid supply to, and the recruitment of, brown adipose tissue are not sufficiently developed. This deficiency, combined with the thin skin and the larger surface/volume ratio of the small preterm infant makes them susceptible to hypothermia.

Volatile anaesthetics are potent inhibitors of brown adipose tissue thermogenesis, although nitrous oxide and intravenous anaesthetics such as thiopental and propofol do not have this inhibitory property. General anaesthesia using volatile anaesthetics places LBW infants at higher risk for hypothermia.

LBW infants should be placed in a warm environment using various warming devices during surgery and transport to and from the operating theatre. Appropriate warming devices include warm operating room, a warming mattress and a forced-air warming system. Keeping the infant’s head covered and skin and drapes dry is also important.

Hypoglycaemia

Hypoglycaemia has been defined as a plasma glucose concentration of less than 25 mg/dl in the LBW infant and less than 35 mg/dl in the term infant up to 72 hours of age. After this age, plasma glucose concentration should be at least 45 mg/dl. LBW infants are susceptible to both hypo- and hyperglycaemia. Although the highest incidence of hypoglycaemia is seen in preterm small-for-date infants, preterm appropriate for gestational age (AGA) infants also develop hypoglycaemia. In addition to diminished oral and parenteral intake in the LBW infant, immature gluconeogenic and glycogenolytic enzyme systems are ascribed to the propensity to hypoglycaemia in preterm infants.

Infants who utilise glucose at an increased rate are prone to hypoglycaemia. Infants experiencing perinatal asphyxia are subject to hypoxia, leading to an increased rate of glycogenolysis. Since the Embden–Meyerhof anaerobic pathway requires 18 times more glucose to generate the same amount of ATP than does aerobic oxidation, hypoxia causes a more rapid depletion of stored glycogen. Infants born to diabetic mothers are also subject to hypoglycaemia. Maternal hyperglycaemia causes foetal hyperinsulinaemia, which will exaggerate the infant’s normal post-delivery fall in plasma glucose concentration. Other risk factors for hypoglycaemia include a cold environment, neonatal sepsis and exchange transfusion.

Glucose levels in infants at increased risk of hypoglycaemia should be checked during surgery. Intravenous infusions should contain glucose to maintain a glucose infusion rate of between 4–6 mg/kg min\(^{-1}\).
PAIN SENSATION IN PRETERM INFANTS

Evidence is accumulating that preterm infants are also sensitive to pain and stress (see Chapter 1). Cutaneous hypersensitivity can be produced as a result of painful procedures in preterm infants. Fitzgerald and colleagues used the flexor reflex threshold as a measure of sensation in 11 newborn infants born at 26–32 weeks in whom heel lancing, used routinely to collect blood samples, was confined to the lateral side of one heel. The flexor reflex thresholds were tested daily and measured on both heels using calibrated von Frey hairs. In all cases, the threshold on the injured (lanced) heel was lower than it was on the control side, indicating hypersensitivity to injury. Grunau et al assessed pain reactions in 136 VLBW infants of 23–32 weeks of gestational age using the Neonatal Facial Coding System and heart rate variability. They found that previous invasive procedures since birth altered behavioural and autonomic pain reactivity at 32 weeks PCA. They also found that previous exposure to morphine was associated with diminished responses to painful stimuli. Painful procedures hinder the progress of behavioural maturation. Johnston and Stevens reported that preterm infants who had spent PCA weeks 28 through 32 in a neonatal intensive care unit were less mature in their pain response than newborn premature infants of 32 weeks’ PCA.

The appropriate use of analgesics and sedatives are indicated for painful procedures in preterm infants as well as in full term infants and older children.

PHARMACOKINETICS OF DRUGS IN PRETERM INFANTS

The minimal alveolar concentration (MAC) of inhalational anaesthetics is lower in neonates than in older children. The MAC of volatile anaesthetics is considered to be lower in preterm infants compared with that in full term neonates and older infants. Isoflurane has been the only inhalational anaesthetic whose MAC has been measured in preterm infants. The MAC of isoflurane for various age ranges is shown in Table 2.

The action of opiates may last longer in preterm infants. The clearance rate of morphine in premature infants is considerably longer than previously thought. The elimination half-life of fentanyl is reported to be longer in neonates than in older children. Koehntop et al reported that the elimination half-life (t1/2β) of fentanyl was 317 min in neonates and even longer in preterm infants. Collins et al reported that

<table>
<thead>
<tr>
<th>Age range</th>
<th>MAC of isoflurane (%)</th>
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<tbody>
<tr>
<td>Preterm infants &lt; 32 weeks</td>
<td>1.28 (±0.17)</td>
</tr>
<tr>
<td>Neonates 32–37 weeks of gestation</td>
<td>1.41 (±0.18)</td>
</tr>
<tr>
<td>Infants 0–1 month</td>
<td>1.6 (±0.01)</td>
</tr>
<tr>
<td>Infants 1–6 months</td>
<td>1.87 (±0.12)</td>
</tr>
<tr>
<td>Infants 6–12 months</td>
<td>1.8 (±0.01)</td>
</tr>
<tr>
<td>Children 1–3 years</td>
<td>1.6 (±0.16)</td>
</tr>
<tr>
<td>Children 3–5 years</td>
<td>1.6 (±0.06)</td>
</tr>
</tbody>
</table>

the elimination half-life of fentanyl was 6–32 hours in infants with a PCA of 29–43 weeks compared with 2–3 hours in older children and adults.

The action of sedatives may also be prolonged in preterm infants. The clearance of midazolam is decreased and the elimination half-life is prolonged in VLBW infants compared with that of term infants and older patients. Infants weighing less than 1000 g at birth have a significantly lower clearance than those weighing more than 1000 g.

Bupivacaine has a longer half-life, lower clearance and greater volume of distribution in VLBW infants than in term infants when given by the interpleural route. Repeated doses should be given with longer intervals than in older infants and adults to avoid toxicity.

**ANAESTHESIA**

The most frequent diseases for which surgery is required in VLBW infants are ROP, PDA, NEC and inguinal hernia. Figure 2 shows the number of surgical interventions performed in preterm infants in our institution. General guidelines for anaesthetic management in VLBW infants are described first and specific anaesthetic considerations for typical operations will follow.

**Anaesthesia apparatus**

The anaesthesia breathing circuits for VLBW infants should have minimal dead space and minimal resistance. For this purpose, the T-piece (Mapleson D type)
circuit is the most suitable, since it has neither unidirectional valves nor a CO₂ absorber. Figure 3 illustrates the breathing system we currently use. Corrugated tubes are made of light-weight plastic with an internal diameter of 15 mm. A driving gas hose from the ventilator can be connected to the breathing circuit via the port for the reservoir bag after removing the bag. The end of the expiratory limb is connected to a gas scavenger system through an overflow valve. A driving gas hose from the ventilator can be connected to the breathing circuit via the port for the reservoir bag after removing the bag.

The Jackson Rees apparatus can also be used for VLBW infants and is actually used worldwide in many institutions but there is a difficulty in connecting the circuit with a ventilator and gas scavenger system and in using a humidifier.

**Induction of anaesthesia**

If the tracheal tube is not in place, endotracheal intubation should be performed after induction of anaesthesia except for rare cases of moribund patients and emergency cases, such as during cardiopulmonary resuscitation. Endotracheal intubation without anaesthesia or sedation may cause an acute rise in arterial and intracranial pressure, leading to IVH. Before induction of anaesthesia, a venous line is inserted, if one is not in place.

As a classical standard, thiopental or thiamylal (4 mg/kg) and pancuronium or vecuronium (0.1 mg/kg) are administered intravenously. Ketamine (1.5–2 mg/kg) can be used in hemodynamically compromised patients and muscle relaxation can be achieved by other muscle relaxants (rocuronium or cisatracurium especially). Mask ventilation should be applied with a F\textsubscript{IO₂} of less than 40%. The tip of a straight-bladed laryngoscope is placed behind the epiglottis to get a good view of the larynx.
and the tracheal tube is inserted. A size 0 blade is suitable for LBW infants, although a size 1 is usually better for full term infants.

Fentanyl (2–5 μg/kg) and pancuronium with or without midazolam can be used as an induction agent instead of thiopental.

The proper position of the tracheal tube should be carefully confirmed to avoid endobronchial intubation. The tube is advanced until the breath sound is diminished in the left lung, which indicates endobronchial intubation. The tube is withdrawn by 0.5 cm increments at each step until the breath sound on the left side is resumed, which indicates the tube end is at the carina. From this point, the tube is further withdrawn by 1 cm and fixed to the perioral skin.

Maintenance of anaesthesia

Fentanyl–air–oxygen combined with muscle relaxants is a standard anaesthesia method for cardiovascular surgery in neonates including VLBW infants. A high dose of fentanyl (20–50 μg/kg) is reported as being suitable without detrimental effects on haemodynamics in neonates and preterm infants if adequate fluid is infused. Fentanyl is also useful in other major surgical interventions in preterm infants. Lower doses of fentanyl (10–20 μg/kg) should be administered to infants with increased intra-abdominal pressure, since the elimination half-life is predictably prolonged.

Sufentanil, 5–10 μg/kg is reported to be equivalent to fentanyl 50 and 75 μg/kg in producing haemodynamic stability and blunting haemodynamic responses to tracheal intubation and surgical incision. Propofol (50–200 μg/kg min⁻¹) is also used with supplementation of fentanyl.

Nitrous oxide is not suitable for the anaesthesia in VLBW infants, since the FIO₂ should be titrated with air and oxygen to maintain the PaO₂ and SpO₂ at the most suitable value for the patient. Furthermore, nitrous oxide should be avoided in abdominal surgery because it tends to enlarge the intestines. Sevoflurane and isoflurane can be used as a main anaesthetic in some cases, such as in older infants. Sevoflurane and isoflurane can be cardiodepressant when used in high doses in infants and children, although it is less arrhythmogenic than halothane.

Non-depolarising muscle relaxants can be used to paralyse the patient, to prevent chest wall rigidity induced by fentanyl, to obtain a relaxed abdomen and to reduce the anaesthetic concentration or doses. Pancuronium increases heart rate and may be preferable when used in combination with fentanyl. Vecuronium has a tendency to decrease the heart rate. When vecuronium is used with fentanyl, atropine (0.01 mg/kg) given intravenously, may be added to prevent bradycardia.

Almost all anaesthetic agents decrease blood pressure. The volatile anaesthetics are usually more potent in lowering the blood pressure than fentanyl and other intravenous anaesthetics. Haemodynamic 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 haemorrhage or cerebral ischaemia. Hypoxia, hypercapnia, hypoglycaemia and anaemia are all associated with a rise in cerebral blood flow, predisposing the infant to the development of intracerebral haemorrhage and, inversely, hyperoxia and hypocapnia are associated with a decrease in cerebral blood flow, predisposing to cerebral ischaemia.
Emergence from anaesthesia

VLBW infants who were mechanically ventilated before surgery should not be weaned from the ventilator soon after surgery and should be transported to a neonatal intensive care unit while being ventilated.

The trachea need not be extubated in the operating room immediately after the surgical procedure in VLBW infants, even if the infant was not on a ventilator before surgery. When apnoea or desaturation is noted during transportation to the neonatal intensive care unit, mask bagging of a small infant in the incubator is difficult and opening the lid of the incubator is likely to expose the infant to a cold environment. The trachea can be extubated later in the neonatal intensive care unit when full recovery from the remaining effects of the anaesthetic is obtained.

Preterm infants tend to have apnoeic spells postoperatively. The generally accepted limit of such a risk in neonates is 44–46 weeks PCA. Monitors should be applied to detect apnoea, desaturation and bradycardia in these infants for at least 48 hours postoperatively.

Regional anaesthesia

Regional anaesthesia has proved to be beneficial in newborns, infants and children as well as in adults. Epidural anaesthesia has been shown to decrease the need for postoperative ventilatory support in neonates undergoing major surgery.44 There is accumulating evidence to show the benefits of regional anaesthesia when used alone or in combination with general anaesthesia in VLBW infants. Huang and Hirshberg45 showed that regional anaesthesia decreased the need for postoperative mechanical ventilation in infants with a mean gestational age of 26 weeks and a mean PCA at surgery of 38 weeks, when undergoing herniorrhaphy.45 Technical feasibility and low complication rates have also been reported. In 18 consecutive cases with a gestational age of 26 (± 2.6) weeks and birth weights of 877 (± 310) g, Webster et al46 reported a 100% success rate for lumber epidural anaesthesia after one or two attempts and analgesia was obtained in all cases. In their report, 39% had periodic breathing along with oxyhaemoglobin desaturation which responded to increased FIO₂.46 Williams et al47 reported a success rate of 100% for spinal anaesthesia and 89% for epidural catheterisation in 19 infants (aged 29 weeks PCA to 7 months) who received a combined spinal and continuous epidural anaesthesia. All their patients underwent upper or lower abdominal surgery without intraoperative opioids or general anaesthesia. No patient required postoperative ventilation.47 A single-dose caudal anaesthesia in conscious infants has been reported to be useful in major intra-abdominal operations in high-risk infants.48

A brachial plexus block raised the success rate of venous catheterisation in VLBW infants.49 Topical anaesthesia with lidocaine and prilocaine was beneficial in attenuating the lability of vital signs during line insertion with no evidence of toxicity.50 The infiltration of local anaesthetics, e.g. lidocaine, at the incision site is also useful in ameliorating haemodynamic changes at incision and reducing the dose of general anaesthetic.51

Intraoperative monitoring

Precordial stethoscope, electrocardiogram, blood pressure, pulse oximetry, end-tidal carbon dioxide and rectal or oesophageal temperature are basal monitoring
techniques. Pulse oximetry and end-tidal carbon dioxide tension ($P_{ET}$CO$_2$) are valuable monitoring tools, the use of which reduces the number of arterial gas analyses that are performed. $P_{ET}$CO$_2$ is often displayed as being lower than the actual value when monitored in tiny babies with a considerable leak around the tracheal tube and with a small tidal volume compared with the dead space. The Pediatric/Low Deadspace Neonatal Adapter$^\circledR$ (Datex-Ohmeda, Helsinki, Finland) is a useful device in these infants for decreasing the dead space when monitoring $P_{ET}$CO$_2$ and thus obtaining a more accurate value. Insertion of a urinary catheter can be withheld in small infants less than 800 g especially in males in order to avoid urethral damage. A urinary pouch can be attached at the groin instead.

Arterial indwelling catheters are required for major surgery including cardiovascular, thoracic and abdominal surgeries. Regarding central venous catheters, PI catheters$^\circledR$ (Tyco Health Care) are useful, and they enable a peripheral approach and long-term use. Through this catheter the inotropes can be administered continuously, although central venous pressure cannot be monitored due to the calibre being too small and the considerable length of the catheter.

ANAESTHETIC CONSIDERATIONS FOR TYPICAL SURGICAL PROCEDURES

Anaesthetic management of ROP

Common surgical procedures for ROP are laser photocoagulation and cryosurgery. Since these procedures are stressful and last for more than 1 hour, anaesthesia is required to minimise the surgical stress and to immobilise the patient. A peripheral vein should be cannulated, but an arterial line is usually not necessary. Sevoflurane can be used as the sole anaesthetic agent, although fentanyl or ketamine can be used equally well.

The SpO$_2$ should be aimed at 85–95% and not at 100%, although an SpO$_2$ of 98–100% may be displayed while the patient is breathing air. The $F_{IO2}$ should be kept as low as possible, including during the transfer of the patient to and from the operating theatre to avoid the danger of worsening the ROP by exposing the infant to high inspired oxygen levels. Infants whose trachea were not intubated before surgery, can usually be extubated in the operating room, provided their body weight is more than 1500 g. Infants with a lower body weight should be transported with the trachea intubated and extubated later in the neonatal intensive care unit.

Anaesthetic management of PDA ligation (or clipping)

PDA ligation candidates are usually in the 600–1000 g range for body weight. Most patients are intubated, mechanically ventilated and anuric. Some patients have episodes of pulmonary haemorrhage, which may be associated with other debilitating diseases such as NEC and ROP. In most cases, the infants have undergone several trials with indomethacin along with fluid restriction and have remained in a hypovolaemic state. Adequate volume load should be done before the surgical procedure can be started.

A peripheral venous line and arterial line are needed before induction of anaesthesia. A combination of fentanyl and a non depolarizing muscle relaxant is the most popular anaesthetic technique. Induction of anaesthesia may cause hypotension down to 30 mmHg or less of systolic blood pressure, especially in hypovolaemic patients.
The \( F_2O_2 \) should be maintained at as low a value as possible to keep \( SpO \) between 85 and 95% in order to minimise pulmonary high flow. The lungs may be ventilated using the same ventilator that was used in the ward preoperatively. The operation is usually performed in the right decubitus position. To decrease the chances of intraoperative accidental extubation, the tracheal tube can be changed from an orotracheal to a nasotracheal one. Oesophageal stethoscope, pulse oximetry (right hand and lower extremity) and end-tidal \( CO_2 \) are essential monitoring techniques. An increase in \( F_2O_2 \) is often necessary to maintain adequate \( SpO_2 \) during surgical manoeuvres using a lung spatula in the lateral position.

Ligation of a PDA may cause an acute increase in systemic blood pressure and an abrupt blood pressure increase in the ascending aorta may induce IVH. To avoid this, systemic blood pressure should be lowered immediately before the ligation of the ductus by increasing the inspired fraction of sevoflurane or by adding fentanyl. There are some reports describing the safety of the ligation of a PDA with regard to the occurrence of perioperative intracranial haemorrhage. A pulse oximeter applied to a foot is useful for detecting a disastrous clipping erroneously applied to the descending aorta. After the operation, the nasotracheal tube is exchanged for an orotracheal tube. The urine output has to be controlled postoperatively in the ward.

Iatrogenic events of PDA ligation or clipping include vocal cord paralysis. The prevalence of vocal cord paralysis caused by PDA ligation in preterm infants is reported to be as high as 10% and it is even higher in preterm than in full term infants. The use of a metal clip may predispose to the iatrogenic vocal cord paralysis more than a silk ligature. Vocal cord paralysis may cause hoarseness, inadequate respiration, delayed bottle feeding and recurrent aspiration.

**Anesthetic management of NEC**

Perforation of the intestines and clinical deterioration are often the indications for laparotomy with resection or peritoneal drainage for the infant with NEC. ELBW infants presenting with NEC are very sick and may have other associated morbidities such as RDS, PDA and ROP. In severe cases, septic shock, multiple organ failure and disseminated intravascular coagulation might be further complications.

Almost all infants suffering from NEC have an endotracheal tube in place, receive mechanical ventilation and, in many cases, inotropic drugs such as dopamine and dobutamine are continuously infused.

Anaesthesia can be induced and maintained with fentanyl combined with non depolarising relaxant. Local infiltration with 1% lidocaine at the incision site may help to reduce the required dose of fentanyl.

A peripheral venous line, arterial line and central venous line (PI catheter) are required before surgery. A central venous catheter with a small bore inserted from the periphery is not suitable for the measurement of central venous pressure or a rapid infusion, but is useful for the administration of inotropic drugs. Difficulties encountered during anaesthesia include the assessment of intravascular blood volume and the maintenance of body temperature. Bowel oedema and inflammation cause a large amount of exudation of extracellular fluid that is rich in protein. A high infusion rate, such as 20 ml/kg hour \(^{-1}\) or more is usually required to maintain adequate intravascular volume, with 10–20 ml/kg hour \(^{-1}\) of 5% albumin or fresh frozen plasma (FFP) being infused in combined with 10 ml/kg hour \(^{-1}\) of crystalloid solution. Blood loss should be replaced with FFP, red blood cells and albumin. If coagulopathy exists, bleeding increases and the administration of FFP and platelets may be necessary to control bleeding.
There exist very few indices of intravascular volume, which are blood pressure, estimated blood loss and bulginess of anterior fontanel. Many cases are lacking in urine output, so, urine output is not a very good index. But if a urine output of more than 2 ml/kg hour$^{-1}$ is obtained during surgery, it indicates that intravascular volume is adequate and the patient’s prognosis is usually good. Inotropic support should be continued during surgery and an increase in dosage may be needed.

Maintenance of body temperature is difficult with the intestines exposed and drapes wet with irrigation.

**CHOICE OF OPERATION SITE**

There is much discussion regarding which site should be chosen for surgery in VLBW infants, operating theatre or NICU.

The main advantage for performing surgery in an operating theatre is that the anaesthesiologists and surgeons can work in a familiar place with the full aid of operating nursing staff. A variety of surgical equipment is ready to be used. More hands of anaesthesiologists and nurses can be obtained easily as needed. Operative conditions are more sanitary in the operating theatre.

In contrast, the main advantage of performing the surgery in the neonatal intensive care unit is that the transportation which may be accompanied by a degree of risk can be avoided. In order to transport the sick patient under similar conditions to those in the neonatal intensive care unit, an incubator, ventilator, batteries, oxygen and air cylinders and many volumetric syringe pumps must be carried together while maintaining the same ventilatory and inotropic support.

We use the operating theatre for surgical procedures in VLBW and ELBW infants because the neonatal intensive care unit is located on the same floor and not far from the operating theatre. The site for surgical procedures for these small infants should be chosen according to each institution’s setting and conditions.

**SUMMARY**

VLBW and ELBW infants are susceptible to prematurity-related diseases, which include RDS, ROP, PDA, IVH, periventricular leukomalacia and NEC. Precautions should be taken in order to deliver a safe anaesthesia to these seriously ill small infants. Inspired oxygen concentration should be adjusted to avoid hyperoxia, since high inspired oxygen is the main contributing factor to the development of ROP. Infants undergoing PDA ligation are usually dehydrated due to fluid restriction and the use of diuretics in a trial of medical closure of the ductus and therefore they should be given enough infusion before the start of surgery. Infants presenting with NEC usually need a large amount of infusion, although the assessment of intravascular volume is difficult. Haemodynamic parameters should be kept stable in order to avoid IVH and cerebral ischemia in these infants with impaired cerebral autoregulation. Prevention of hypothermia and hypoglycaemia is also essential. In VLBW and ELBW infants, the MAC of inhalational anaesthetics is lower and smaller doses of opiates and sedatives are required with an interval between repeat doses that is longer when compared with that needed for term neonates and older infants.
REFERENCES


