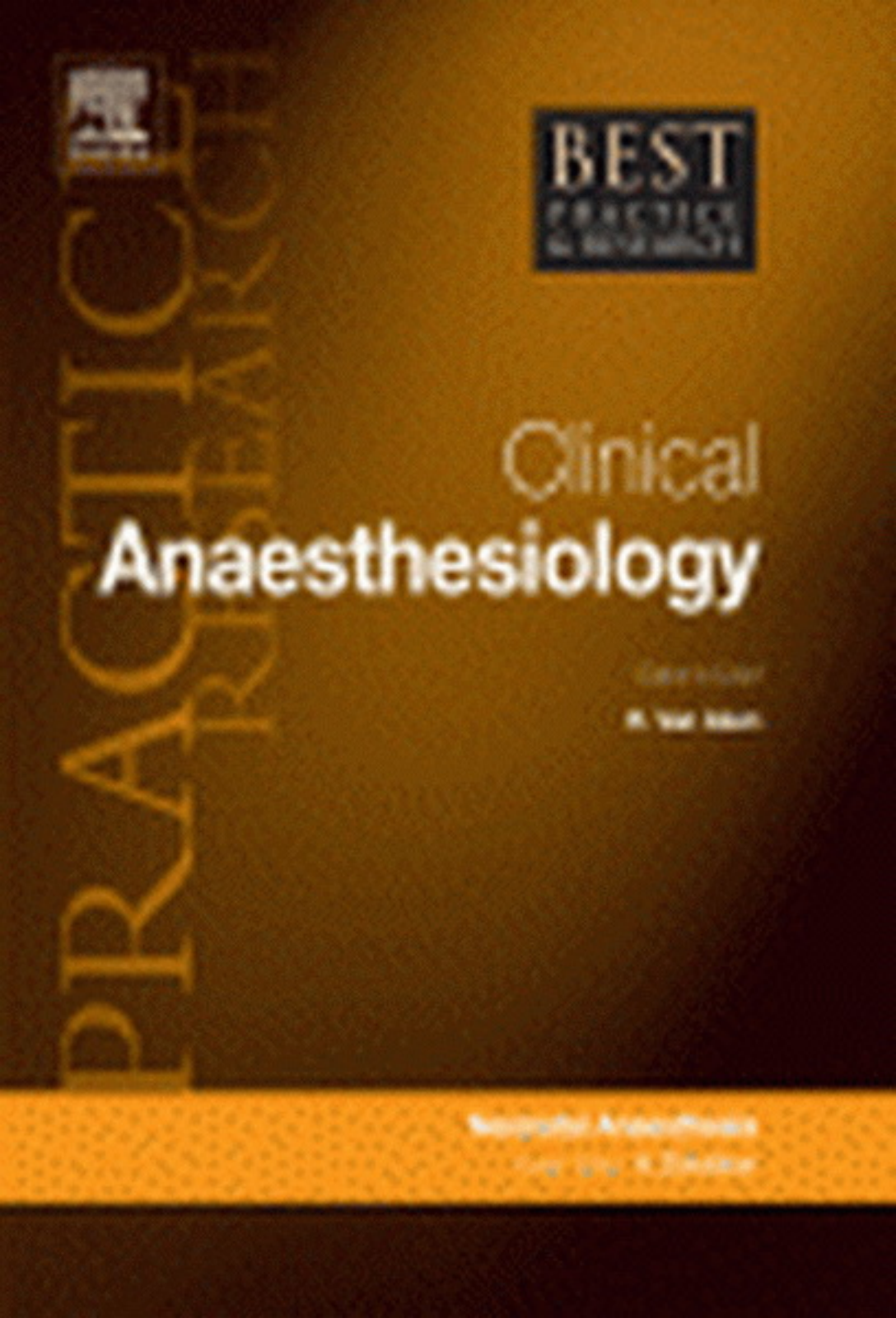
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Practical pain management in the neonate

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Neonatal care is advancing to levels where more neonates are now offered more invasive interventions, exposing them to more prolonged hospital care. Consequently, the provision of effective and consistent management of pain in these neonates has become a pressing challenge. Advances in neonatal care have not only increased the number of neonates, who are exposed to noxious stimuli, but, over recent decades, also altered the patterns of exposure. Both procedural and postoperative pain remain distinct in nature, prevalence and management, and need to be addressed separately. Recent advances in the management of neonatal pain have been facilitated by improved methods of pain assessment and an increased understanding of the developmental aspects of nociception. Over the past decade, there have been some advances in the available pharmacological armamentarium, modest clarification of the risks of both untreated pain and aggressive analgesic practice and a greater recognition of non-pharmacological analgesic techniques.

However, even advanced health systems fail to consistently articulate pain management policy for neonates, institute regular pain assessments and bridge the gaps between research and clinical practice.

The unique physiology of the human neonate continues to provide challenges to both the practical and academic aspects of the hospital care of a sick newborn. Effective and consistent management of neonatal pain and distress remains one of the most obvious and persistent challenges. The noxious stimuli that an acutely sick neonate is exposed to during clinical care are vastly different in range and

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duration to the normal (limited) pain experiences of an otherwise healthy neonate. This contrasts with the experiences of hospitalised infants and children whose development has brought a natural interaction with the environment at large and, with this, the typical pain experiences of childhood.[1] In this older paediatric population, the painful experiences of hospitalisation occur within a context of prior normal pain experiences and associated analgesic and comfort measures. The acutely sick neonate, on the other hand, is exposed to clinical care and stimuli that bear no relation to anything that could conceivably be termed a 'normal pain experience'.

The pain and distress imposed by procedures and surgical interventions in neonates were first brought to scientific and public attention by a small but seminal study conducted in the 1980s on neonates undergoing thoracotomy.[2] Since then, the epidemiology of neonatal pain within the acute care environment has been studied and patterns over the past decade have been well documented.[3–5] These patterns consistently reveal that neonates in acute care settings are regularly subject to repeated painful or stressful stimuli and, often, little or no analgesic is administered. Procedure rates of 10–16 per day have been repeatedly documented in well-conducted epidemiological studies within modern neonatal intensive care settings.[6] It should be emphasised that the focus of these studies has principally been on brief procedures during intensive care rather than on surgical interventions, postoperative pain or ongoing noxious stimuli (chronic pain). The most common procedures include nasal and tracheal aspiration, heel lance and adhesive removal. Although slightly less frequently observed, gastric tube insertion, venepuncture, arterial puncture and venous cannulation also figure highly in these studies. There are far fewer studies addressing post-surgical pain and ongoing or chronic pain in neonates. Approaches and management strategies for these types of pain are often simple modifications of those used in infants and older children.

Importantly, advances in neonatal care have not only increased the caseload but may also alter the epidemiology of neonatal pain. The widespread use of antenatal steroids, postnatal surfactant and nasal continuous positive airway pressure has resulted in a marked reduction in the need for and duration of ventilation of premature babies and, consequently, the need for related invasive procedures.[7]

Despite this, procedural pain clearly remains one of the more pressing issues facing neonatologists. Anaesthetists, on the other hand, are more usually concerned with postoperative pain. These two pain types – procedural and postoperative – are distinct in nature, prevalence and management. The distinction may be further accentuated by differences in care settings (i.e., operating room and surgical intensive care unit (ICU) as opposed to neonatal nursery) as these areas are subject to different caseloads and clinical input. This review will cover aspects of both types of pain.

Procedural pain is an unavoidable aspect of neonatal intensive care and is characterised by repeated episodes of short duration and minimal tissue damage. It must be assessed and managed quite differently to inflammatory (post-surgical) pain. Procedural pain activates pain pathways in a way that can be seen as a 'warning system'. When mature, these pathways provide for responses that are rapid, well localised and closely tied to withdrawal reflexes and attention. These pathways are now known to be functional by 24 weeks' gestation but in early development, tend to facilitate generalised and/or exaggerated responses to acute noxious stimuli.

Post-surgical pain, on the other hand, is characterised by ongoing activity and modulation of these same nociceptors and pathways as they innervate damaged tissues. This activity and its modulation are linked to inflammatory and healing processes within these tissues. The pain experiences associated with surgery and tissue damage may be termed a 'pain state', implying an altered neurophysiology. This form of pain, expressed as hyperalgesia, spontaneous pain and allodynia, may be better seen as a 'protective reminder system' – causing the subject to shield, protect and immobilise the affected body part. The neurobiological mechanisms underpinning this state have been well studied and include both central and peripheral sensitisation of primary afferent nociceptive fibres. In studying the developmental aspects of these mechanisms, important questions about the duration and severity of hyperalgesia following surgery in neonates are being answered.[8]

In both neonates and adults, the distinction between procedural pain and post-surgical pain provides the basis for understanding why typical analgesic techniques and drugs (e.g., paracetamol and morphine) are often ineffective in relieving procedural pain[9–11] and why procedural pain must often be managed using anaesthetic and sedative agents instead.[12,13]

Recent advances in neonatal pain management have been facilitated by improved methods of pain assessment, an increased understanding of the developmental aspects of nociception and some evidence of measurable effects of early noxious stimuli on later neurological development.[14]

Pain assessment

Without the advantage of self-report, clinical assessments of pain in the neonate are dependent on indirect measures. These measures include physiological, behavioural and contextual parameters. Contextual factors include the neonates' behavioural state (asleep/awake), gestational age, severity of illness and the carer's perception. Each of these may influence the assessment or response of a neonate to a noxious stimulus.

Taken independently, behavioural, physiological and contextual measures lack specificity and sensitivity and most will change with clinical context. Correlation between physiological and behavioural measures is often poor.[15] Novel approaches such as heart rate variability, cry analysis[16,17] and skin conductance measures have all proved to be no more specific or sensitive than simpler observational scales.[18] Newer technologies such as near-infrared spectroscopy (NIRS), electroencephalogram (EEG) and functional neuroimaging, which attempt to assess degrees of cortical activation in response to noxious stimuli,[19,20] have as yet undefined utility, feasibility and clinical significance.[21] These more technically demanding measures remain research tools that require further validation. They may yield fascinating insights into the relationships between behavioural responses, physiological changes and cortical activation in response to noxious stimuli. Despite the documented dissociation between physiological and behavioural indicators of pain, composite scoring tools that include both have been reasonably validated and are widely accepted.[22]

Many pain and distress scoring tools have been described in the past three decades, following the acceptance that pain in neonates cannot be ignored. The study and validation of these tools have tended to focus on procedural pain and less work has been done with these tools in the setting of postoperative or chronic pain. Although no single tool can reasonably expect to cover the range of clinical settings in which neonates find care, there still remains a need for greater consistency in the use and choice of the scoring tool across neonatal care centres.

In recent years, seven pain scoring tools have found widespread use: the Neonatal Infant Pain Scale (NIPS), the Children's Revised Impact of Event Scale (CRIES), the Premature Infant Pain Profile (PIPP), the Liverpool Infant Distress Scale (LIDS), the Distress Scale for Ventilated Newborn Infants (DVSNI), the Pain Assessment Tool (PAT) and the COMFORT scale. Each of these has been validated and show reasonable internal consistency and reliabilities (see Table 1). Two scales (NIPS and LIDS) are behavioural scales, while the others are composite tools. More recently, the behavioural Indicators of Infant Pain (BIIP) scale has been shown to be valid and reliable in measuring procedural pain in pre-term neonates.[23] Rather uniquely, this tool includes two specific hand actions (finger splay and fist clenching).

Two particular areas of weakness are shared by all neonatal pain assessment tools. First, up to 20% of extremely premature infants may show no measurable response to noxious stimuli.[24] Whether this represents a true lack of nociception, a distinct (energy saving) pain state, a failure of pain measuring tools or exhaustion is unknown. Second, there are very few tools for measuring responses to continuous noxious stimulation (chronic pain) in neonates and these are not in widespread clinical use. One such scale – the EDIN (Echelle Douleur Inconfort Nouveau-Ne) scale uses five behavioural indicators including the quality of sleep, quality of contact with nurses and consolability. Importantly, these are scored after several hours of observation and clinical interaction.[25] Chronic or ongoing pain can reasonably be assumed to arise from inflammatory conditions, for example, inflammatory and desquamating skin conditions, necrotising enterocolitis, indwelling/ percutaneous catheters and intercostal drains and surgical wounds.[26] Prolonged intubation and nasal mask application are also sources of continuous noxious stimulation.[25]

It would appear self-evident that regular documented objective pain scoring of all neonates admitted for acute care is essential for optimising the provision of analgesia. Unfortunately, even advanced health systems can fail to institute regular pain assessments and develop management policy based on objective scores as shown by a recent Australian survey.[27]

Table 1
Pain scoring tools for neonates.

	Description	Validity/internal consistency	Reliability (Cronbach's alpha)	Suggested clinical utility	Reference
NIPS	Variables include: facial expression, crying, breathing pattern, posture and arousal.	Face, construct and concurrent ($r = 0.53–0.84$)	Interrater >0.92	Procedural pain in term and pre-term neonates 28–38 weeks	Lawrence Neonatal Network 1993; 12 (6): 59–66
CRIES	Variables include: crying, changes in vital signs, oxygen saturation, facial action and wakefulness.	Face, content, discrimination and concurrent ($r = 0.53–0.84$)	Interrater >0.72	Postoperative in neonates 32–60 weeks	Krechel Paed Anaesth 1995; 5: 53–61
PIPP	Variables include: changes in heart rate, oxygen saturation, facial action and neurobehavioural state. Weighted for gestational age	Face, content, construct – in pre-term and term neonates. Internal consistency: 0.59–0.76	0.89 or greater	Procedural pain in premature and term neonates	Ballantyne.[23] Stevens et al. Clin J Pain 1996; 12: 13–22
LIDS	Variables include: facial expression, sleep pattern, cry, movement, posture and tone.	Established content and concurrent validity	0.84 or greater	Postoperative in term neonates	Horgan 1996 Paediatric Nursing 8 (10): 24–7
DSVNI	Variables include: Facial expression, movement and colour , vital signs, oxygenation and temperature			Ventilated, neonates	Sparshott 1996 Journ Neonatal Nursing;2:5–11
PAT	Variables include: infant behaviour, facial expression, vital signs and nursing impression	Requires regular calibration. Good correlation with CRIES score (0.76).	Interater reliability 0.85	Postoperative pain in neonates	Spence 2005 Obstet Gynecol Neonatal Nurs
COMFORT	Variables include: movement, behavioural state, facial tension, vital signs and muscle tone	Established congruent validity	Good inter-rater reliability (Kappa: 0.63–0.93)	Ventilated neonates Postoperative pain and PICU distress.	Dijk van M et al Pain 2000; 84:367–77

Although clear evidence is still awaited, linking objective pain scores to care interventions and analgesia should foster better outcomes and provide the necessary incentive to maintain the effort of repeatedly measuring and documenting pain scores.

Minor surgery

In general, the advances in analgesic pharmacology that characterise adult acute postoperative pain management have gradually been translated into clinical practice changes in many paediatric centres. The ethical drive for this has been helped by economic pressures on acute care settings. There is strong incentive to reduce hospital length of stay and good perioperative analgesia facilitates early discharge. With some natural delay, advances in paediatric pain management have driven change in neonatal perioperative care. Neonates undergoing surgical interventions form a distinct subgroup within neonatal nurseries and modern care of these infants regularly includes general anaesthesia, local anaesthesia, paracetamol and, for more major surgery, systemic opioids.

Many lesser surgical procedures (e.g., circumcision, pyloromyotomy and inguinal hernia repair) in neonates can now be managed on a 'short-stay admission' basis. This model of care is now limited only by concerns about postoperative apnoea, hydration and feeding, and parental anxiety rather than postoperative pain. Successful perioperative care and postoperative analgesia is based on local anaesthesia and regular paracetamol. Rescue analgesia is rarely required and an early return to feeding

and normal sleep patterns can be expected. The relative success of these regimens reduces the need to expose neonates to the risk of opioid-induced respiratory depression and more invasive analgesic techniques in this care setting.

Local anaesthetic agents include the amides lignocaine, bupivacaine, ropivacaine and levobupivacaine. All are absorbed rapidly and are hepatically metabolised by cytochrome P450 enzymes. The metabolism of the latter three longer-acting agents is subject to a lower hepatic extraction ratio (0.4) than that for lignocaine (0.7). Ropivacaine is mainly metabolised by the CYP1A2 isoform, which may mature later than the CYP3A4 form that is responsible for the metabolism of bupivacaine.[28] Pharmacokinetic parameters for these drugs have been established in infants and show that younger age predicts a larger volume of distribution, lower clearance and longer half-life.[29] Being alkaline, the amide anaesthetic agents are bound in plasma by alpha-1-acid glycoprotein (a low capacity, high affinity site). This phase reactant protein is present in only low concentrations in neonates, rising to adult values between 6 and 12 months of age. Although this is an important consideration, the risk of toxicity with large doses or prolonged continuous infusion is related principally to the reduced intrinsic clearance of the drugs.[29]

Pharmacodynamic differences between agents have been debated and as yet have not been clearly demonstrated in a paediatric population. Both ropivacaine and levobupivacaine have been advertised as safer agents, based on a small number of case reports and laboratory studies. Apart from differences in potency, there appear to be no fundamental differences between the effects of these drugs on sodium channel electrophysiology.[30] The pharmacology of these drugs is described in greater detail in a subsequent section. Recommended maximum doses for single-dose infiltrations are given in Table 2.

Paracetamol. Perioperative analgesia usually includes the use of oral or rectal paracetamol and is rarely required for more than 48 hrs following minor surgery. The effectiveness of paracetamol has been well documented in infants and children undergoing a variety of surgical procedures.[31] Although similar evidence is yet to be published for neonates, it is reasonable to extrapolate analgesic efficacy data for paracetamol to the younger age groups.[32] In neonates, it can be delivered orally or rectally for most minor surgical procedures. Dosing schedules in wide clinical usage and based on the available pharmacokinetic data tend to be more liberal than licensed recommendations (see Table 3).[33] Paracetamol is conjugated in the liver with glucuronide or sulphate and then renally excreted. These phase II reactions continue to mature up to 3 months of age. Neonatal immaturity in these systems results in a lower clearance rate compared to infants and is the basis of the reduced dose (and increased dosing interval) recommendations given below. The ontogeny of the enzyme system involved (glucuronosyl transferase isoenzymes) has been recently studied. These studies confirm major variability in the metabolic capacity of neonates and that this variability is only partly explained by gestational and postnatal age. A significant effect of repeated dosing was detected – implying that the enzyme system undergoes a degree of 'induction'.[34] Hepatotoxicity is related to metabolic products of oxidative reactions. These phase I pathways are less well developed in neonates providing some rationale for the relative safety of the drug in neonatal practice.[35,36]

Circumcision

Circumcision in the neonate for social reasons is no longer supported in most publicly funded health jurisdictions. It remains a common practice outside of this milieu and raises, among other issues, pain

Table 2
Local anaesthetics for single-dose infiltrations.

	Typical concentration	Max dose With adrenaline (mg/kg)	Max dose Without adrenaline (mg/kg)
Lignocaine	0.5%	5	4
Bupivacaine	0.25%	2	2
Levobupivacaine	0.25%	2	2
Ropivacaine	0.2%	2	2

Table 3

Paracetamol dosing								
Age group	Oral			Rectal				
	Loading dose (mg/kg)	Maintenance dose (mg/kg)	Dosing interval (h)	Loading dose (mg/kg)	Maintenance dose (mg/kg)	Dosing interval (h)	Maximum daily dose (mg/kg/d)	Duration at maximum dose (h)
Neonate								
28–32 weeks PCA	20	10–15	8–12	20	15	12	40	48
>32 weeks PCA	20	10–15	6–8	30	20	8	60	48
Infant								
1–3 months	20	15	6	30	20	8	60	48
3–12 months	20	15	4–6	40	20	6–8	90 (for 48 h) then 60	72

Adapted from Arana and Morton et al.[31] (PCA: Post-conceptional age).

management in newborns as provided by general practitioners and obstetricians. American training programmes have responded to these issues by teaching topical or local anaesthetic techniques but these may not be universally applied.[37] In many jurisdictions, circumcisions in infants are performed under general anaesthesia and circumcision in the awake neonate has become less frequent. Circumcision without analgesia is no longer acceptable in any medical setting.

Recommended analgesic regimens typically include oral or rectal paracetamol and some form of local analgesia (topical anaesthesia, dorsal penile nerve block (DPNB), ring block or caudal injection). Ring blocks and DPNBs should not be performed with adrenaline-containing solutions. In awake neonates, topical anaesthesia with lignocaine–prilocaine is more effective than placebo but is less effective than DPNB.[38] Liposomal lignocaine may provide some advantages over lignociane–prilocaine.[39]

When combined with general anaesthesia, there is no data to suggest that one or other of these local techniques is superior. Bupivacaine confers better analgesia than lignocaine as judged by the need for rescue analgesia.[40] Penile nerve block and caudal injection studied in young children are equally effective and safe when performed by experienced practitioners.[41]

Herniotomy/pyloromyotomy

Pain management for these neonatal surgeries is now well established and is based on the use of local analgesic drugs and simple analgesics. Local anaesthetic agents are most commonly injected subcutaneously just prior to skin incision after induction of anaesthesia.

For herniotomy surgery, deeper injection into the plane between transversus abdominis and the internal oblique muscle blocks the ilio-hypogastric and ilio-inguinal nerves. Further injection by the surgeon around the genital branch of the genito-femoral nerve allows complete regional analgesia. Transversus abdominis plane (TAP) blocks, while technically feasible in neonates,[42] have not been shown to be any more efficacious than simple wound infiltration. Typically, bupivacaine, levobupivacaine or ropivacaine are used in volumes of 1 ml kg^{-1} to a maximum dose of 2 mg kg^{-1}. There are no data comparing the safety or efficacy of these agents in neonatal subjects. Clinical choices are based on the limited data from infants, older children and adults. Pre-clinical (animal or adult volunteer) studies suggest that levobupivacaine may have less adverse effects on cardiovascular and central nervous system physiology[43] but, like bupivacaine and ropivacaine, it also has significantly reduced clearance in neonates. The pharmacology of these local anaesthetic drugs in neonates will be covered in subsequent articles.

If herniotomy is performed under spinal or caudal epidural anaesthesia, postoperative pain is usually managed with simple oral or rectal paracetamol and postoperative distress usually responds to immediate feeding.

Major neonatal surgery

Opioids remain the mainstay of pain management following major neonatal surgery. Morphine, in particular, has proved effective and has widespread use despite its well-recognised limitation of a prolonged duration of action in neonates. Fentanyl is finding increasing use during neonatal surgery and post-operative care. Greater haemodynamic stability associated with the synthetic opioid must be balanced against recognised disadvantages such as the early onset of tolerance[44] and the development of thoracic muscle rigidity ('frozen chest').[45] Both opioids display narrow margins between analgesic doses and those that cause respiratory depression and apnoea. This generally means that neonates, who undergo major surgery, will require postoperative ventilation. Several small studies of morphine form the basis of our understanding of opioid pharmacology in neonates.[46] These studies demonstrate distinct differences in metabolism of the drug in neonates and infants compared with older children and adults. The ability to conjugate morphine into either the glucuronide or sulphate derivative is present in the newborn (including pre-term neonates) but the capacity may be limited by immaturity of the enzyme systems. While sulphation has been documented in pre-term and term neonates, it remains a minor metabolic pathway and is soon surpassed by glucuronidation during neonatal life.[47] Possibly due to the reduced metabolic capacity, a larger proportion (16–80%) of administered morphine is excreted unchanged in the urine in term neonates than in older children and adults (3–15%).[48,49] Debate continues regarding the relative ratios of morphine-6-glucuronide and morphine-3-glucuronide to morphine, but potential differences in the levels of these metabolites are unlikely to completely explain the widely appreciated sensitivity of neonates to opioids.

While volumes of distribution (mean value $2.8 \pm 2.6\,l\,kg^{-1}$) appear to be stable across early development and consistent with adult values, both half-life and clearance change rapidly during the first few weeks of life.[47] The pooled estimate for morphine's half-life in pre-term neonates is 9.0 ± 3.4 h and this decreases to 6.5 ± 2.8 h in term neonates. This value decreases further still to 2.0 ± 1.8 h in children and infants over 11 days.[47] The elimination phase in neonates is extended by a long terminal half-life (24.8 ± 4.6 h), which may be particularly important when managing the sick ventilated neonate.[50] Clearance of morphine also shows strong developmental patterns going from pre-term values of $2.2 \pm 0.7\,ml\,min^{-1}\,kg^{-1}$ to $8.1 \pm 3.2\,ml\,min^{-1}\,kg^{-1}$ at term. Values close to those found in adults have been measured in neonates older than 11 days and are consistently more than $20\,ml\,min^{-1}\,kg^{-1}$ in babies older than 2 months.[47] The precise effect of either gestational or postnatal age on these developmental patterns remains elusive. Keeping in mind a large inter- and intra-individual variability, it is reasonable to assume that babies achieve adult-like values for half-life and clearance by 2 months of age.[47]

Morphine is typically delivered by continuous infusion or intermittent bolus doses with or without a continuous background infusion (NCA). Differences in analgesia between continuous infusion regimens and intermittent injections are difficult to demonstrate.[51] Infusion rates typically range between 10 and $30\,\mu g\,kg^{-1}\,h^{-1}$. Slightly lower rates ($5–10\,\mu g\,kg^{-1}\,h^{-1}$) have been recommended for pre-term neonates[52] and for neonates under 7 days of age.[50]

Safe delivery of opioids is predicated on close observation. Regularly measured and documented pain scores as well as respiratory observation and continuous pulse oximetry are mandatory.

The pharmacodynamic effects of opioids are particularly difficult to study in neonates and the few available studies allow only limited conclusions. There is clearly large individual variation and seemingly little correlation between plasma concentration and drug effect. Susceptibility to the respiratory depressant effects of morphine has been studied in ventilated neonates, infants and children following cardiac surgery. While a plasma concentration threshold for respiratory depression was detected, a clear change in sensitivity across the age groups was not detected.[53]

Paracetamol is recommended as an analgesic adjunct to opioids in neonates following major surgery, although evidence of its efficacy is extrapolated from studies in older infants and children.[32,54] Dosage recommendations summarised by Arana and Morton et al. have widespread acceptance.[31] See Table 3.

Intravenous paracetamol has been available (at least as a pro-drug) for the past two decades and has been a significant advance in the analgesic formulary. It is generally only indicated when other routes of administration are not possible. It is becoming better accepted for use in neonates as kinetic data and studies of safety have been published.[55,56] These studies confirm that both postnatal and post-

conceptional age (PCA) effect the metabolic conjugation of paracetamol to glucuronide. Importantly, repeated administration is also correlated with increasing glucuronidation capacity.[34] Despite significant gaps in our knowledge of paracetamol pharmacology in neonates, the regimen based on that originally proposed by Allegaert has the most currency and can be recommended until further data become available (see Table 4).

Table 4
Intravenous paracetamol dosing.

Age group	Maintenance dose (mg/kg)	Dosing interval (h)	Maximum daily dose (mg/kg/d)
Neonate			
28–32 weeks PCA	7.5–10	6–8	40
32–36 weeks PCA	7.5–10	6	50
>36weeks	15	6	60
Infant			
1–3 months	15	6	60
3–12 months	15	4–6	60

From Allegaert 2004.

Non-steroidal anti-inflammatory drugs (NSAIDs) now have an established place in the provision of analgesia in infants and children. Good evidence for their safety and efficacy in a variety of surgical settings has been published.[57–59] Their use in neonates has been relatively limited to the medical closure of persistent ductus arteriosus.[60] In this setting, the risk of cerebral, gastrointestinal or reversible renal injury is balanced by the significant advantage of decreasing pulmonary haemorrhage and intraventricular haemorrhage.[61] Medical closure has the added advantage of avoiding general anaesthesia and thoracotomy.[62] A significant negative effect on glomerular filtration rate has been demonstrated in neonates including premature babies.[63–65]

Despite these well-documented risks, ketorolac has been administered to small cohorts of well-selected neonates for pain relief following surgery and data showing efficacy have been published.[66] Unfortunately, evidence of safety and an adequate risk: benefit ratio for the use of NSAIDs for analgesia in neonates is not available. Selective NSAIDs (cyclooxygenase (COX)-2 specific drugs) find occasional use in children despite a serious lack of pharmacokinetic and safety data.[67] The evidence for any advantage over non-selective drugs in children is limited and there are no data on the use of these drugs in neonates.[68] Routine use of NSAID drugs for analgesia in neonates cannot be recommended until further pharmacokinetic and safety data are available.[69–71]

Neuraxial blockade and infusions. As in infants and children, local anaesthetic agents have a significant opioid-sparing effect. Following neonatal surgery, this can critically influence the decision to extubate a baby and thereby avoid postoperative ventilation.[72] The advantages of early extubation and a return to 'kangaroo care' (i.e., nursing the neonate on the chest of a parent) are not always immediately obvious as care of the ventilated neonate in modern nurseries is both effective and relatively safe. Early extubation of a neonate following major surgery demands a higher nursing acuity in the immediate post-extubation/operative hours. This is later followed by decreased nursing acuity due to earlier parental re-involvement in the neonate's care and an earlier return to feeding.

Local infiltration of surgical wounds provides effective immediate perioperative analgesia but currently available agents cannot provide relief beyond a few hours.

Caudal injection of local anaesthetics provides good analgesia for lower abdominal wall and perineal surgery that may be expected to extend well into the early recovery phase following surgery.

Newer techniques such as the transverse abdominis plane block have recently been described for upper and mid-abdominal surgery in neonates.[42] While technically feasible, advantages over simple wound infiltration are yet to be demonstrated.

Continuous epidural analgesia in paediatrics has not been subject to the meta-analysis that has been applied to adult practice.[73] Many conclusions from the latter are extrapolated to varying degrees perhaps explaining the variety of approaches taken by different institutions. Early experience from major paediatric centres confirmed that continuous epidural analgesia was able to facilitate early or immediate postoperative extubation.[74] In fact, continuous postoperative epidural infusions are predicated on the distinct assumption that the neonate will be extubated in the immediate postoperative

period so that spinal cord function can be assessed. Although bupivacaine infusions have been successfully used in several large neonatal series,[74] concern regarding the risk of rising plasma concentrations and reduced clearance suggests that continuous infusion should always be closely monitored.[75] Ropivacaine for epidural infusion in neonates has been found to provide acceptable analgesia without evidence of drug accumulation despite a clearance calculated to be lower than that in infants >30 days old.[76]

Epidural analgesia can offer benefits to well-selected neonates, parents and neonatal nurseries. It requires dedicated follow-up care for it to work as neonatal epidural infusions often need regular adjustment. Also, caring for the awake postoperative neonate is quite different from the care required for the ventilated neonate. While we await a strong evidence base for neonatal epidurals, current practice depends on individual enthusiasts and close communication between the anaesthetists and neonatologists involved in postoperative care. Epidural analgesia in neonates will be enhanced by ultra-sonographic imaging (placement and monitoring) and further advances in pharmacology.

From anecdotal reports, continuous regional techniques such as rectus sheath catheter infusions have proved effective when used in well-selected cases and can avert the need for postoperative ventilation.

Intrathecal opioids have occasionally been used with success in managing neonates undergoing upper abdominal or thoracic surgery where avoidance of postoperative ventilation has significant advantages.[77] Morphine ($10\ \mu g\ kg^{-1}$) can be combined with a postoperative intravenous naloxone infusion ($5\ \mu g\ kg^{-1}\ h^{-1}$). This practice is suited to major paediatric centres with a large neonatal experience that regularly report outcomes to the wider paediatric community.

Procedural pain in neonates

In the first days of life, almost all neonates are subject to two or three painful percutaneous procedures including intramuscular injection (e.g., vitamin K injection and immunisation) and heel lance for metabolic screening. The past decade has seen a significant amount of research confirming the efficacy of several strategies including breast-feeding, sucrose,[78] maternal holding and pacifier use (non-nutritive sucking)[79] for these painful procedures.[80] Clearly, these interventions reduce the size of behavioural and physiological responses to single acute noxious stimuli. It must be emphasised though, that none of these interventions have been shown to have a specific anti-hyperalgesic effect. Moreover, while this remains so, it is not possible to distinguish a sedative effect from a true analgesic effect.[12]

Cuddling or swaddling, skin-to-skin contact, verbal reassurance and feeding are part of the mothercraft repertoire to sooth a neonate. Within acute care environments, separation of the neonate from its mother often precludes these simple, effective and psychologically important interactions. Mechanical ventilation of the critically ill neonate prolongs this separation and often commits the neonate to repeated procedures during acute illness, surgical intervention and/or the management of prematurity.

Ensuring that *non-pharmacological interventions* are a part of clinical practice will provide not only effective management of neonatal distress but also much greater satisfaction to both parents and clinical staff.

The evidence for the effectiveness of sucrose and breast milk in reducing pain scores in newborn infants is now reasonably strong. The effectiveness of sucrose has been confirmed for heel lance and eye examinations.[81] Postulated mechanisms remain vague but regularly mention release of endogenous neuropeptides including endorphins[82] endocannabinoids[83] and cholecystokinin.[84] An understanding of the mechanism could provide an explanation for the observed lack of efficacy of these measures in inflammatory and postoperative pain. A Cochrane review[85] confirmed equivalent analgesic efficacy of breast milk and sucrose and that this was greater than that of swaddling and pacifiers.

Kangaroo care has been shown to significantly reduce both physiological[86] and behavioural indices of pain[87,88] during heel lance. Kangaroo care was found to be more effective than oral glucose in at least one randomised trial.[87]

Non-nutritive sucking has also been shown to be effective in reducing crying and pain responses during both heel lance[79] and awake circumcision.[89]

Where possible, maternal holding and or swaddling and breast-feeding should be encouraged during heel lancing.[90]

Immunisation

Has provided a valuable model for the study of procedural pain and many of the analgesic interventions mentioned above. While more studies address immunisation in infants than in neonates,[91] several patterns emerge. Oral sucrose solutions (12–50% in volumes between 0.5 ml and 2 ml) have been shown to be effective when administered just prior to injection. They can be administered as oral drops or on a pacifier (see Table 5). As an analgesic intervention, it appears to be effective in neonates but has a more modest effect beyond the newborn period.[92]

Heel lance and venepuncture

Are the most common and most studied painful stimuli in neonatal acute care. Although topical anaesthesia would appear to be an obvious analgesic modality, efficacy has proved to be inconsistent.[38,93,94] This is possibly related to limb exposure and positioning, skin cleansers, the use of tourniquets for venepuncture and the degree of handling and squeezing that heel lancing generally requires.[95] Topical preparations include liposomal lignocaine 4% ointment (LMX4® Ferndale Labs), lignocaine–prilocaine 5% cream (EMLA®, Astra Pharma) cream, amethocaine ointment and Tetracaine 4% gel (Ametop® Smith and Nephew). Lignocine–prilocaine has been used effectively in neonates[96] but has been associated with methaemoglobinaemia. This is particularly important in premature neonates, who have more permeable skin[97] and lower activity levels of methaemoglobulin (MetHb) reductase.[98] Adverse effects can occasionally be dangerous.[99] The onset of analgesia may take up to 60 min and skin penetration can reach 6 mm after prolonged contact.[100] Tetracaine and liposomal lignocaine, on the other hand, do not cause methaemoglobinaemia and have shorter onset times (40 min), thus increasing their clinical utility.

In recent years, automated (spring-loaded) devices have been shown to be associated with less bruising,[101] improved blood collection,[102] less time taken and reduced pain and distress.[103] Reducing the pain of heel lance and venepuncture must rely heavily on non-pharmacologic techniques including sucrose, breast-feeding, skin-to-skin contact, maternal holding and swaddling.

Lumbar puncture

In a pattern similar to that of analgesia for venepuncture, the effectiveness of topical anaesthesia and local infiltration for lumbar puncture is inconsistent. While topical analgesia may reduce pain responses to needle insertion and withdrawal,[104] responses to skin preparation, positioning and handling during the procedure are not affected. This may explain the failure of several randomised trials to detect a significant effect of topical anaesthetic agents on pain from lumbar puncture.[105] Local infiltration does not obscure anatomical landmarks nor reduce success rates of puncture and is therefore mandatory for this procedure.[106]

Table 5
Oral sucrose administration – dosing schedule for procedural pain.

Gestational age/wt range	Sucrose concentration	Maximum in 24 h	Dose per procedure
<1500 g	25%	2.5 mL	0.5 mL
>1500 g	25%	5 mL	1 mL
3–6 months (corrected)	75%	5 mL	2 mL

From Children's Hospital at Westmead Practice Guideline.

Intubation in the neonatal nursery

Endotracheal intubation of neonates is stressful and provokes a strong sympatho–adrenal response that may be deleterious for some babies. Providing effective analgesia and sedation without disturbing cardio-respiratory stability is often a challenge. 'Awake intubations' are no longer considered optimal care as newer agents provide better alternatives. Intravenous opioids combined with muscle relaxants can provide stable intubating conditions and high success rates for even less-experienced personnel.[107] It is important to note here that benzodiapzepines do not provide analgesia. Critically ill neonates, particularly those with suspected cardiac lesions, must be identified early and managed by clinicians skilled in neonatal resuscitation.

Remifentanil is widely used in paediatric anaesthesia practice and may provide significant advantages in neonatal practice. A profile of rapid recovery, good titratability, predictable sedation, relative haemodynamic stability and an absence of major side effects has been demonstrated in case reports of short-term infusions (up to 8 h).[108] Studies on longer-term infusions addressing safety, opioid tolerance, opioid-related chest-wall rigidity and opioid-induced hyperalgesia are still required.

Analgesia for mechanical ventilation

Although modern ventilator technology has vastly improved the ability of the neonatologist to individualise ventilation parameters, reduce the work of breathing and maximise ventilator synchrony, mechanical ventilation is still generally thought to be stressful for neonates. Most neonatal intensive care units (NICUs) regularly mandate analgesia in the form of systemic opioids.[109] The neuroendocrine responses (catecholamine release and cortisol secretion) to mechanical ventilation can be obtunded by the administration of opioids[110] and ventilator synchrony,[111] and pulmonary function may be improved.[112] While there is good evidence that morphine infusions in ventilated neonates reduces indices of pain and stress, there is little evidence that routine use improves long-term outcomes.[110,112] In fact, the NEOPAIN study – which randomised 898 ventilated babies (receiving open-label morphine) to a continuous background infusion of either morphine or placebo – demonstrated an association between continuous infusion and poorer respiratory outcomes, duration of ventilation, hypotensive episodes and feeding intolerance.[113] Careful analysis allowed the authors to conclude that morphine infusion *per se* was not related to the risk of severe adverse effects, except in neonates, who were hypotensive.[113] While a Cochrane review of opioid use in ventilated neonates found insufficient evidence to support 'routine' use of opioids in ventilated neonates,[114] it remains standard practice to treat objective signs of pain and distress with titrated doses of opioids. Morphine remains the most commonly used drug and infusion rates typically commence at 10 micrograms/kg/h in neonates under 37 weeks of age and 20 micrograms/kg/h in term neonates. Rates are subsequently adjusted to response. Nurse Controlled Analgesia (NCA) with bolus doses titrated to carefully documented pain scores represents a rational choice supported by the available literature.[115] Fentanyl is an attractive alternative providing a stable haemodynamic profile and wide therapeutic index but, unfortunately, can generate rapid tolerance[44] and may provoke chest-wall rigidity.[45] Remifentanil, a potent and rapidly metabolised opioid, has also been postulated to be a better sedative and analgesic agent during ventilation in the ICU. Its rapid offset of action has been confirmed in a recent meta-analysis of 11 randomised controlled trials in adult patients. The reduced time to extubation following cessation of infusion, however, was not associated with any improvement in mortality, duration of ventilation, length of ICU stay or risk of agitation.[116] Despite these findings, remifentanil may still provide neonatologists with specific advantages. Both intubation conditions[117] and the ability to rapidly awaken a neonate[117] appear to be better with remifentanil than with morphine. This may facilitate an 'intubate–surfactant–extubate' strategy in the management of neonatal respiratory distress syndrome.[118]

Future challenges

One of the greatest impediments to improved neonatal pain management is the lack of clarity regarding the long-term risks and benefits of analgesic practice. While both untreated neonatal pain

and neonatal drug exposure can be associated with short-term adverse effects,[119] the long-term implications remain to be defined. Reports of altered pain sensitivity,[120] greater somatisation[121] and altered responses to pain experiences in later life in children, who have undergone neonatal surgery and intensive care, have not been consolidated by either large or extended cohort studies or meta-analysis. At least one cohort study suggests that neonatal surgery may result in subsequent and long-term alterations in nociception within the operated dermatome.[122] In a case-controlled study, tenderness thresholds in ex-premature adolescents were found to be lower than their term counterparts.[123] A similar but smaller well-conducted study confirmed subtle sensory changes around scarred skin but failed to demonstrate a significant impact of early neonatal surgery on pain sensations in daily life in children (9–12 years), who had undergone neonatal surgery. While these findings suggest important neurobiological changes due to early pain and inflammation, their clinical significance is unclear.[124] While plasticity of the central nervous system has often been quoted as the basis of potential adverse effects of pain and analgesic medication on neonatal neural development, it may well be that this plasticity is, in fact, the basis of the resilience of the immature brain to repeated insult.

Strategies for the management of inflammatory and postoperative pain within neonatal nurseries are slowly finding clinical priority. Many of the advances that acute pain services have brought to general paediatric wards, such as regularly documented pain scores, NCAs as well as continuous neuraxial and regional infusions, are being implemented within progressive nurseries. The challenge remains to provide potent analgesia for neonatal surgery without incurring the costs of prolonged ventilation, delayed enteral feeds, drug tolerance and withdrawal symptoms.

While efforts continue to find analgesic solutions to the problem of procedural pain, attention perhaps needs to be turned to reducing its incidence. The reduced need for prolonged ventilatory support for many pre-term babies has reduced the number of related invasive procedures (tracheal suction, arterial punctures, etc.) in individual babies. Technological advances that allow less-invasive monitoring and more clinical tests to be done at the bedside without invasive sampling (i.e., via per- or transcutaneous means) may further lessen the burden of neonatal pain. Similarly, better solutions to the recurring problems of neonatal venous access will reduce pain associated with drug and fluid delivery, which require venous cannulation and the application of skin adhesives. By reducing the burden of medical interventions, it may be possible to facilitate a greater degree of parental contact. Even if this does not bring about improved long-term clinical outcomes, it will likely provide greater satisfaction for parents.

Conclusions

Exactly 10 years ago, Larsson, in a prescient review of pain management in neonates,[125] outlined a range of safe and effective methods for the management of procedural and postoperative pain in neonates. He urged clinicians, then, to implement these in clinical practice. Ten years on, there have been limited advances in the available pharmacological armamentarium, modest clarification of the risks of untreated pain and aggressive analgesic practice and a greater recognition of non-pharmacological analgesic techniques.

Advanced health systems need to consistently articulate pain management policy for neonates, institute regular pain assessments and bridge the gaps between research and clinical practice.

Practice points

- Regular documented objective pain scoring of all neonates admitted for acute care is essential for optimising the provision of analgesia.
- Lesser surgical procedures in neonates can be effectively managed using paracetamol and local anaesthetic agents.
- Carefully titrated opioids remain the mainstay of analgesia for major surgery in neonates.
- Non-pharmacological analgesic interventions provide not only effective management of neonatal distress but also much greater satisfaction to both parents and clinical staff.

Research agenda

- Correlations between physiological and behavioural parameters and indices of cortical activation in neonates exposed to noxious stimuli need to be explored.
- The risk of clinically relevant long-term adverse effects of untreated neonatal pain still needs to be clearly defined.
- Advances in intravenous catheters' technology and non-invasive bedside monitoring are required to reduce the burden of venous access interventions, venepuncture and heel-sticks.
- Much neonatal analgesic pharmacology needs to be studied including pharmacokinetics of alternative opioids such as oxycodone, safety profiles of newer local anaesthetic agents and the risk–benefit ratios of NSAIDs.

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Conflict of interest statement

None.

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Regional anaesthesia and analgesia in the neonate

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A large number of published studies have shown that the use of diverse regional anaesthetic techniques is associated with high-quality pain relief following the different types of surgery and painful procedures that are commonly performed in neonatal patients. Apart from pain, few studies have examined other outcomes in this setting. Some data suggest a benefit with regional anaesthesia. In a retrospective study, Bosenberg et al. found that the use of epidural analgesia in neonatal patients undergoing tracheo-oesophageal fistula repair resulted in a reduced need for postoperative mechanical ventilation. Furthermore, epidural analgesia was found to be associated with a significant and beneficial modification of the neuroendocrine surgical stress response after major abdominal surgery in infants when compared to postoperative morphine infusions. The use of local anaesthetics in association with neonatal circumcision has also shown a benefit as neonates not treated with eutectic mixture of lidocaine and prilocaine (EMLA) or a penile block had an exaggerated pain response to later vaccinations as compared with neonates treated with a local anaesthetic technique. Finally, safety data generated from large, prospective studies and audits clearly show that the use of paediatric regional anaesthetic techniques is associated with adequate safety also in neonatal patients. In conclusion, a large variety of local and regional anaesthetic techniques can be safely used in neonatal patients. The use of such techniques must obviously be associated with sufficient knowledge about the various

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techniques, as well as adherence to adequate dosage guidelines and other safety precautions. However, if these prerequisites are met, regional anaesthesia may offer great advantages to our smallest and most vulnerable patients.

Since the 1980s, a large number of studies and scientific data have shown that both neonates and premature babies do possess the neuro-anatomical and synaptic prerequisites to perceive nociceptive stimulation. Clinical studies by Anand and co-workers, focussing on the importance of providing adequate analgesia to our smallest patients, have clearly shown that insufficient intra- and post-operative analgesia does result in an exaggerated neuroendocrine stress response, increased morbidity and even increased mortality in the case of neonatal cardiac surgery. There is also evidence that the foetus has a similar response. It has also been shown that, compared to puncture of the non-innervated umbilical cord, intrauterine exchange transfusions performed through the innervated abdominal wall of the foetus result in a greater neuroendocrine stress response and subsequent behavioural changes.[1,2] Not only may insufficient pain relief be associated with negative short-term effects but insufficient neonatal analgesia also has long-term effects. Taddio et al. have clearly shown that neonatal boys who were circumcised without analgesia have a more pronounced pain experience to later immunisation injections, compared with boys who had received active analgesia by means of EMLA cream (EMLA, eutectic mixture of lidocaine and prilocaine).[3,4] Thus, there is no doubt that both neonates and premature babies should receive adequate pain relief for both surgical interventions as well as painful procedures outside the operating theatre, for example, in the neonatal intensive care unit (NICU).

One of the best, and may be also the safest, ways to provide high-quality analgesia is with the use of local anaesthesia, either alone or in combination with other drugs. The small size of neonatal patients does not in any manner preclude the use of local or regional anaesthetic techniques. The aim of this review is to provide clinically useful information on how to use regional anaesthesia and analgesia in a safe and effective way in neonates and premature babies.

Topical application and local infiltration

All newborn babies should undergo metabolic screening and are therefore subjected to blood sampling soon after birth. This is frequently accomplished by heel lancing, which is associated with a significant pain experience. Although not licensed for use in neonates, attempts to use EMLA cream prior to heel lancing have not produced good analgesia for this procedure.[5] A possible explanation for this may be the high skin blood flow in this area (the reason for performing sampling at this anatomical point).[6] By contrast, a recent Cochrane report has found the use of EMLA cream to have beneficial effects on pain caused by circumcision; being better than placebo but less effective than a penile nerve block.[4] Thus, although it appears that the efficacy of EMLA cream in this age group is dependent on the site of application, it can be successfully used for a number of different procedures in neonates and infants.[7,8] One must also be careful with regard to the amount of EMLA cream that is applied so as not to subject the child to the risk for symptomatic methaemoglobinaemia caused by the prilocaine component of EMLA. There are limited data describing the use of the other local anaesthetic creams (Ametop or Rapidan) in neonates and premature babies.

In neonates, the topical spray of lidocaine to the larynx and trachea can successfully minimise the nociception and haemodynamic stress response associated with airway manipulations. Since the actual spraying in these situations is often performed by the ear, nose and throat (ENT) surgeon, it is of great importance for the anaesthetist to note the concentration of the lidocaine used and limit the dose to reduce the risk of systemic toxicity. In a study by Gjonaj et al., it has been found that 8 mg kg^{-1} of lidocaine can be nebulised without reaching toxic plasma concentrations.[9]

For more localised procedures, such as cut-down for silastic catheter placement, intra-osseous needle insertion for vascular access and bone marrow aspiration, the injection of local anaesthetics at the site of the procedure is an easy but often-forgotten technique. As with other regional anaesthetic

techniques, it is important to keep to a safe total dose of local anaesthetic. One should also note that the adjunct use of adrenaline is associated with pronounced injection pain/burning and should thus best be avoided if the child is not under general anaesthesia already.

Equipment

Data from the 1996 French Language Society of Paediatric Anaesthesia (ADARPEF) study show that 50% of the complications of regional anaesthesia were due to the use of the wrong type of regional anaesthesia equipment; most often, the use of adult-sized equipment in paediatric patients.[10] Currently, age-specific regional anaesthesia equipment is commercially available. Epidural catheter kits with Touhy needles down to the size of 19–20-G as well as 24-G styletted caudal needles are now produced by various manufacturers. Further, recently, a specific kit to facilitate the use of the Tsui method (see below) has also been made commercially available. Thus, there is currently no support or rationale for not using age-adequate equipment in children.

Central nerve blocks

Spinal (intrathecal) blockade

This technique has been described in detail elsewhere in this issue. Awake spinal (intrathecal) blockade is a well-described technique to produce surgical anaesthesia mainly for inguinal hernia repair in the ex-premature child.[11] Surprisingly large amounts of local anaesthetics are necessary to produce an adequate block (0.14 ml kg^{-1} of bupivacaine 0.5%).[12] A prolongation of the block can be achieved by the addition of clonidine (1 mcg kg^{-1}).[13] The use of a spinal block technique to produce a complete spinal blockade in association with neonatal cardiac reconstructive surgery has also been recently described (with or without an intrathecal catheter that will allow the administration of top-up doses) and is reported to produce excellent conditions for this type of advanced surgery, including beneficial modification of the neuroendocrine surgical stress response.[14] This method has so far only been used in patients who are supported by extra-corporeal bypass, which provides adequate safety should excess haemodynamic reactions occur. Against this background, this technique should at present not be used outside this specific indication except as part of an approved clinical trial.[15]

Caudal blockade

This block is one of the most basic regional anaesthetic techniques in children, and is also well-suited to the smallest patient category.[16] It is one of the easiest blocks to learn with one study suggesting only 32 blocks are necessary before reaching adequate success rates.[17] A caudal block can, depending on the dose and volume of the local anaesthetic, produce adequate anaesthesia up to the mid-thoracic region and, thus, can be used either alone as an awake technique, or as a supplement to general anaesthesia for all surgical procedures from the mid-thoracic level down (Table 1). With ultrasound, it is now possible to visualise the injection of local anaesthetics in the caudal space as well as monitor the cranial spread.[18] The use of ultrasound is highly recommended in neonates who receive concomitant general anaesthesia, but is much more difficult to use in the awake and mobile baby.

Although this block can be used for almost all surgical interventions below the level of the umbilicus in neonatal babies, the use of this technique in association with neonatal inguinal hernia repair is by far the most common one.

Table 1
Caudal blockade. Levels of surgical anaesthesia in relationship to injected volume of local anaesthetic. Modified according to Armitage.[72]

Volume of caudal injectate (ml kg^{-1})	Typical surgical procedures
0.5	Urogenital + club foot surgery
1.0	Subumbilical surgery
1.25	Surgical procedures below the mid-thoracic level

The awake caudal technique is a useful alternative to general anaesthesia in ex-premature infants who often suffer from various degrees of bronchopulmonary dysplasia. Such babies often have had great difficulties to be weaned from mechanical ventilation and both parents and neonatologist frequently want to avoid the risks involved with general anaesthesia and re-intubation of the trachea. The use of the awake caudal technique will also limit the risk for postoperative apnoea in this specific patient category. However, for this to be true, the block must be carried out without the use of adjunct sedatives (e.g., midazolam, ketamine and low-concentrations sevoflurane by nasal prongs); otherwise the risk for postoperative apnoea will not be reduced as expected. Even in the case of a 'pure' awake caudal technique, these neonatal patients cannot be transferred to an ordinary ward after surgery but must remain in an neonatal intensive care unit/high dependency unit (NICU/HDU) environment overnight. This is particularly true if supplemental drugs such as ketamine or clonidine have been used as adjuncts to the local anaesthetic solution.[19]

The use of supplemental sedation, however, is often not necessary since the systemic absorption of the local anaesthetic together with loss of sensory input from the lower body usually make the child sleepy/sedated approximately 15–20 min following injection.[20] Care must be taken not to exceed the maximum dosage recommendations, particularly since these patients do not receive any sedative drugs that would usually increase the seizure threshold. The administration of 3 mg kg^{-1} of racemic bupivacaine has been shown to produce pre-toxic EEG signs in this patient category.[20] The administration of oral sucrose can also be helpful in neonates with awake caudal anaesthesia. It not only alleviates the discomfort of preoperative starvation but also has significant analgesic properties.[21]

Even if the most frequent indication for the awake caudal technique in neonates is inguinal hernia repair, this technique can also be very useful for venous catheter placement in the saphenous or femoral vein, and other lower limb procedures. One specific indication, that has proven useful in the author's experience, is to provide adequate analgesia and abdominal wall relaxation when performing an awake reduction of gastroschisis according to the Bianchi technique[22] soon after birth (unpublished data).

Epidural blockade

Since the popularisation of this technique for use in paediatric patients in the late 1980s, this technique to produce intra- and postoperative pain relief has become a standard procedure in children. Bosenberg and co-workers have been the pioneers with regard to its use in neonatal patients[23] and could show in an early study that epidural blockade drastically reduced the need for postoperative ventilation in neonates undergoing tracheo-oesophageal fistula repair.[24] Furthermore, Wolf et al. have clearly shown that the use of epidural blockade in infants undergoing major abdominal surgery results in significantly better modification of the neuroendocrine surgical stress response than postoperative intravenous morphine infusion.[25] The use of epidural analgesia may also shorten the period of postoperative paralytic ileus in small babies.[26] Large observational studies have shown that the use of epidural analgesia, even in neonates is associated with an acceptable risk–benefit profile.[27] Although the use of epidural blockade in neonates and infants has been questioned by some,[28] this method for intra- and postoperative analgesia represents one of the cornerstones of high-quality analgesia for neonates undergoing more extensive surgical interventions. Some technical aspects of neonatal epidural blockade are discussed below.

Loss-of-resistance (LOR)

The use of air for loss-of-resistance (LOR) has been much debated since the use of air has been reported to cause both intravascular air embolism as well as permanent spinal cord injury.[29–31] Although this argument is not finally settled, it has been recommended to use only saline for LOR in paediatric practice.[32]

Use of test dosing

Due to the limited size of the equipment used in small children, inadvertent intravascular placement of the epidural catheter cannot be reliably identified solely from spontaneous backflow in the catheter or from an aspiration test. There is also controversy over the utility of using an adrenaline containing test dose. The occurrence of a heart rate increase or changes in T-wave appearance on the

electrocardiograph (ECG) as a result of inadvertent intravascular administration is influenced by the inhalational anaesthetic agent used and if the child has received atropine prior to the administration of the test dose.[33] Since a negative result of the use of a test dose is not conclusive, many clinicians do not routinely use this safety precaution in children.

Insertion at the appropriate dermatomal level in relation to the surgical intervention

Of paramount importance to achieve a well-functioning epidural block is that the tip of the epidural catheter is situated at an intraspinal level that corresponds to the dermatomal centre of the surgical procedure. Thus, having the tip of the catheter at the lumbar level will not produce adequate analgesia if the patient is undergoing a thoracotomy. The most straightforward approach to get the catheter tip at the right intraspinal level is to perform the epidural puncture at the appropriate dermatomal level, for example, at Th 8 for a major upper laparotomy or at Th 5 for a posterolateral thoracotomy. However, to make this technique really reliable, it is important not to insert more than a few centimetres of the catheter into the epidural space.

Despite the low risk for major damage associated with thoracic epidural use in children[10,27] the risk for traumatic spinal cord injury does still exist, as has been demonstrated by occasional case reports.[34,35] In order to avoid even the slightest risk for traumatic cord injury, and to reduce the risk of catheter dislodgment many paediatric anaesthetists, favour alternative methods for epidural catheter insertion.

Blind caudal catheter technique

Since neonates and non-walking infants have not yet developed the adult pattern of spinal curvatures, it is possible to access the epidural space at the caudal hiatus, and then insert a predetermined length of the catheter to reach the desired spinal level. If using this technique, which was first described by Bosenberg,[36] it is important not to use a Touhy needle since it is very difficult to get the right alignment of the eye of the Touhy needle with the spinal canal. To improve the chance of success the use of a Crawford needle or a regular intravenous catheter is recommended. A very high success rate has been claimed with this blind approach, even to the extent that certain authors have suggested that radiographic verification of the catheter tip location is unnecessary.[37] However, other publications have amply shown that catheters threaded from the caudal space do not at all behave in a predictable way, and that radiographic verification is clearly indicated.[38] Although this approach is appealing due to its simplicity, the need for radiographic verification increases complexity. Note that if the tip position is suboptimal the administration of epidural morphine may be considered, as its effect is not dependent on precise anatomical administration.

The method of threading the catheter via the caudal route may have a renaissance if it proves possible to easily check the catheter tip position with the aid of high performance ultrasound imaging, something that unfortunately is not sufficiently reliable at present.

Nerve stimulation-guided technique: 'Tsui-technique'

Tsui et al. has recently described a method whereby the catheter is attached to a nerve stimulator.[39] After insertion of the catheter through the sacral hiatus into the caudal space, the current is increased to 1–10 mA. The catheter is then slowly advanced in the cranial direction in a similar manner to the blind technique described by Bosenberg. The major advantage with this technique is that the operator will be able to follow the muscular response as the tip of the catheter advances through the spinal canal (this obviously requires that the patient be not paralysed!). The tip of the catheter is advanced until muscle contractions are visible or palpable at the appropriate level for the planned surgical procedure. An unexpected muscular response will alert the clinician that the catheter is not threading as expected and the catheter is slightly withdrawn and the patient position modified and the catheter advanced again until the desired response is achieved. Tsui et al. have reported very good success rates with this technique, and a special kit for this technique is now commercially available (although being quite expensive).

Ultrasound-guided epidural technique

Recently, Willschke et al. have described an ultrasound-guided approach to perform epidural blockade in neonates and infants.[40,41] This method does provide real-time visualisation of the epidural puncture as well as catheter insertion. Despite the merits of this technique, it is technically very

demanding since it requires the help of a well-experienced ultrasound assistant ('experienced third arm'), and it is also difficult to find good working space and conditions during the performance of the block. The future will tell whether this new approach will become standard procedure or if it will be reserved for very special indications.

Peripheral nerve blocks

Peripheral nerve blocks represent a very elegant way of producing analgesia for surgery or painful procedures. However, the indications for peripheral nerve blocks in neonates are limited. One very useful indication is infraorbital nerve blocks for neonatal cleft lip surgery.[42] Ultrasound-guided ilioinguinal/iliohypogastric nerve blocks represent a relevant alternative to caudal blocks for inguinal hernia repair,[43–45] but can only be used as a supplement to general anaesthesia and not as an 'awake' technique. Other types of peripheral nerve blocks may, of coure, be used in specific instances, for example, axillary plexus block for upper limb ischaemia following arterial cannulation in premature babies[46] or transverse abdominal plane (TAP) blocks for major neonatal abdominal surgery.[47] Indications for continuous peripheral catheter techniques are rare in the neonatal population but continuous thoracic paravertebral nerve blocks can provide an alternative to epidural analgesia and may be used for unilateral surgical procedure on the trunk, for example, posterolateral thoracotomy or renal surgery.[48,49]

Wound-infiltration techniques

Local infiltration and wound instillation with local anaesthetic have been described in association with inguinal hernia repair but only produce a brief effect. In adult practice, the use of catheters in the surgical wound has recently become quite popular for a variety of surgical interventions, and recently, Tirotta et al. described the successful use of wound catheters after paediatric cardiac surgery by median sternotomy, with better pain relief, less opioid consumption and less need for sedative supplementation compared to a placebo wound infusion.[50] The study adhered to the recognised dosage guidelines, and plasma concentrations of levo-bupivacaine were found to be within safe limits. However, only infants and children older than 3 months and/or weight more than 5 kg were included in the study. Successful use of continuous wound infiltration for iliac bone grafting in older children has also recently been described.[51]

The technique of continuous wound catheters represents an attractive avenue to achieve adequate postoperative pain relief in neonates and small infants as the catheter can be placed under direct vision by the surgeon, and therefore, the risk for complications is minimised. No published data so far exist in this patient category but, at the Karolinska University Hospital, we are currently conducting studies both in term neonates as well as in premature babies undergoing ductus ligation using this technique. Preliminary results from the ductus ligation study show that the use of indwelling wound catheters reduces the duration of the supplemental morphine infusion from 4.5 to 2 postoperative days as well as lowers the total postoperative morphine requirements by more than 50% (Fig. 1). However, more data are needed to clarify if wound catheter techniques can challenge other alternatives to produce good-quality postoperative pain relief in neonatal patients.

Risk of complications and safety issues

During the early days of the more widespread use of regional anaesthetic techniques in infants and children, there were a number of case reports and case series of serious complications, including both systemic toxicity (seizures and ventricular arrhythmias), traumatic injury of the spinal cord and air embolism. These reports prompted both an Anesthesia Patient Safety Foundation (APSF) study resulting in the generation of dosage guidelines (see below) as well as a prospective study on the complications associated with the use of regional techniques in children.[10] This later study performed by ADARPEF included more than 24 000 paediatric regional blocks and found the incidence of complications to be approximately 1/1000; of which none resulted in any long-term sequalae or legal action. Of further interest, peripheral nerve blocks were not found to be associated with any major complications at all. Use of caudal blocks in the age group term–6 months of age was found to be associated with the highest incidence of complications (0.37%). A very recent follow-up study by the

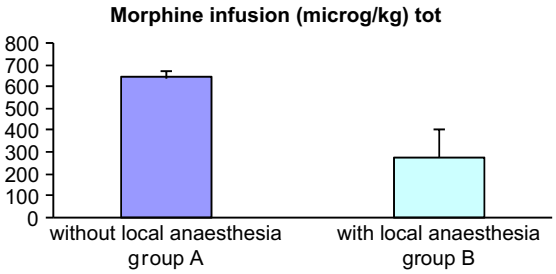

Fig. 1. Effect of wound catheter infiltration with levobupivacaine following ductus ligation in premature babies. The need for morphine infusion was significantly shorter (1,8 vs. 4,5 days) and the total morphine consumption was significantly lower in the group treated with wound catheter infiltration with levobupivacaine (274 vs 641 μg/kg).[74]

same organisation has corroborated their earlier results, reporting an overall complication rate of approximately 1/1000 blocks. An interesting trend in this new study was the use of many more peripheral nerve blocks, including continuous catheter techniques compared with central nerve blocks (Ecoffey C, ADARPEF, personal communication).

The results of a large prospective safety study concerning the use of paediatric epidural analgesia, including more than 10 000 epidural blocks, has recently been published by the Association of Paediatric Anaesthetists of Great Britain and Ireland.[27] The incidence of permanent complications that could be attributed to the use of the epidural block was approximately 1/10 000 blocks, whereas the incidence of less severe complications were found to range between 1/1000 and 1/2000. The neonatal subgroup, comprising 529 neonatal epidural blocks, had a 1.13% overall incidence of complications, which was significantly higher than in other age groups. However, most complications were due to drug errors or systemic toxicity and no complications related to catheter insertion were reported. The overall conclusion drawn from this large prospective audit was that the use of paediatric epidural analgesia, regardless of age group, is associated with an acceptable risk–benefit profile.

Although the risk for systemic toxicity has been substantially reduced following the publication of the Berde dosage recommendations, systemic toxicity can still occur after inadvertent intravascular injection. The more precise injection of local anaesthetics that follows the use of ultrasound guidance may, in fact, increase systemic absorption of the local anaesthetics if the amount is not appropriately reduced.[45] Since it is possible to reduce the volume of local anaesthetics used by at least 50% when using ultrasound guidance,[52] volume reduction is strongly recommended when using this new technique.

The infusion of a lipid emulsion to treat systemic toxicity of local anaesthetics has recently been described, and has been found surprisingly effective both in animal studies and in case reports. Excellent web-based guidelines for dose are currently available.[53,54] If regular measures to treat systemic local anaesthetic are not immediately successful, then lipid should be used (bolus of 20% lipid emulsion: 1.5 ml kg^{-1} followed by infusion of 0.25 ml kg^{-1} min^{-1}; if not successful, two additional bolus injections can be given 5 min apart). Successful use of this new treatment modality has also recently been reported in an infant.[55]

Current discussion points regarding lipid for local anaesthetic toxicity include whether this novel treatment should be started earlier in the therapeutic sequence than what is currently recommended, and if the dose of adrenaline used should be limited to a bolus injection of $\leq$10 mcg kg^{-1}. The latter issue is based on an animal study showing that higher doses of adrenaline are associated with less favourable outcome.[56] Interestingly, a recent study has suggested that lipid is only effective if bupivacaine has been administered and not if the less lipid soluble local anaesthetics ropivacaine or mepivacaine are used.[57]

Considering caudal blockade, there has been an ongoing discussion if normal sharp bevel needles can be used or if it is mandatory to use a styletted needle design. The reason for this discussion is that certain experts, for example, Dalens, claim that the use of non-styletted needles carries the risk of introducing living skin cells into the caudal space, thereby causing the risk for epidermoid growth in the caudal space. This view has been questioned by others because centres that have performed thousands of caudal blocks have never experienced this complication as well as due to the lack of well-described case reports in the literature. Recently, new data have shown that only dead stratum

Table 2
Clinically relevant key points concerning complications to regional anaesthesia in neonates and infants.

1. Always use paediatric equipment of correct size.
2. Only use saline for loss-of-resistance.
3. Remember that a negative test dose does not provide 100% security against inadvertent intravascular injection.
4. Do not exceed the maximum dosage recommendations for local anaesthetics.
5. Have Intralipid 20% immediately available in case of systemic toxicity.
6. Remember that epidural abscesses may present weeks and even months after the removal of the epidural catheter.
7. Re-evaluate the need for continuous epidural analgesia, especially in neonates and/or if the caudal insertion approach has been used, after 48 h in order to minimise the risk for systemic toxicity and infection. Continue only if the risk-benefit analysis shows that the use of continuous epidural analgesia is clearly in the best interest of the patient.

corneum cells may be carried during the use of a normal sharp bevel needle.[58] This does infer that the risk of epidermoid growth is negligible if using a non-styletted needle. Despite this recent reassuring report, it is still recommended to use the commercially available styletted caudal needles when performing caudal blocks in neonates.

Some relevant clinical key points regarding potential complications are listed in Table 2.

Dosage recommendations

When paediatric regional anaesthesia, and especially continuous epidural techniques, became popular during the late 1980s, no consensus existed regarding dosage guidelines. This resulted in a number of case reports of systemic toxicity, especially in the context of continuous infusion techniques. As a result of this, an APSF sponsored study was performed in the US. In this study, all children who had systemic toxicity had infusion rates in excess of 0.5 mg kg^{-1} h^{-1} of racemic bupivacaine.[59] Based on the results of this study, guidelines were issued for the safe dosage of racemic bupivacaine (Table 3).[59] Following the introduction of these guidelines, the incidence of systemic toxicity of local anaesthetics is more unusual, although toxicity due to inadvertent intravascular injection still occurs. However, it should be pointed out that using the maximum recommended dosage of racemic bupivacaine for continuous epidural infusions in neonates may result in borderline toxic plasma levels of bupivacaine, and infusions in excess of 48 h should only be used in infants who are judged to have considerable benefit of their continuous regional anaesthetic block.[60]

Since the introduction of the guidelines for racemic bupivacaine, new long-acting local anaesthetics (e.g., ropivacaine and levo-bupivacaine) have been introduced and some pharmacokinetic data are now available for these new agents in neonatal patients. Both these drugs are associated with a larger safety margin regarding systemic toxicity and are also associated with less motor blockade, both distinct advantages compared to racemic bupivacaine. With regard to the choice of ropivacaine or levo-bupivacaine, no decisive differences exist for paediatric use and the choice is up to personal preference or market availability.

In studies by Bosenberg et al., it has been shown that a caudal bolus injection of 3 mg kg^{-1} of ropicavaine or a continuous epidural infusion of 0.2–0.4 mg kg^{-1} h^{-1} of the same drug was clinically effective and did not result in excessive plasma levels of the drug.[61,62] Relevant pharmacokinetic information with regard to the use of levo-bupivacaine in neonates and small infants has also been

Table 3
Maximum doses of racemic bupivacaine, modified according to Berde.[59] Although it may be possible to use slightly higher doses of levo-bupivacaine or ropivacaine the author still recommends not exceeding the maximum doses outlined for racemic bupivacaine.

Bolus injection	
Neonates	1.5–2.0 mg kg^{-1}
Children	2.5 mg kg^{-1}
Continuous infusion	
Neonates	0.2 mg kg^{-1} h^{-1}
Children	0.4 mg kg^{-1} h^{-1}

published.[63] However, even if these new drugs appear to have a lower potential for systemic toxicity, it is still recommended not to exceed the maximum dosage limits as outlined by Berde.[59]

Local anaesthetics and adjunct drugs

The use of adjunct drugs to prolong and enhance postoperative analgesia is common in paediatric regional anaesthesia.[64,65] In a relatively recent survey, Saunders report that approximately 60% of UK paediatric anaesthetists routinely use adjunct drugs in combination with local anaesthetics for caudal blocks with ketamine and clonidine being the most commonly used.[64] The common use of adjunct drugs outside the UK has also recently been confirmed by data from Eich and Strauss.[65] In patients outside the neonatal age group, the use of a caudal block with a combination of S-ketamine and clonidine in saline (no local anaesthetics used) has been reported to produce good quality of postoperative analgesia during the first 24 h following inguinal hernia repair.[66]

While clonidine and ketamine represent the most commonly used adjunct drugs to enhance the effect of caudal blockade (Table 4), the use of other drugs has also been described. Unfortunately, the use of opioids has a questionable efficacy (with the only exception being preservative-free morphine) and opioids are also associated with a high incidence of side effects (e.g., PONV, pruritus and paralytic ileus), making their routine use highly debatable.[67] Like all new drugs, or new modes of drug delivery, the use of adjunct drugs should only be used routinely once there is good evidence for efficacy and safety.

In ex-premature babies scheduled for inguinal hernia repair, an awake regional technique (i.e., spinal or caudal blockade) is often used and advocated to avoid general anaesthesia and endotracheal intubation. In this setting, clonidine has been used to extend the duration of the block as well as to enhance postoperative analgesia.[13,19] However, the use of an awake regional technique in ex-premature babies does not rule out the risk of postoperative apnoea.[19] Thus, such patients must postoperatively be cared for in an environment that allows close supervision and monitoring during at least the first postoperative night even if only plain local anaesthetics are used. There are no data on how the use of clonidine influences the risk of apnoea.

No data with regard to adjunct use of drugs for continuous epidural analgesia or peripheral nerve blocks are currently available in the neonatal surgical population, but data from older children show that the adjunct use of clonidine for epidural analgesia is beneficial[68,69] as is the adjunct use of clonidine in peripheral nerve blocks.[70]

The evidence base for neonatal regional anaesthesia

A large number of published studies have shown that the use of diverse regional anaesthetic techniques is associated with high-quality pain relief following the different types of surgery and

Table 4
Adjunct drugs used to enhance the effects of local anaesthetics in children; from Mazoit & Lönnqvist.[73]

	Dose
Morphine	
Caudal/epidural bolus	33–50 mcg/kg
Fentanyl	
Caudal/epidural bolus	1.0–1.5 mcg/kg
Epidural infusion	5 mcg kg^{-1} 24 h^{-1}
Sufentanil	
Epidural bolus	0.6 mcg/kg
Epidural infusion	2 mcg kg^{-1} 24 h^{-1}
Clonidine	
Caudal/epidural bolus	1–2 mcg/kg
Epidural infusion	$\geq$0.1 mcg kg^{-1} h^{-1}
Ketamine	
Caudal bolus, racemic ketamine	0.25–0.5 mg/kg
Caudal bolus, S(+) ketamine	0.5–1.0 mg/kg

painful procedures that are commonly performed in neonatal patients. Apart from pain, few studies have examined other outcomes in this setting. Some data suggest a benefit with regional anaesthesia. In a retrospective study, Bosenberg et al. found that the use of epidural analgesia in neonatal patients undergoing tracheo-oesophageal fistula repair resulted in a reduced need for postoperative mechanical ventilation.[24] Furthermore, epidural analgesia was found to be associated with a significant and beneficial modification of the neuroendocrine surgical stress response after major abdominal surgery in infants when compared with postoperative morphine infusions.[25] The use of local anaesthetics in association with neonatal circumcision has also shown a benefit as neonates not treated with EMLA or a penile block had an exaggerated pain response to later vaccinations as compared with neonates treated with a local anaesthetic technique.[3,71] Finally, safety data generated from large, prospective studies and audits[10,27] clearly show that the use of paediatric regional anaesthetic techniques is associated with adequate safety also in neonatal patients.

In conclusion, a large variety of local and regional anaesthetic techniques can be safely used in neonatal patients. The use of such techniques must obviously be associated with sufficient knowledge about the various techniques, as well as adherence to adequate dosage guidelines and other safety precautions. However, if these prerequisites are met, regional anaesthesia may offer great advantages to our smallest and most vulnerable patients.

Practice points

- Regional anaesthetic techniques can be used in all paediatric age groups including neonates and premature babies.
- Both central and peripheral nerve-blocking techniques are associated with adequate safety if performed according to established practice.
- As in adult regional anaesthesia practice, the current trend in paediatrics is to more frequently use peripheral nerve blocking techniques as compared with central approaches, including the use of continuous catheter techniques.
- The use of ultrasound guidance offers clear advantages when used in association with most peripheral nerve-blocking techniques. The advantages, when used in association with central nerve blocks, are less clear at present.
- Clonidine can be used as an adjunct both to central and peripheral nerve blocks.
- An emerging trend in paediatric regional anaesthesia is the use of wound catheter techniques.

Research agenda

- Regional anaesthetic techniques should be compared with general anaesthesia in premature babies and neonates to investigate if regional techniques may prove beneficial with regard to the currently much-discussed issue of apoptosis.
- Regional anaesthetic techniques should be compared to other methods of postoperative analgesia in neonatal surgery with regard to clinically significant differences in morbidity, mortality and length of hospital stay.
- Further studies comparing central versus peripheral nerve-blocking techniques concerning quality of analgesia, incidence of side effects and risk of potential complications are clearly indicated.
- Further adjuncts to local anaesthetics should be investigated for use in children and neonates following adequate safety and efficacy trials performed in animals and adults.

Conflict of interest statement

None.

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Neonatal apnoea

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Premature infants have immature respiratory control that predisposes them to apnoea, haemoglobin oxygen desaturation and bradycardia. Apnoeas are loosely classified, according to the presence or absence of respiratory effort, into central, obstructive or mixed.

There are a variety of conditions, in the perioperative period, that predispose an infant to apnoea, including: central nervous system (CNS) lesions, infections and sepsis, ambient temperature fluctuations, cardiac abnormalities, metabolic derangements, anaemia, upper airway structural abnormalities, necrotising enterocolitis, drug administration (including opiates and general anaesthetics) and possibly gastro-oesophageal reflux.

Various monitoring techniques are discussed; the mainstay are pulse oximetry and abdominal-pressure transduction. There is some evidence of both short- and long-term complications of repeated apnoeas in the neonatal period, but the causal relationship is difficult to establish.

Continuous positive airway pressure and caffeine therapy (up to 10 mg kg^{-1}) are the most common treatments of neonatal apnoea. The less soluble volatile agents and regional anaesthetic techniques (without concurrent sedation) are associated with a lower incident of postoperative apnoea.

Apnoea of prematurity

The physiological changes required to progress from foetus to neonate are large. There are complex physiological mechanisms that facilitate the transformation from dependence on maternal placental circulation to life as a separate stand-alone organism. Being born prematurely throws the evolved transformational process into disarray; previously physiologic reflexes become detrimental and certain reflexes needed for independent living have not yet developed.

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Premature infants have immature respiratory control resulting in a propensity for respiratory apnoeas, which increases with increasing prematurity and improves as the infant reaches term-corrected age. Apnoeas can occur spontaneously in premature infants but can be provoked, or the frequency or duration increased, with certain physiological insults. There are some reports that apnoeas >20 s may be associated with impaired neurodevelopmental outcome.[1]

There are a number of questions of particular relevance to the anaesthetist involved in the care of these infants:

- What are apnoeas and why do they occur?
- What conditions are associated with apnoea?
- Do apnoeas matter and if so, how can we minimise the perioperative risk?

Classification of apnoea

Neonatal apnoea is usually defined as a cessation of respiratory flow and is considered to make a classical triad of signs with oxygen desaturation and bradycardias, but is also commonly associated with sudden onset of palor and hypotonia. Exact definitions vary as to the required duration of airflow cessation to constitute an apnoea, which reflects the uncertainty of the significance of apnoea duration. The American Academy of Pediatrics defines apnoea as a respiratory pause of >20 s; however, a more common definition is a pause of >15 s or <15 s if the apnoea is associated with a desaturation or bradycardia. The definition of a significant desaturation or bradycardia is similarly inconsistent and includes a haemoglobin saturation falling to <90%, <80% or a change of >20% of the pre-existing value; a bradycardia is most commonly defined as heart rate <100 beats per minute (bpm).

Apnoeas have been subclassified into central, obstructive or mixed, depending on the presence of respiratory effort and upper-airway obstruction (Figs. 1 and 2). These distinctions are becoming less clear-cut as, for example, there is evidence that central apnoeas can occur with airway obstruction: 'silent obstruction'. Pure-central apnoeas and obstructive apnoeas account for approximately 20% each of all causes with the majority (over 50%) of all apnoeas being of mixed origin.[2]

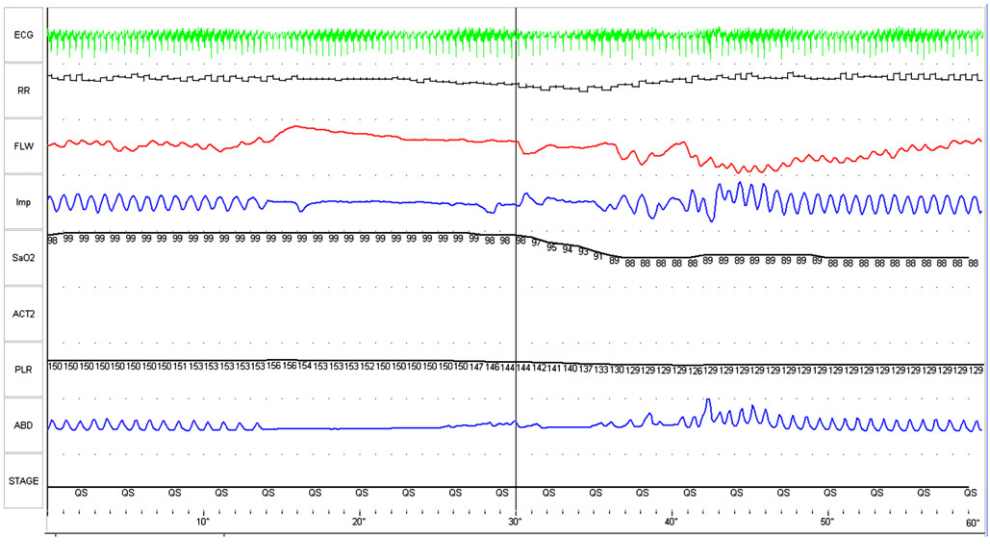

Fig. 1. Central apnoea. FLW, imp and ABD all cease. After 15 seconds the patient begins to desaturate. There is spontaneous resolution but delayed resolution of the desaturations. Polysomnographic monitoring of a neonate. ECG – electrocardiogram, RR – R-R interval, FLW – nasal thermistry, imp – thoracic movement derived from ECG impedence, SaO2 – saturation, ACT2 – movement sensor on lower limb, PLR heart rate from SaO2 channel, ABD – Respiratory inductance plethysmography. Stage – this channel is not used.

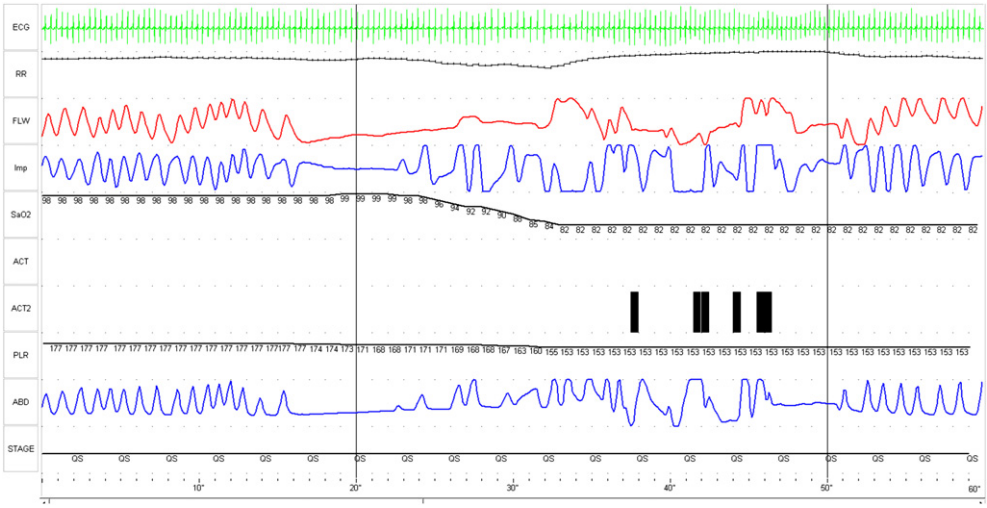

Fig. 2. Mixed apnoea. There is initial central apnoea lasting approximately 6 seconds after which there is respiratory effort (imp and ABD channel activity) but no flow until at least 15 seconds (FLW channel), the patient desaturates to 82% and becomes aroused (movement demonstrated via ACT2 channel). Polysomnographic monitoring of a neonate. ECG – electrocardiogram, RR – R-R interval, FLW – nasal thermistry, imp – thoracic movement derived from ECG impedence, SaO2 – saturation, ACT2 – movement sensor on lower limb, PLR heart rate from SaO2 channel, ABD – Respiratory inductance plethysmography. Stage – this channel is not used.

Apnoeas occur in 7% of babies born between 34 and 35 weeks, 14% born between 32and 33 weeks, 54% between 30 and 31 weeks and in 80% of neonates born <30 weeks gestation.[3] While most apnoeas resolve by the time the infant reaches 37 weeks post-conceptional age (PCA), 80% of very low birth-weight infants, in one study, still had significant apnoeas at 37 weeks.[1]

Central apnoea occurs when airflow ceases in the absence of respiratory effort. In obstructive apnoea, there is no flow but the infant attempts to breathe throughout the pause, that is, has continuous thoracic and abdominal movement throughout the apnoea. Mixed apnoeas usually start with a central apnoeic phase, followed by upper-airway obstruction. The site of obstruction is not entirely understood, but is a combination of passive pharyngeal collapse and either active or passive laryngeal closure.[2]

Ruggins and Milner used a fibre optic scope to visualise the larynx of 12 infants having apnoeic episodes and found the larynx to be closed in some central apnoeas.[4] Al-Sufayan et al. used a different method of determining upper-airway closure: they used the presence or absence of magnified cardiac-airflow oscillations to infer whether the airway was open or closed. They found that 'silent' airway closure occurred in 20% central apnoea and preceded 59% of mixed apnoeas.[2] Closed glottis during a central apnoea may confer benefit by maintaining lung volume and providing auto-peep, thereby maintaining oxygenation, although this was not found to be the case in the 15 neonates observed by Al-Sufayan. Conversely, return of spontaneous ventilation with a closed airway (turning a central apnoea into a mixed apnoea) may trigger inhibitory cardio-respiratory reflexes prolonging the apnoea and worsening the hypoxaemia. Purely obstructive apnoea is usually associated with an anatomical or positional cause and is otherwise unusual.

Another breathing pattern often observed in infants is periodic breathing, consisting of three or more respiratory pauses of >3 s with <20 s of normal respiration between the pauses (Fig. 3). This is considered normal in term infants, but can be associated with hypoxaemia in premature infants.[5]

Physiology of control of breathing

The purpose of the respiratory control system is to maintain normal partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2) and hydrogen ion concentration (pH) in the face of

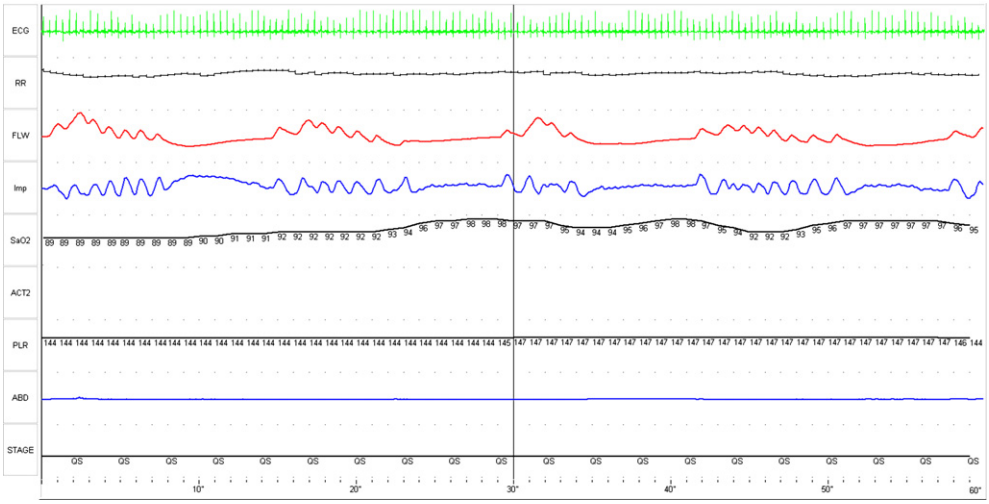

Fig. 3. Periodic breathing. Polysomnographic monitoring of a neonate. ECG – electrocardiogram, RR – R-R interval, FLW – nasal thermistry, imp – thoracic movement derived from ECG impedence, SaO2 – saturation, ACT2 – movement sensor on lower limb, PLR heart rate from SaO2 channel, ABD – Respiratory inductance plethysmography. Stage – this channel is not used.

large changes in oxygen (O_2) consumption and carbon dioxide (CO_2) production. This complex control involves central and peripheral chemoreceptors, irritant and mechanoreceptors and central brainstem processing.

Central control of breathing starts in the inspiratory centre in the medulla oblongata and operates as a negative feedback system. The brainstem controls the periodicity of respiration and receives afferent input from the upper airways, the lungs and the peripheral and central chemoreceptors, through the vagus and glossopharyngeal nerves. It controls respiration by oscillating between three distinct respiratory phases: inspiration, post-inspiration and expiration. Efferent control occurs through the vagus (laryngeal nerves), the phrenic and the intercostal nerves. Various endogenous neuroregulators either stimulate or inhibit the respiratory centre, including adenosine, gamma-aminobutyric acid (GABA), serotonin, endorphins and prostaglandin. It is through these neuroregulators that drugs administered to the infant will affect breathing.[6,7]

Central and peripheral chemoreceptors located in the aorta, the carotid arteries and the brain, further control the basic respiratory pattern. Peripheral chemoreceptors in the carotid body contain specialised cells that detect oxygen. The chemoreceptors are sensitive to CO_2, pH, glucose, osmolality and temperature changes. The laryngeal mucosa is sensitive to chemical or mechanical stimulation, which will cause a strong inhibitory reflex – the laryngeal chemoreflex.

There is a complex coordination of upper-airway muscles of the pharynx and larynx, the diaphragm and the chest-wall muscles that ensures that the airway and larynx dilate during inhalation, thereby improving airflow. This complex control is also responsible for the protective laryngeal chemoreflex, which causes glottic closure by the laryngeal adductors in response to laryngeal stimulation. Glottic closure is also important for maintaining lung volume through end expiratory braking or 'glottic stop'.[8]

Stretch receptors in the lungs cause reflex negative feedback to respiration. The Herring–Breuer inflation-stretch reflex results in a decrease in respiratory drive whilst the deflation reflex leads to an increased respiratory rate.

The change from foetus to neonate

The foetal milieu is markedly different from that of the neonate: foetal respiratory efforts result in no change in arterial O_2 and CO_2; the foetus will become apnoeic when hypoxic, which confers some

advantage by decreasing oxygen consumption, but may be a detrimental reflex as a neonate; partial pressure of oxygen in arterial blood (PaO_2) changes from 25 mmHg as a foetus to 50 mmHg in the first few breaths of extra-uterine life, rising to 70 mmHg in the first few hours. Consequently, this relative excess of oxygen renders the carotid bodies insensitive to oxygen changes until they get reset.

Foetal breathing movements begin at about 10 weeks of gestation and increase as the foetus develops towards term. These movements are paradoxical and asynchronous and, as the foetus approaches term, occur only in rapid eye movement (REM) sleep. The foetal response to hypoxia is a decrease in respiratory effort and to hypercapnia is an increase in breathing depth, but not frequency.[8] These foetal reflexes change over the first few weeks of life to become more like the normal adult reflex: hypoxia and hypercapnia both causing reflex increase in respiration. It is during this maturation phase that both term and pre-term infants are at risk of apnoeas, following a hypoxic stimulation. The pre-term neonate will show foetal respiratory characteristics such as periodic breathing and paradoxical ventilation. Poor synchronisation of the respiratory phase and respiratory muscular control, combined with weak, easily fatigable muscles, predisposes the neonate to airway obstruction (as the diaphragm contracts, creating a negative intrathoracic pressure, the chest-wall is unable to be stabilised effectively causing paradoxical inward-chest movement and higher likelihood of obstructive apnoea).

Neonates exhibit a biphasic response to hypoxia; if they receive a hypoxic gas mixture they will initially have increased respiratory drive; however, this drive will subsequently diminish and the neonate will become apnoeic. This late ventilatory depression is possibly mediated through descending inhibitory-pontine tracts.[9] This response continues for about 3 weeks in term neonates. Hyperoxia, by silencing the carotid body, can induce irregular respiratory patterns and apnoeas.

The neonatal response to hypercapnia, unlike the response to hypoxia, is similar to adults. The central chemoreceptor response is initially down-regulated in pre-term neonates, more so in those pre-term neonates that exhibit frequent apnoeas, when compared with age-matched controls. The degree of the increased ventilatory drive, to raised PCO_2, increases with both gestation and postnatal age and reaches adult levels by about 4 weeks of age. The response to hypercapnia increases with increasing postnatal age and with increasing gestational age. These responses are impaired in apnoeic infants.[10]

Physiological features

Apnoea is the end result of immaturity of the regulation of breathing, immature response to hypoxia and hypercapnia and an exaggerated response to stimulation of the upper airway. There is poor myelination of the brainstem with reduced dentritic arbourisation and fewer synaptic connections.[11] The pre-term brain is more sensitive to the inhibitory neurotransmitters such as GABA and adenosine; up-regulation of the GABA receptor seems to have an important role in apnoea, resulting from hypoxia and hypercapnia.

All types of apnoea are usually preceded by a period of ventilatory disruption with short apnoeas and periods of hypoventilation preceding a prolonged clinically significant apnoea. Central apnoeas and mixed apnoeas are closely related; the occurrence of either results from failure of the coordination of the diaphragmatic stimulation and upper-airway dilation. Central apnoeas occur either following stimulation of the laryngeal or mechano-stretch receptors or as a result of hypoxia, hypercapnia or acidosis – the second phase of the biphasic reflex. Upper-airway closure occurs in up to 47% of central apnoeas and in all central apnoeas >20 s.[12] This is as a result of loss of upper-airway tone; mixed apnoeas occur when the central apnoea is prolonged by airway obstruction, thereby speeding up the onset of hypoxaemia and bradycardia.

Whatever the exact aetiology, the neonate's low functional residual capacity, coupled with a relatively high metabolic rate ensures that onset of hypoxaemia is rapid, following apnoea.

Oral and pharyngeal receptors have afferent input through the superior laryngeal nerve and, in response to low chloride-containing fluid, will elicit a powerful airway protective reflex of glottic closure, swallowing and apnoea. This reflex is exaggerated in the pre-term.[6]

Associated conditions causing apnoea

Immature respiratory control is the primary underlying cause of apnoea of prematurity; however, there are many co-existing conditions that may either predispose or worsen apnoea (Table 1). These should be specifically excluded in any infant with apnoeas being considered for theatre. Prudent screening investigations to be considered in such an infant will include lumbar puncture, urinalysis, viral screen, serum electrolytes, calcium, haemoglobin, chest X-ray and cranial ultrasound.

The relationship between gastro-oesophageal acid reflux (GOR) and apnoea is much discussed in the literature, but remains confused. GOR is very common in newly born infants. This is presumed to be due to decreased gastric compliance, increased oesophageal compliance and immature motor control of gastric emptying. There is some evidence that supports the link between GOR and apnoeas[13], but there is more suggesting a lack of causal relationship that concludes that they are both frequently occurring events and will co-exist in the majority of pre-term infants.[14–16] Many of these studies use pH monitoring with a $pH < 4$ considered as evidence of reflux; some evidence suggests that higher pH reflux occurs and is temporally associated with apnoeas and bradycardias through vagal reflex. Paul and colleagues investigated 29 infants born before 36 weeks gestation. They used comprehensive polygraphic monitoring to investigate the cause of apnoeas in infants, who had not responded positively to aminophylline therapy. They found a temporal relationship between the onset of apnoea and electroencephalographic (EEG) and electromyographic (EMG) signs of arousal, rather than inhibition. They also found that bradycardias were frequently not associated with hypoxaemia and thus were symptoms of vagal reflex. Anti-reflux treatment improved apnoeas in the subgroup of infants, who had not demonstrated an improvement following methylxanthine therapy.

Any central nervous system (CNS) lesion can predispose to apnoeas, including intracranial haemorrhage, seizures and hypoxic ischaemic encephalopathy. Apnoea may also be associated with infection and may be the presenting sign, prior to the development of other systemic manifestations. It is associated with systemic sepsis, bacteraemias from colonised intravenous catheters or localised infections such as abscesses.

Several drugs are known to predispose the infant to apnoea. General anaesthetic agents, magnesium, prostaglandin (PGE1) and opioid drugs (used for analgesia or sedation of the ventilated infant) have all been implicated in the aetiology of apnoeas.

Anaemia has been considered to increase the risk of apnoea; Cote, in his combined analysis of available studies investigating the effects of anaesthesia on postoperative apnoea, found a haemoglobin less than 8 g/dL to be a significant risk factor, particularly in infants over 43 weeks post-conceptual age. It is assumed that the lower oxygen carrying capacity of the anaemic patient leads to a hypoxia-induced respiratory depression and red-cell transfusions have been found to reduce short respiratory pauses.[17] However, recent investigations have not corroborated this assumption. Poets studied 21 preterm infants (median gestational age 28 weeks) and found that red cell transfusion made no difference to the frequency of significant apnoeas although there was a trend to shorter apnoeas.[18]

Neonates, when compared to older infants, have softer, more compliant soft tissues in their upper airway and neck that makes positional obstruction more likely. Therefore care needs be taken with

Table 1
conditions associated with increased prevalence of apnoeas in the preterm infant.

Gastro-oesophageal reflux
Central nervous system lesions: intracranial haemorrhage, seizures
Infection: systemic or localized, NEC, meningitis
Ambient temperature fluctuations: hyperthermia, hypothermia
Cardiac abnormalities: patent ductus arteriosus, heart failure
Post immunization
Metabolic derangements: glucose and electrolyte imbalances
Drug administration: opioids, prostaglandin (PGE1), magnesium, general anaesthesia
Anaemia
Upper airway obstruction: macroglossia, micrognathia, choanal atresia
Abdominal distention: NEC
Chronic lung disease of prematurity

positioning, avoiding excessive flexion of the head and neck; this can occur easily if care is not taken. Special vigilance needs be taken in the postoperative period when the infant is recovering from anaesthesia and is at a much higher risk. Neonates are predominately nasal breathers but will breathe through the mouth if the nose is blocked with tubes or oedema; however, in the preterm, the oral-airway resistance is higher than the term infant, which may contribute to apnoeas. Upper airway secretions can stimulate the laryngeal chemoreflex causing glottic closure.

Gastric and abdominal distension can cause respiratory compromise and predispose to apnoeas and bradycardias either through vagal stimulation or as a direct mechanical effect leading to a decrease in lung volume and accelerated hypoxaemia.

Chronic lung disease of prematurity predisposes infants to apnoeas; decreased lung compliance and increased lowerairway resistance contribute to poor oxygenation and are associated with a decreased responsiveness of the peripheral chemoreceptors. One explanation for this unresponsiveness is that during the first few weeks of life the infant is exposed to a hyperoxic environment causing abnormal maturation of the peripheral chemoreceptors.[5]

Monitoring techniques

Monitoring for apnoeas with at-risk infants is essential. There are a variety of monitoring techniques available. The most simple is an abdominal pressure sensor: a diaphragm taped to the anterior-abdominal wall transmits a small pressure change to a sensing box that alarms if abdominal movement stops for a defined period. Most neonatal unit cardio respiratory monitors utilise transthoracic impedance pneumonography: electrodes are placed on either side of the infant's chest, above and below the diaphragm; as air flows into and out of the chest, the electrical impedance between the electrodes changes as air has low impedance. The monitor can then display a live respiratory waveform and a calculated respiratory rate. This monitoring technique will usually be used in conjunction with (SpO_2) monitoring. SpO_2 monitoring alone is usually insufficient as it is associated with a high degree of movement related false alarms; desaturation events have been excluded as alarm triggers in many studies using home pulse oximetry.[19] However, newer movement resistant pulse oximeters may prove to be more reliable indicators of true hypoxaemic events.[20]

A major problem with impedance pneumonography is that it is unable to identify obstructive apnoeas; chest and abdominal movement in the absence of upper-airway airflow will cause intrapulmonary gas flows and will result in similar impedance changes to normal respiration. Nasal thermistry can be used to detect oral or nasal gas flow and will identify both central and obstructive apnoeas. Nasal thermisters or thermocouples are devices that detect the temperature changes during both inspiration and expiration. These devices are surprisingly well-tolerated being attached above the upper lip. They have a non-linear relationship to flow and cannot be relied on to provide any quantitative measurement of flow.

Respiratory inductance plethysmography measurements can estimate the tidal volume using coil bands around the infant's chest and abdomen. The chest and abdominal excursions are then summated and, following calibration, a tidal volume can be derived. However, the calibration of the bands is very sensitive to positional change; every time the infant moves, calibration needs to be repeated. This monitoring method is more useful as a qualitative measurement: it has the advantage of being able to distinguish between central and obstructive apnoeas. During an obstructive apnoea, the paradoxical chest and abdominal movements will summate to approximately zero. It is to be noted that some degree of paradoxical breathing is a normal physiological feature of REM sleep in newborns due to the inhibition of postural muscles and the increased chest-wall compliance.

Consequences of apnoeas

Short term

Apnoeas, by themselves, do not pose any threat to the neonate. However, the associated cardio-respiratory manifestations can cause detrimental outcome, especially in the pre-term neonate. These manifestations include hypoxaemia, hypercarbia, bradycardia and changes in blood pressure.

If apnoea is the first event and is significant for that neonate, then hypoxaemia may follow, associated with a reflex bradycardia, mediated by the peripheral chemoreceptors in the carotid body. The speed of onset and severity of the hypoxaemia will depend on the baseline haemoglobin oxygen saturations, the functional residual capacity and the degree of intrapulmonary shunting. When the neonate's saturation and lung volumes are both low to begin with, then, an apnoea will result in accelerated hypoxaemia and cause further loss in lung volume.

Bradycardia can also occur simultaneously with the apnoea, prior to hypoxaemia, as the result of a direct inhibitory vagal reflex following pharyngeal and laryngeal stimulation (such as insertion of a laryngoscope) or following tracheal or pharyngeal suction. Bradycardia may initially be associated with an increase in stroke volume and pulse pressure; however, if it persists, then the blood pressure will fall resulting in a reduction of major-organ perfusion, including the brain.

Near-infrared spectroscopic examination of neonates' brains has shown a relationship between apnoeas associated with bradycardia and desaturation below 85%, and reduced cerebral oxygenation and blood volume.[21] Heart rates below 80 bpm decrease blood-flow velocity in the anterior-cerebral arteries. Following severe prolonged apnoea, the associated hypoperfusion and the subsequent potential compensatory hyperperfusion may contribute hypoxic-ischaemic injury to the pre-term neonatal brain.[22]

Long term

The long-term consequences of recurrent apnoea remain controversial. A problem with many studies of premature neonates is establishing causal relationships in patients with severe co-existing medical problems. Linking recurrent apnoeas with poorer neurodevelopmental outcome is difficult. Janvier, in a study of 175 pre-term, very low birth weight (VLBW) neonates found an increased number of apnoeas to be associated with neurodevelopmental impairment defined by either a Bayley Mental Developmental Index <70 or Psychomotor Index <70, blindness or cerebral palsy. However, this study could not identify whether the apnoeas were the cause of the neurological impairment or a result of neurological damage by an undetermined cause.[23]

The other important question is whether neonatal apnoeas predispose the infant to other cardio-respiratory complications. Although infants born before 32 weeks gestation have a three-times- higher risk of sudden infant death syndrome (SIDS), there appears to be no link with history of apnoeas in these infants. Incidence of SIDS in the formerly premature infants is closely associated with socio-economic and demographic factors such as maternal age, tobacco smoking and number of previous pregnancies and is not associated with infants, who have had pre-existing respiratory-control abnormalities.[24]

Established preventative therapies

Methylxanthines

Methylxanthines have been used in clinical practice for over 30 years and are still very popularly prescribed drugs in the neonatal period. Caffeine is the most commonly used methylxanthine; it has a safer profile with a wider therapeutic window than theophylline and aminophylline; consequently, blood levels are not routinely monitored. Caffeine has an elimination half-life of 100 h compared with 30 h for theophylline.[5]

Methylxanthines reduce the severity of apnoeas and the requirement for intermittent positive pressure ventilation for treatment of severe apnoeas in the 2–7 day period after starting treatment.[25] They block two sub-types of adenosine receptors; however, the exact mechanism by which they reduce apnoea is not known.[26] Recent work by Abu-Shaweesh and colleagues suggests that the mechanism of apnoea reduction of methylxanthines is through central blockade of the adenosine A_{2A} receptors on GABAergic neurons, thereby preventing the release of GABA and diminishing respiratory inhibition.[11] Possible mechanisms include improved respiratory muscle function, generalised CNS stimulation and enhanced chemoreceptor responsiveness to CO_2. Several systematic reviews of methylxanthine effects have been published in the Cochrane library supporting the efficacy of methylxanthines for the treatment and prevention of apnoeas.[27–29]

The long-term safety is also little understood; there is some evidence that non-specific adenosine blockade in the very premature infant has some deleterious effects on neurological and cognitive development in later childhood and can result in behavioural problems.[30] It is known that methylxanthines increase energy expenditure and oxygen consumption; in a small pre-term infant, this may be enough to decrease growth.

Adenosine has been found to be neuroprotective during acute hypoxia and ischaemia and as methylxanthines block adenosine receptors, it is possible that they may actually worsen the hypoxic–ischaemic injury in high-risk pre-term neonates. A large prospective trial is underway with over 2000 VLBW infants having been recruited into the caffeine for apnoea of prematurity (CAP) trial that is following up the infants for 5 years with outcomes to include tests of cognition, neuromotor function and higher executive function. An interim 18-month follow-up of these children has revealed that those treated with caffeine as neonates had significantly improved survival without neurodevelopmental disability.[31]

Caffeine and general anaesthesia

There are three small studies investigating the efficacy of caffeine at reducing postoperative apnoea and hypoxaemic events following general anaesthesia; they all compared a single intra-operative dose of caffeine (either 5 or 10 mg kg^{-1}), to placebo.[32–34] All infants were born between 30 and 32 weeks of gestation and received the anaesthesia at 40–44 weeks of postmenstrual age. The Cochrane meta-analysis of these studies found that the absolute risk difference for postoperative apnoea was −0.58, indicating that less than two infants needed to be treated with a single dose of caffeine to prevent one postoperative apnoea. However, the clinical significance is not certain as no infant in any trial required intubation and mechanical ventilation and no adverse incidents were reported in either treatment group.[27]

Doxapram

Doxapram, similar to the methyl xanthines, stimulates breathing. Its action is on both the central and peripheral chemoreceptors and causes an increase in tidal and minute ventilation and inspiratory flow.[35] It is usually used as an intravenous preparation as the bioavailability after oral preparations is only 50%. Short-term side effects include hypertension, gastrointestinal disturbances, heart block and excessive CNS stimulation. Sreenan observed an association between the dose and duration of doxapram administration for severe apnoeas in infants weighing under 1250 g and isolated mental developmental delay.[36] Although the causal relationship is unclear, the underlying cerebral dysfunction may be presenting in these infants as apnoea and be unrelated to the doxapram administration. Only one study compares doxapram with placebo. There was some short-term benefit in the doxapram treatment group, but this benefit was not sustained beyond 48 h and the numbers were too small to draw conclusions either way as to the benefit or harm of doxapram.[37] There are insufficient data to recommend doxapram for the treatment of apnoeas in infants, and more research is needed.

Carnitine

Carnitine is a quaternary amine that is essential for the transport of fatty acids across the mitochondrial membrane for beta-oxidation metabolism. It is synthesised from the amino acid, lysine. Carnitine deficiency results in reduced mitochondrial availability of long-chain fatty acids and consequent decreased energy production in the muscles.[38] Pre-term infants have been observed to have lower carnitine levels than term infants. This seems to be related to immature biosynthesis pathways and reduced dietary intake from breast milk and parenteral nutrition solutions. Iafolla noticed a reduction in episodes of apnoea and periodic breathing following 48 h oral carnitine treatment in a report of two infants.[39] However, there is insufficient evidence to recommend the use of carnitine currently.

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) at 4–6 cm H_2O reduces the incidence of obstructive and mixed apnoeas, but not central apnoea. CPAP can be delivered through nasal prongs, nasal cannulae or a nasal mask with low bulk, portable equipment. The most common anatomical sites for airway obstruction in the neonate are the upper pharynx and the entrance to the larynx; CPAP will distend the upper airways preventing anatomical obstruction. The incidence of pure central apnoeas will not be reduced by CPAP but the obstructive component that can occur silently at the end of the central pause will be reduced. Longer central apnoeas are mostly associated with an obstructive contribution prolonging the apnoeic period. CPAP will also increase functional residual capacity and may reduce intrapulmonary shunting by distending and recruiting alveolar units; these combine to improve oxygenation and provide more oxygen reserve such that hypoxaemia onset is delayed if an apnoea does occur. The use of high-flow nasal cannulae therapy is increasingly used as a convenient, more portable alternative to CPAP delivery devices but the safety of the unregulated high flow has not been fully investigated.

Treatment

Most apnoeas are self-limiting and require no intervention. However, additional intervention may be required to avoid harmful consequences. Tactile stimulation is the first intervention, which will often terminate the apnoea by providing general CNS stimulation. When tactile stimulation is insufficient, rapid progression to more invasive interventions such as positive pressure ventilation is needed. Increased fraction of inspired oxygen may be needed in the acute treatment of a prolonged apnoea, but should be used cautiously as fluctuations in PaO_2 and relative hyperoxia may contribute to post-apnoea respiratory instability.

Anaesthesia

For over 10 years, it has been the understanding and common teaching in paediatric anaesthesia that formerly premature infants, following a general anaesthetic, have a higher risk of postoperative ventilatory complications. Furthermore, having a regional anaesthetic technique (either spinal and/or caudal anaesthesia) without the use of sedative agents may confer some protection from these respiratory complications. There is evidence that this is correct for the older volatile general anaesthetic agents including halothane, enflurane and isoflurane, but the evidence is controversial for the newer less-soluble anaesthetic agents, sevoflurane and desflurane.[40] Respiratory complications are the most frequently occurring anaesthesia-related complications in this age group with hypoxaemia, airway obstruction and apnoeas being much more common than in the older infant.[41]

General anaesthetic agents, inhalational and intravenous, produce a dose-dependent depression in conscious level and produce a similar depression of ventilatory control. Inhalational anaesthetics produce a dose-dependent flattening and right shift of the CO_2-ventilation response: with increasing Anaesthetic concentration a higher partial pressure of carbon dioxide in arterial blood ($PaCO_2$) results in the same ventilation.[42–44] Anaesthesia may also enhance the primitive reflexes that result in a greater susceptibility to apnoeas.

Cote performed a combined analysis of the original data from all available studies investigating apnoeas in infants prior to 1995. He included eight studies and concluded that the main determinants of risk of postoperative apnoea were gestational age and PCA, the presence of continuing apnoeic episodes at home and anaemia (haematocrit $<30\%$), especially in the older infants. Infants with a gestational age of 35 weeks had a risk of postoperative apnoea of more than 5%, up to a PCA of 48 weeks. Infants, who are 'small for dates' had a lower incidence of apnoea compared with gestation–matched infants, who had an appropriate weight.[45]

Unlike volatile anaesthesia, awake regional anaesthesia does not appear to exacerbate this background incidence of ventilatory disturbance[46,47], but spinal anaesthesia has a significant failure rate of 10–20% and has not been widely adopted as a technique.[48–50] Caudal anaesthesia, in awake

infants, has been described, but is technically difficult and has problems of limited duration.[51] An alternative technique is to use light general anaesthesia and a caudal epidural block with local anaesthesia. The newer inhalational agents, desflurane and sevoflurane, have enhanced recovery characteristics compared with other volatile agents, including isoflurane. Desflurane confers the fastest emergence time with sevoflurane, up to 50% slower, and isoflurane, twice as long, following an anaesthetic duration of less than 1 h.[52–54] There is some evidence that this difference in emergence times will become even more pronounced after longer duration anaesthetics as desflurane does accumulate in the tissues as readily as the more fat-soluble agents, sevoflurane and isoflurane.[55]

Opioids produce a dose-dependent respiratory depression with decreased responsiveness to CO_2, characterised by a right shift of the CO_2-response curve without the flattening. Opioids also interfere with the periodicity of breathing and may cause respiratory pauses, periodic breathing and apnoeas.[42]

The author, along with colleagues, studied 30 premature infants having inguinal herniorrhaphies under general anaesthesia. The infants were randomly allocated to receive either desflurane or sevoflurane as the sole centrally acting agent for their procedure. Comprehensive polysomnographic monitoring was applied to the infants for a 12-h period before surgery and for the first 12 h postoperatively.[53] The monitor recording was then analysed in 30 s windows and all desaturations, bradycardias and apnoeas were confirmed and classified (Figs. 1–3 were obtained from this study). We were unable to demonstrate differences between the two groups in terms of postoperative apnoea, or the relationship of pre- and postoperative respiratory events within the groups. This lack of change, associated with surgery and anaesthesia, was interesting and unexpected. Despite comprehensive monitoring, we could not show a relationship with either desflurane or sevoflurane in terms of an increase in postoperative respiratory events, as previously demonstrated. While several patients had a considerable increase in apnoea rate in the postoperative period, a large proportion had a reduction in observed apnoea. Also of note was the lack of temporal relationship between the events and the timing of the anaesthetic. The events were scattered throughout the 12-h observation period. If there were a significant link between general anaesthesia and respiratory events, it would be expected that the events would, as in previous studies, be grouped early in the postoperative period. However, this was not the case. Whilst it is not advisable to draw conclusions from such a small study, this does support the hypothesis that the newer insoluble anaesthetic agents provide a safer perioperative course for these high-risk infants.

While there are currently no large, prospective, population studies in this field, there are two recent retrospective institutional audits that add much interest to this debate. Kim and colleagues from the Children's Hospital of Eastern Ontario,retrospectively studied a series of 133 pre-term infants having inguinal herniorrhaphies.[50] A total of 63 infants had a successful spinal anaesthetic, without sedation; a total of 60 infants had a general anaesthetic and nine infants had a spinal anaesthetic, but subsequently required a general anaesthetic as the spinal anaesthetic was inadequate. The overall incidence of apnoea was 10.5% with an incidence of 6.3% in the spinal group and 10% in the general anaesthesia-alone group (no statistical difference between the groups). Of the nine infants, who had failed spinals, four had apnoeas (44.4%); it has been postulated that the sedative effect of neuroaxial blockade acts synergistically with the additional sedation.[56] This has the effect that these infants are at much greater risk of postoperative apnoea than either of the other groups. Davidson and colleagues conducted a similar retrospective audit of 127 infants and used logistic regression to identify risk factors for 'early' (within 1 h) and 'late' apnoea.[48] They concluded that, while it is difficult to predict which infants are at risk of early apnoeas, spinal anaesthetic alone confers low risk and, similar to Kim, they found that a failed spinal with subsequent general anaesthesia confers high risk. They found late apnoeas to be more strongly associated with low post-menstrual age (PMA) than either the type of anaesthesia, the gestation at birth or the weight. As these studies were both retrospective, they relied on case-note recording of significant apnoeas by the post anaesthesia care unit (PACU) and ward staff; the overall number of apnoeas in both studies was considerably lower than the author's study using comprehensive polysomnographic monitoring; this calls into question the clinical significance and validity of such sensitive monitoring. It is uncertain whether clinically unrecognised apnoeas are important to the developing infant.

Practical management options

Several questions should be answered when considering a neonate for surgery:

- What are the risks associated with anaesthesia?
- Would delaying the procedure decrease the risks?
- What is the safest anaesthetic technique?
- What postoperative monitoring is required?
- Which infants can be discharged on the day of surgery?

Each patient should be assessed individually and the risk associated with anaesthesia balanced with the cumulative risk of delaying surgery. The most common infant procedure is inguinal hernia repair that, for the premature infant, is often the final event in a long inpatient course, delayed until just prior to discharge home; for these patients, the benefit of increased ventilatory maturity has to be balanced with the risk of bowel incarceration with any delay in surgery. If feasible, elective surgery should be delayed in infants less than 46 weeks' PMA. The patient's risk of apnoea in the perioperative period will depend on:

- PMA;
- gestation;
- bull; history of apnoea; and
- lung function and oxygen requirements.

It is important with all infants to be vigilant for associated perioperative triggers for apnoea and treat appropriately:

- hypoglycaemia;
- hypoxia;
- hypercarbia;
- sepsis;
- anaemia;
- hypocalcaemia and
- ambient temperature fluctuations.

After deciding the appropriate timing of surgery, the next consideration is the safest choice of anaesthesia technique. Lower-body procedures, such as inguinal herniotomy, can be readily performed with regional anaesthesia either as a sole technique or as a supplement to general anaesthesia; both methods reduce the requirements for opiate drugs and therefore have a less-detrimental effect on ventilatory control. Spinal anaesthesia alone is a very effective technique but has a significant failure rate (reference review on regional techniques in this journal). General anaesthesia with fat-insoluble, modern volatile agents, such as desflurane, provide rapid emergence characteristics with a possibly reduced incidence of postoperative apnoea when compared with the more fat-soluble volatile agents (isoflurane and halothane). Local anaesthesia administered through the caudal route is easy to administer, provides good intra- and postoperative analgesia and does not increase the risk of apnoea, as long as local anaesthetic agents are used alone (Clonidine, ketamine and opiates administered neuroaxially, have all been associated with increased risk of apnoea). While alternative airway devices, such as the laryngeal-mask airway, are available in sizes to fit neonates, tracheal intubation provides the safest airway control; tracheal extubation is safest when the infant is wide awake with vigorous purposeful movement. Particular care should be taken when ventilating the infant to avoid hyper or hypo-ventilation or oxygenation. Preoperative SaO_2 and PCO_2, if available, can be used as a guide for intra-operative SaO_2 and end-tidal CO_2.

All infants under 62 weeks PMA should be monitored in the postoperative period with a minimum of: haemoglobin saturation and an abdominal pressure transducer. Infants over 62 weeks PMA should

be assessed and those with a significant history of apnoea or respiratory disease should be similarly monitored.

Infants over 62 weeks PMA can be discharged home after an appropriate period of recovery (4 h minimum) if: the surgery is minor, they have an uneventful recovery period and if they are otherwise medically well. Appropriate discharge of infants under 60 weeks must be dictated by the infants' risk factors for apnoea; the risk for apnoea, following general anaesthesia, will return to the preoperative risk over the subsequent 12 h, with the greatest risk in the immediate recovery period. High-risk infants will need overnight monitoring.

Research agenda

- Further research is required to finally decide whether a general anaesthetic or a spinal block is safest in neonates at risk of apnoea. Research should ideally target both short-term (1st postoperative day) and long-term (several years) outcome measures.
- The long-term safety of methyl xanthines is not established.

Conflict of interest statement

None.

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Spinal anaesthesia in the neonate

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Postoperative apnoea in ex-premature infants is inversely proportional to gestational age at birth and postmenstrual age (PMA). Spinal anaesthesia is an important technique in ex-premature infants as it reduces the risk of postoperative apnoea, provided intra-operative sedation is avoided. Recent studies have provided more data on recommended doses of local anaesthetics for infant spinal anaesthesia as well as adjuvants used to prolong the duration of surgical anaesthesia. Spinal anaesthesia is also used for surgical procedures other than inguinal hernia repair. There are a variety of reasons why awake regional is not the preferred technique for ex-premature infants undergoing lower abdominal surgery in many centres, and there is also controversy over the appropriate anaesthetic technique for outpatient surgery in infants <60 weeks PMA. A pragmatic decision analysis on the selection of anaesthetic techniques for inguinal hernia repair in infants is presented.

History

Spinal anaesthesia was described originally by Bier in 1895.[1] In 1901, Bainbridge[2] described 12 spinal anaesthetics in children aged 4 months to 6 years using 1–2% cocaine with a dose of 1–2 mg kg^{-1}.

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Subsequently, Tyrell Grey[3,4] reported the experience of 300 stovaine spinal anaesthetics in infants at the Great Ormond Street Hospital. Spinal anaesthesia was described as a safe technique even in gravely ill infants and children. For that era, the overall mortality rate (1.5%), even in the presence of sepsis, peritonitis and impending septic shock, was impressively low. The postoperative morbidity (largely vomiting) was 25% despite infants being fed milk during surgery and older children being given cake.

The ex-premie

The renaissance of spinal anaesthesia was triggered by a marked increase in the survival rate of extremely pre-term infants (63% since the early 1980s). In Australia, 1.3% of all live births are born at <31 weeks gestational age (GA). This equates to 3450 premature births per year. The 50% survival threshold of live-born infants is achieved between 23 and 24 weeks. The neonatal mortality rates then fall exponentially with survival rates of 89% at 27 weeks gestation and 99% at 31 weeks. Of the survivors, nearly half will suffer moderate to severe disabilities including deafness, blindness, cerebral palsy, behavioural dysfunction and poor school performance. Data from the Australian and New Zealand neonatal network (ANZNN) suggest that of 1112 infants born at <28 weeks GA, 53% are oxygen dependent at 36 weeks and 20% require home oxygen for discharge.[5] A significant number of ex-premature infants require surgery. In particular, inguinal hernias develop in 13% of infants born at <32 weeks gestation and in 30% of those born with a birth weight <1000 g.[6]

A number of authors have identified ex-premature infants as a group at risk of postoperative apnoea and desaturation (Table 1).[7–9] Cote[10] combined data from eight prospective studies (255 patients) to identify risk factors for postoperative apnoea.[11,12] Cote's review found that GA at birth and postconceptual age (PCA) were independent risk factors. (Note: The terms postmenstrual age and postconceptual age are often used interchangeably and indeed mean the same; both ages are measured or calculated from the last menstrual period. If the pregnancy was conceived *in vitro*, then the PCA is still calculated by adding a couple of weeks to the actual date of conception. To avoid confusion, the American Academy of Pediatrics suggests only PMA is used.) There was no relationship between the incidence of apnoea and necrotising enterocolitis (NEC), neonatal apnoea, respiratory distress syndrome (RDS), bronchopulmonary dysplasia Broncho Pulmonary Dysplasia (BPD) or the intra-operative use of opioids or muscle relaxants. Anaemia, however, was an independent risk factor, particularly for patients <43 weeks post conception. The conclusions drawn in this article were that the incidence in an infant born at 35 weeks is not <5% until a PCA of 48 weeks and not <1% until a PCA of 54 weeks (with 95% statistical confidence), and that the risk of apnoea an infant born at 32 weeks does not decrease to <5% until 50 weeks and not <1% until a PCA of 56 weeks.

To reduce the risk of postoperative respiratory compromise, in 1984, Abajian advocated awake spinal anaesthesia for ex-premies.[13] Numerous uncontrolled reports[14–19] followed suggesting a reduced risk for postoperative apnoea with spinal anaesthesia compared to general anaesthesia. Since 1990, five randomised controlled studies comparing spinal with general anaesthesia have been reported.[9,20–23] Welborn[20] demonstrated no apnoeas after awake spinal anaesthesia but intramuscular ketamine prior to spinal anaesthesia produced apnoea in 90% of patients. A Cochrane meta-analysis of 108 infants from four prospective trials comparing GA with spinal anaesthesia[9,20–22,24] suggested overall "there was no convincing evidence to support the use of spinal anaesthesia as standard practice in inguinal

Table 1
Infants in whom spinal anaesthesia offers significant advantages.

Ex-premature infants born at less than 35 weeks gestational age
All Infants with a Post conceptual age less than 45 weeks
Past or current Apnoea of prematurity requiring Caffeine or Methylxanthines
Chronic lung disease requiring home oxygen
Significant neonatal history including IVH, NEC, Retinopathy of prematurity
High-risk infants with congenital heart disease & airway anomalies
Any infant without absolute contraindications.
Infants booked as day-case surgery

herniorrhaphy in ex-premature infants."[25] However, if infants having preoperative ketamine or sedatives were excluded then there was a reduction in postoperative apnoea in the SA group and a reduction of borderline significance in the use of postoperative assisted ventilation in the spinal anaesthesia group. Avoiding supplemental sedation appears to be key in maximising the apnoea-reducing benefit of spinal anaesthesia.

Techniques

Anatomy

The spinal cord ends between L2 and L3 vertebrae in 90% of premature infants and between L1 and L2 vertebrae in 92% of term infants.[26] The dural sac is at the S4 level at birth and reaches the S2 level by the end of the first year (Fig. 1). The line joining the two superior iliac crests (inter-cristal line) crosses at the L5–S1 interspace at birth, L5 vertebra in young children and L3–L4 interspace in adults. As a result, lumbar puncture at the inter-cristal line will always be below the spinal cord.

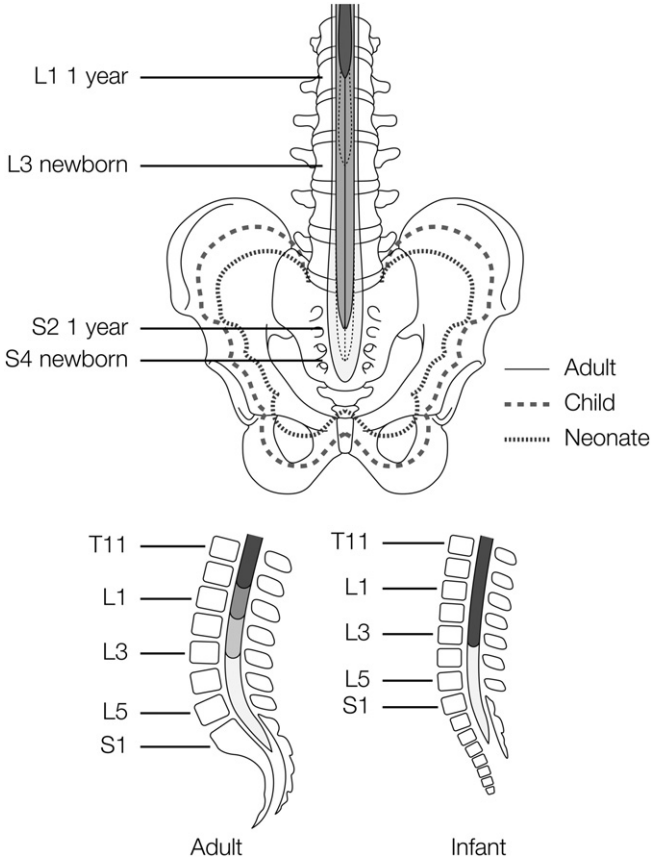

Fig. 1. The spinal cord (dark grey) terminates at a more caudad level in neonates and in infants compared to adults. The conus medullaris ends at approximately L1 in adults and at the L2 level in neonates and infants. In infants the line across the top of both iliac crests (the intercristal line) crosses the vertebral column at the L4–5 or L5–S1 interspace, well below the termination of the spinal cord. The dural sac (light grey) in neonates and infants also terminates in a more caudad location compared to adults, usually at about the level of S3 compared to the adult level of S1. The lack of a lumbar lordosis in infants compared to older children predisposes the infant to high spinal blockade with changes in positioning.

Positioning

Correct positioning and firm holding of the child are crucial to success of the technique. Lumbar puncture can be performed with the infant in either the sitting or lateral decubitus position. The neck should be in extension for lateral positioning as cervical flexion may obstruct the airway during the procedure.[27] The lateral decubitus position is easier to maintain by an assistant. In the sitting position, the patient is less mobile, bony landmarks are more prominent and the cerebrospinal fluid (CSF) hydrostatic pressure is higher but maintaining head support and spine flexion is more difficult. In a study on 30 pre-term infants for inguinal herniotomy, Vila[28] found spinal anaesthesia to be equally effective in both lateral and sitting positions. Apiliogullari[29] recommended 45° head up-tilt in the lateral decubitus position to increase lumbar puncture success and reduce bloody-tap rates.

The distance from the skin to epidural space is age dependent, being 6 mm at birth and increasing to 10–12 mm at 1-year of age.[30] Bosenberg[31] estimated that the distance from skin to epidural space is 1 mm kg^{-1}, whereas Ecoffey[32] reported that the skin to epidural distance ranges from 10–18 mm at the lumbar region to 7–14 mm at the thoracic region in infants <3 years of age. A 25 G quincke spinal needle is 50-mm long and a 25 G hypodermic needle is 16-mm long.

The needles available for paediatric use range from 24 to 29 G, either short-bevelled Quincke or Sprotte and Whitacre with or without introducer with a length shorter than that in adults. Styletted cutting-point Quincke needles, 22 or 25 G with a length of 25 mm are most frequently used. Use of non-styletted needles should be avoided because these can introduce epidermal tissue into the spinal canal resulting in epidermoid tumours.[33] The extent of the sensory block can be assessed with a peripheral nerve stimulator set at tetanus or by a pinch. A L1-level blockade of motor function can be shown by loss of hip flexion.

Drugs and doses

On a per-kilogram basis, infants require doses which are three to five times that of adult doses but with duration that is a quarter of the time of adult spinal anaesthesia.[34] Adult spinal anaesthesia usually requires 12–14 mg of bupivacaine (0.17–0.2 mg kg^{-1} in a 70-kg adult). An infant dose for inguinal hernia repair is 0.8–1 mg kg^{-1} because of a larger volume of distribution (CSF volume of 4 ml kg^{-1} is twice that of adult values) and greater clearance. Infants have a lower pulsatility of CSF but a higher heart rate generates a greater total flow and turnover than adults.

Tetracaine, mepivacaine, lidocaine, racemic bupivacaine and, more recently, levobupivacaine and ropivacaine have all been employed for paediatric spinal anaesthesia (Table 2).[35–37] In the United States, the vast majority of infant spinals have been with hyperbaric tetracaine or hyperbaric bupivacaine with

Table 2
Reported doses of isobaric and hyperbaric local anaesthetics for infant spinal anaesthesia for inguinal hernia repair.

	Agent	Weight	Mean dose	Duration	Author
Hyperbaric	1% tetracaine	<2 kg	0.91 mg/kg	105 min	Williams[53]
		2–3 kg	0.62		Abajian[13]
		3–4 kg	0.54		
		4–6 kg	0.45		
		>6 kg	0.37		
	0.5% tetracaine		0.4 mg/kg	86 min	Rice[54]
	0.5% tetracaine with adrenaline		0.4 mg/kg	128 min	Rice[54]
	0.75% bupivacaine in 8.25% dextrose		0.6–1 mg/kg	84 min	Parkinson[39]
	0.5% bupivacaine		0.3 mg/kg	75 min	Gallagher[16]
Isobaric	0.5% bupivacaine	<2 kg	0.6 ml		Murat[55]
		2–3 kg	0.8 ml		
		>5 kg	1 ml		
			1 mg/kg	82	Frawley[40]
			0.8 mg/kg	70	Mahe[38]
			0.6–0.8 mg/kg	46	Somri[21]
	0.5% bupivacaine with adrenaline		0.86 mg/kg	81	Mahe[38]
	Levobupivacaine		1 mg/kg	87.5	Frawley[36]
	Ropivacaine		1 mg/kg	85	Frawley[35]

or without adrenaline. A common mix consists of an equal volume of 1% tetracaine and 10% dextrose, combined with 0.02 ml of 1:1000 adrenaline (an 'epi wash') with an average dose of 0.5 mg kg^{-1}. Bupivacaine has been used as isobaric (mean dose: 0.8 mg kg^{-1}) [38]or hyperbaric solutions (bupivacaine 0.75% in 8.25% dextrose at 0.6–1 mg kg^{-1}).[39] In our institution, 1 mg kg^{-1} of isobaric 0.5% bupivacaine has recently been replaced by ropivacaine and levobupivacaine. Levobupivacaine, ropivacaine and bupivacaine have different potencies because of differences in formulation, lipid solubility and intrinsic vasoconstrictor activity. In a recent infant spinal potency study[40], ropivacaine and levobupivacaine were 39–45% less potent than bupivacaine at ED50 values but 19–21% less potent at ED95 values.

Additives and adjuncts

Adrenaline was probably first used by Braun in 1903, and by Tyrell Gray in 1909, to prolong the action of cocaine. Fosel[41] demonstrated that adding 1:200 000 adrenaline to 0.6 ml of isobaric 0.5% bupivacaine increased the duration of spinal anaesthesia from 50 to 95 min. In contrast, Mahe[38] noted that the addition of adrenaline to 0.8 mg kg of isobaric 0.5% bupivacaine increased the duration from 70 to 81 min.[38,42]

Dextrose (in a concentration ranging from 3% to 5%) is frequently added to subarachnoid local anaesthetic solutions to alter the distribution of the local anaesthetic, and hence success and spread of the blockade in children. In 100 children, in the age range of 2–115 months for paediatric day-case surgery under spinal anaesthesia, Kokki[37] compared bupivacaine 5 mg ml^{-1} in saline 0.9%(isobaric) with bupivacaine 5 mg ml^{-1} in 8% glucose (hyperbaric). The success rate of the block was greater with hyperbaric bupivacaine (96%) compared with isobaric bupivacaine (82%). Onset was delayed marginally in the hyperbaric group. Spread and duration of sensory block showed a similar wide scatter in both groups.

Intra-spinal α2-adrenergic agonists (e.g., clonidine and dexmedetomidine) induce analgesia by a pathway involving nitric oxide and acetylcholine release and are potentiated by intra-thecal neostigmine. Rochette added 1 μg kg^{-1} clonidine to spinal isobaric bupivacaine in newborns and doubled the duration of the block without cardiovascular or respiratory side effects.[43] In a subsequent trial of clonidine 1 μg kg^{-1} added to bupivacaine 1 mg kg^{-1} comparing pre-term to term infants, Rochette[44] demonstrated a 22% incidence of postoperative apnoeas in the premature group and a 19% incidence in the term group without sustained bradycardias or significant desaturations. Rakesh reported cephalad migration of intra-thecal clonidine (1 μg kg^{-1} with hyperbaric bupivacaine) with prolonged sedation and respiratory depression in an infant undergoing herniorrhaphy. These authors have advocated caution in the use of intra-thecal Clonidine in ex-premature infants.[45]

Batra[46] reported the use of intra-thecal neostigmine in 75 infants having lower abdominal and urogenital procedures. The infants received 0.5 mg kg^{-1} of hyperbaric bupivacaine with 0.25, 0.5, 0.75 and 1 μg kg^{-1} of neostigmine. They demonstrated there was a linear increase in duration of block from 52 to 92 min with increasing dose of neostigmine. In addition, with doses of neostigmine $>$0.75 μg kg^{-1}, there was a significant increase in the pain-free interval. The authors further claim that neostigmine does not cause any decrease in spinal cord blood flow or cause any direct spinal cord toxicity in animal or human studies.

Intra-thecal opioids have been reported to reduce the endocrine stress response during infant cardiac surgery.[47–49] Batra[47] reported a dose–response study with four doses of intra-thecal fentanyl (0, 0.25, 0.5 and 1 μg ml^{-1}) added to 0.4–0.5 mg kg^{-1} bupivacaine for lower abdominal surgery in infants. There was a dose-dependent increase in duration of block but four infants developed apnoea requiring bag-and-mask ventilation.

Methylxanthines

The use of methylxanthines is varied. It is not clear whether caffeine needs to be given prophylactically to reduce the rate of postoperative apnoea in ex-premature infants receiving the newer faster insoluble general anaesthetics such as sevoflurane or desflurane. Welborn[50] stated that a single dose of intravenous caffeine (10 mg kg^{-1}) suppresses postoperative apnoea in pre-term infants. In a Cochrane Review, Steer and Henderson-Smart[51], stated that caffeine can be used for this indication, but with a caveat on the small number of patients studied. In general, for any case of irregular breathing after

general anaesthesia, caffeine or aminophylline should be given without delay. Of the methylxanthines, theophylline is the most extensively used but caffeine is at least as effective as theophylline, has a longer half-life, is associated with fewer adverse events and, in addition, has a greater ease of administration.[52]

Why are not spinals the 'Gold standard' of neonatal anaesthesia?

A 1-year study of 24 409 regional blocks in children by the French-Language Society of Pediatric Anaesthesiologists (ADARPEF) suggested spinal anaesthesia represents 18% of all regional blocks in premature infants and 5% of blocks in term infants currently <30 days of age. Rochette[53] reported 10 929 paediatric regional anaesthetic blocks of which 1042 were neonatal spinal anaesthetics. Neonatal spinals represent 30% of all infant neuraxial blocks. Lacroix[54] reported significant decreases in use of caudal anaesthesia from 1994 to 2006, but spinal anaesthesia use increased from 2.1% to 3.2% of all regional procedures. In spite of such widespread use, awake regional techniques are unjustifiably labelled as having an excessive failure rate, inadequate duration of anaesthesia and an unacceptably high rate of unsettled infants requiring intra-operative sedation. Emerging data in animal models have demonstrated accelerated neuronal apoptosis and long-term behavioural changes in rodents exposed in the neonatal period to anaesthetic agents that act on *N*-methyl D-aspartic acid (NMDA) and gamma aminobutyric acid (GABA) receptors.[55] These findings may increase the use of regional anaesthesia in ex-premature infants.

Quality of anaesthesia/success rates

There is a steep learning curve for awake-infant regional anaesthesia. The Vermont registry of spinal anaesthesia in neonates and infants recorded their first infant spinal in 1977[13] and, to date, they have performed >1600 infant spinals (across a 30-year period, this equates to one a week). This database has generated three large series.[13,14,18] In Abajian's first series, the success rate was 100% in high-risk infants but only 76% in larger, term infants. Frumiento[14] reviewed 269 cases of inguinal hernia repair in which successful spinal anaesthesia was achieved in 262 (95% on the first attempt). The success rate in the Vermont Infant Spinal registry's 1554 infants was 97.4%.[56] In contrast, smaller series have reported a significantly higher incidence of failed spinals, bloody taps and blocks requiring supplementation. Williams reported traumatic taps in 20% and failure in four of 17 spinals in ex-premature infants.[22] Shenkman[19] reported a failure rate of 11% and spinal fluid could not be obtained in six of 55 ex-premature infants.

Duration of action

The Holy Grail of Spinal anaesthesia is to have motor block which outlasts even the slowest surgeon. Abajian[13] employed tetracaine at 0.22–0.32 mg kg^{-1} and found that the duration of anaesthesia was 83 min in term infants, 100 min in pre-term infants and 125 min in infants with congenital anomalies. The duration of analgesia increased 29% with 0.01 mg adrenaline (109 vs. 84 min). Harnik[17] used hyperbaric tetracaine doses of 0.24–0.65 mg kg^{-1} in her series of 21 high-risk infants. The duration of block was 71 min and the duration of anaesthesia increased with dose. Rice[57] reported durations of 86 min with 0.4 mg kg^{-1} hyperbaric 0.5% tetracaine, and 128 min in the group receiving 0.4 mg kg^{-1} hyperbaric 0.5% tetracaine with adrenaline. Webster[58] reported a duration of anaesthesia of 70–210 min in 39 high-risk infants receiving 0.5–0.9 mg kg^{-1} hyperbaric tetracaine with adrenaline; however, 12 of these required general anaesthesia and only 59% were unsupplemented.

In neonates, the duration of spinal anaesthesia is less with bupivacaine than with tetracaine. In a recent series[40], duration of motor block at concentrations greater than the ED95 was 81.9 min for bupivacaine, 87.5 for levobupivacaine and 85.2 for ropivacaine. Ramamoorthy reported a series of 60 newborns from 41 to 59 weeks PCA comparing hyperbaric bupivacaine and hyperbaric tetracaine in doses of either 1 or 1.2 mg kg^{-1} with adrenaline. The method of assessment was not mentioned but the duration of spinal anaesthesia was 177 min in the 1 mg kg^{-1} tetracaine group, and 201 min in the 1.2-mg kg^{-1} group. By comparison, the duration of spinal anaesthesia was 147 min in the 1.2 mg kg^{-1} bupivacaine group, and 121 min in the 1-mg kg^{-1} group. Gallagher [16] used 0.06 ml kg^{-1} plus 0.1 ml (mean dose: 0.3 mg kg^{-1}) of hyperbaric 0.5% bupivacaine and reported duration of motor block of 75 min. By contrast,

Somri[21] used 0.6–0.8 mg kg^{-1} isobaric 0.5% bupivacaine and reported durations of 45.9 min. Blaise[59], using 0.6-mg kg^{-1} hyperbaric 0.75% bupivacaine in older children, reported a duration of 70 min. Parkinson[39], using 0.75% bupivacaine in 8.25% glucose with epinephrine, reported a duration of 84 min.

Supplementation and sedation

Supplementation is required for infants with an inadequate spinal block, for unsettled babies and for procedures where the surgical duration exceeds block duration. In the Vermont Infant registry study[56], >75% of infants required only comforting with stroking and a pacifier, 2.7% required local anaesthetic and 1.2% required general anaesthesia for inadequate duration. Other studies recommend small doses of midazolam (20–50 μg kg^{-1}) or propofol (0.25–0.5 mg kg^{-1}) to calm unsettled babies intra-operatively.[37,56] Cassady[60] suggested an alternative for avoidance of general anaesthesia for infants when bilateral inguinal herniorrhaphy outlasts subarachnoid block. They recommend the use of single-shot caudal anaesthesia at the completion of the first inguinal hernia repair if it is likely surgery will proceed past 60 min.

Welborn[20] initially used intramuscular ketamine prior to the lumbar puncture but ceased this practice when excessive apnoea rates were recorded. For unsupplemented spinal anaesthetics, infants were, instead, comforted by a pacifier dipped in either a sugar solution or peach schnapps as needed. A systematic review of studies using sucrose analgesia in newborns has demonstrated the clinical efficacy of doses of 0.05–2 ml of 12–50% sucrose solutions in alleviating procedural pain.[61] These studies demonstrate the superiority of either glucose or sucrose over breast milk. Potential mechanisms include a direct activation of opioid receptors by the sugar, an enhancement of the effects of endogenous opioids on their receptor systems or an indirect effect promoting the release of endogenous opioids in the central nervous system (CNS).[62]

Infants undergoing procedures with spinal anaesthesia commonly fall asleep. Sedation was evaluated by Hermanns[63] using the bispectral index (BIS) score and the 95% spectral edge frequency (SEF95). BIS values began to decrease significantly 15 min after spinal anaesthesia and fell <70 after 25 min. Disma[64], using cerebral state index monitoring, also noted burst suppression. The presumed mechanism for sedation after spinal anaesthesia is a diminished afferent conduction to reticulo–thalamo–cortical projection pathways, reducing their excitability and hence decreasing the arousal level of the brain.

New volatile agents

The uses of new insoluble agents, such as sevoflurane and desflurane, have been associated with fewer adverse respiratory events in the recovery period but are not completely protective for postoperative apnoea. O'Brien[65] compared halothane, desflurane and sevoflurane for the incidence of postoperative apnoea in a study of pre-term infants. No major apnoeic events occurred in any of the 40 infants <60 weeks PCA, although there was at least one episode of breath-holding or self-limiting apnoea in each group. Sale[66] monitored ex-prems for apnoeas and bradycardias using nasal thermistry and impedance for 12 h pre and post operation. The incidence of preoperative apnoeas was 27% in the sevoflurane group and 40% in the desflurane group, with the incidence increasing postoperatively to 33% and 60%, respectively. Two infants in the sevoflurane group and four in the desflurane group recorded new apnoea postoperatively. There is only one published study comparing awake spinal anaesthesia with sevoflurane.[22] In this study, an excess of postoperative cardiorespiratory complications was defined as a threefold increase in the incidence of postoperative apnoeas and bradycardias relative to preoperative values. The sevoflurane group demonstrated excess events in patients with pre-existing apnoeas and also those without respiratory disease. Three patients with oxygen-dependent chronic lung disease accounted for 26 of the 39 episodes of apnoea and bradycardia.

Changing surgical management of hernias and hydrocoeles

In a survey of members of the surgical section of the American Academy of Pediatrics, laparoscopic evaluation for contralateral inguinal hernia was reported by 37% compared to only 6% in the 1993

survey.[67] Compared with a prior survey, more surgeons now prefer an earlier repair of the contralateral side to reduce the risk of incarceration.[68] Despite concerns that laparoscopic evaluation of the contralateral groin prior to hernia repair would increase the failure rate of spinal anaesthesia, the use of spinal anaesthesia has remained constant at 15%.

Day-case surgery?

Current evidence does not define a 'safe' PMA for outpatient surgery in former premature infants. Cote[10] and others[12,69] suggest the risk of apnoeas was nearly absent by 44–46 postconceptual weeks but may persists until 60 weeks PCA. They recommended that any infant who has a history of apnoea or is anaemic should not undergo outpatient surgery. Cote's study, however, was underpowered to predict apnoea risk in infants >45 weeks PCA as only 68 of their 255 patients were 46–50 weeks PCA and only 41 exceeded 50 weeks. In addition, volatile anaesthetic agents currently in use have a markedly different postoperative complication profile to those used (i.e., halothane and enflurane) in the Cote study (collected from 1988–93).

A survey of surgical management of inguinal hernias in infants by the American Society of Pediatric Surgeons in 1996[70] reports that, for an infant who has presented with an inguinal hernia after discharge from neonatal intensive care, 65% will operate when convenient and 35% will operate at 40–60 weeks PCA (mean 53 weeks). For an inpatient born at <29 weeks and weighing <1000 g, 71% would operate just before neonatal intensive care unit (NICU) discharge and 20% would operate at 49 weeks PCA and a weight >3.5 kg. A follow-up survey in 2005[67] suggested no change in this practice.

A number of authors have strongly advocated day-case surgery for ex-premature infants.[14,71–73] Melone[73] reported on 1294 outpatient inguinal herniorrhaphies performed between 1985 and 1990, but only 124 patients (9.6%) were identified as being premature (≤36 weeks GA) and the average PCA was 45.3 weeks. They recommended that "Outpatient inguinal herniorrhaphy can be performed in this patient group with minimal morbidity and no mortality." Veverka et al. [72] observed no apnoea after spinal anaesthesia in 62 ex-premies who were discharged home after an average observation period of 5.6 h for those with a history of apnoea and 3.5 h for those without history. Frumiento[14] even argued against routine overnight apnoea monitoring of outpatients.

Murphy suggested the frequency of apnoea after inguinal hernia repair with new anaesthetic agents was much less (4.7%) than reported by Cote.[71] Sevoflurane was the only anaesthetic factor which predisposed to postoperative apnoeas. The risk of postoperative apnoeas was increased in babies with a past history of apnoeas, those born at a GA of <30 weeks, small for GA, mechanical ventilation after birth and history of patent ductus arteriosus (PDA), Intra Ventricular Haemorrhage (IVH) or BPD.

Abajian and Williams[56] recommend day-case surgery and early discharge for uncomplicated cases in infants who receive unsupplemented spinal anaesthesia and who demonstrate no apnoea, bradycardia or desaturations during the surgery and for 8 h postoperatively (Fig. 2). Infants on apnoea monitors or methylxanthine drugs and those who have received any form of perioperative CNS-depressing medication should be admitted overnight. Postoperative apnoea has been reported after spinal anaesthesia[19,58,74,75], especially in infants with pre-existing apnoea and those who were sedated during the procedure (midazolam, ketamine, etc.) or received morphine or codeine[74] in the perioperative period. In some reports of apnoea, it is likely that a high spinal block contributed to the apnoea.[76] Kim[77] and Davidson[75] have both identified failed spinal anaesthetics requiring ketamine or general anaesthesia as a risk factor for postoperative apnoea. In Kim's series, 44% of infants with inadequate spinal anaesthesia developed postoperative apnoea. They suggest that the sedative effect of neuraxial blockade acts synergistically with supplemental pharmacological sedation to increase risk. Davidson[75] found that, in children where spinal anaesthesia was unsuccessful, early apnoea was particularly common.

Spinal anaesthesia for procedures other than herniorrhaphy

Spinal anaesthesia has been used for a variety of procedures other than inguinal hernia repair (Table 3). The Vermont infant spinal registry[56] has collected data since 1978 on infants or neonates considered to be at risk of postoperative apnoea or respiratory impairment. Inguinal herniorrhaphies

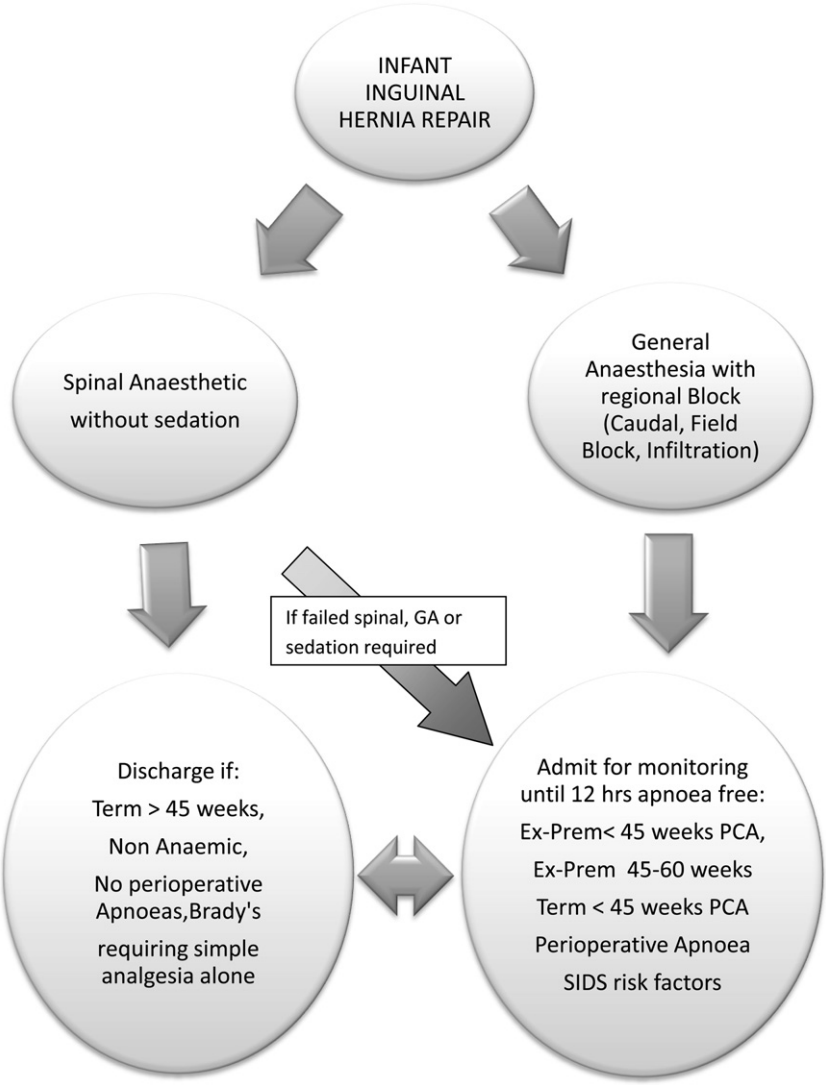

Fig. 2. Decision tree algorithm for management of infants presenting for inguinal hernia repair. Infants at risk of postoperative apnoeas include all those with pre-existing apnoeas, all infants less than 45 weeks post conceptional age (PCA), all on methyl-xanthines, all ex-premature infants with neurological injury and with. Sudden Infant Death Syndrome (SIDS) risk factors include smoking parents, low socioeconomic status and single parents. Analgesics other than paracetamol are associated with postoperative apnoea.

represent 55% of all procedures, but various intra-abdominal procedures were also performed. Williams and Abajian[78] described subarachnoid tetracaine with steep Trendelenburg position for PDA-closure in 14 pre-term and neonates, Hammer[49] used spinal tetracaine (0.5–2 mg kg^{-1}) and morphine (7 μg kg^{-1}) in cardiac surgery with a remifentanil-based anaesthetic technique, and Suominen[79] used 20 μg kg^{-1} intra-thecal morphine to reduce postoperative analgesic requirements after cardiac surgery. The relatively stable cardiovascular properties of spinal anaesthesia have also been used for non-cardiac surgery in infants with complex cardiac lesions.[80]

Table 3
Reported doses for infant spinal anaesthesia for surgery other than inguinal hernia repair.

Procedure		Mean dose (mg kg^{-1})	Agent	Author
Upper abdominal	Gastroschisis	0.5–0.6	0.5% hyperbaric tetracaine	Vane[80]
	Gastrostomy	1	0.5% hyperbaric bupivacaine	Shenkman[81]
	Pyloromyotomy	0.75–1.0	0.5% hyperbaric tetracaine	Williams[53]
		0.8	0.5% isobaric bupivacaine	Somri[82]
Lower Abdominal	Colostomy	0.56	0.5% hyperbaric tetracaine	Williams[53]
	Inguinal hernia	0.50	1% hyperbaric tetracaine	Abajian[13]
	Anorectoplasty	1	0.5% hyperbaric tetracaine with 15 mcg morphine	Tobias[83]
	Peritoneal dialysis catheter	0.95	0.5% isobaric bupivacaine	McCormick[84]
Neurosurgical	Meningo-myelocoele repair	0.56 (1st dose) 0.44 (2nd dose) 0.51 (3rd dose)	0.5% hyperbaric tetracaine with adrenaline	Viscomi[85]
Cardiac	PDA ligation	2.42	0.5% hyperbaric tetracaine	Williams[78]
	Cardiac catheter	1	0.5% hyperbaric bupivacaine	Katznelson[86]
Orthopaedic		0.5	0.5% hyperbaric tetracaine	Aronnson[87]

Continuous spinal anaesthesia and CSEA

In two ex-premature infants with chronic lung disease, Tobias[81] reported the use of continuous spinal anaesthesia with bupivacaine in procedures lasting 2–2.5 h. Payne and Moore[82] described continuous spinal anaesthesia with general anaesthesia for major abdominal surgery in 10 patients in the age range of 2–59 months. In these cases, spinal anaesthesia was provided by intermittent doses of 0.5% bupivacaine (0.2 ml kg^{-1} to a maximum of 1 ml). Infants <1-year of age required repeat boluses at 45–60-min intervals, whereas older infants required re-dosing at 0–80-min intervals.

Bouchet evaluated the tolerance and the efficiency of awake caudal anaesthesia performed in 25 consecutive conscious ex-premature infants for inguinal herniotomies. Two infants with a prior history of apnoea or bronchopulmonary dysplasia had apnoea during and after surgery. Total spinal anaesthesia was the major complication in one infant and prolonged surgery requiring general anaesthesia was the main limitation of this technique in another child.

Somri reported the use of combined spinal–epidural anaesthesia in major abdominal surgery in 28 high-risk neonates and infants.[83] Spinal anaesthesia with isobaric bupivacaine 0.5%, 1 mg kg^{-1} was followed by placement of a caudal epidural catheter to thoracic spinal segments. Satisfactory surgical anaesthesia was achieved in 24 neonates and infants, four patients were converted to general anaesthesia and 20 infants required intravenous midazolam. The issue of epidural volume extension of spinal block was not discussed.

Contraindications

Apart from limitations inherent in duration or site of surgery, there are no clear contraindications to spinal anaesthesia. Contraindications in the adult, such as coagulopathy, are tempered by the fact that coagulation studies[84] are often prolonged in this age group. Spinal anaesthesia has been described even in the presence of a ventriculo-peritoneal shunts devices.[85]

Complications

Complications during infant spinal anaesthesia are rare. A 1-year study of 24 409 regional blocks in children by the French-Language Society of Pediatric Anesthesiologists, reported a complication rate of 1.5 per 1000 in the 60% of children receiving central neuraxial blocks.[86] Intravascular injection was the only reported complication in the 506 spinal anaesthetics.[86]

Systemic absorption of local anaesthetic

Beauvoir[42] measured total and free bupivacaine after spinal anaesthesia in 22 newborns and evaluated a possible influence of adrenaline on bupivacaine absorption. Ten minutes after spinal injection total bupivacaine concentration was 0.31 pg ml^{-1} (87% bound) in the plain group and 0.25 pg ml^{-1} (88% bound) in the adrenaline group. Tetracaine undergoes rapid hydrolysis by plasma esterases including plasma cholinesterase; therefore, in theory, toxicity is less likely. However, there are no reports of total or free plasma tetracaine levels after infant spinal anaesthesia.

High blocks

A unique feature in infants is that there is only one anterior concave curvature of the vertebral column at birth (Fig. 1). The cervical lordosis begins in the first 3 months of life with the child's ability to hold their head upright. The lumbar lordosis starts as the child begins to walk at the age of 6–9 months. Therefore, the spread of hyperbaric local anaesthetics is position dependent in infants and inadvertent high blocks have been reported. Tetracaine has been associated with high spinal blockade with doses as low as 0.5 mg kg^{-1}.[87] Williams[56] used 0.54 mg kg^{-1} hyperbaric tetracaine but reported a 3.8% incidence of high blocks with 0.57 mg kg^{-1} and five infants who required intubation received 0.7 mg kg^{-1}. Jetzek-Zader[88] reported a high spinal in an ex-premature infant undergoing pyloromyotomy but used 1.3 mg kg^{-1} of hyperbaric 0.5% bupivacaine.

Postdural puncture headache

Postdural puncture headache (PDPH) is rare in infants. Kokki[89] found 5% PDPH rate despite 25 G and 29 G Quinke spinal needles, whereas Puncuh[90] reported a 0.5% incidence.

Neuraxial haematoma

Epidural hematoma formation after Sub Arachnoid Blockade (SAB) has not been reported in neonates after neuraxial blockade even following cardiac surgery and patients receiving anticoagulant therapy. It is relevant to note that it is difficult to interpret coagulation studies in infants. De Saint Blanquat[84] performed coagulation studies in 141 ex-premature infants undergoing hernia repair and found prolonged activated partial thromboplastin time (aPTT) values in 60%.

Aseptic meningitis

Aseptic and septic meningitis are rare complications of spinal anaesthesia. Easley and Tobias[91] reported the first documented occurrence of aseptic meningitis in an infant after spinal anaesthesia. Because of the infant's underlying status and recent life-threatening illness, it was not possible to definitely prove a causal relationship between the aseptic meningitis and the spinal anaesthetic.

Conclusion

Infant spinal anaesthesia offers significant benefits to ex-premature infants who are at risk of postoperative apnoea. Infants most likely to benefit include term infants currently <45 weeks PMA and ex-premature infants between 45 and 60 weeks PMA. Recent studies have demonstrated a 98% success rate in performance of the block, but this success rate cannot be expected to be replicated in units where awake regional techniques are uncommonly performed. Even in centres with long-standing experience in spinal anaesthesia, there is a significant incidence of infants requiring intra-operative sedation or supplementation of the block when surgical duration exceeds 75 min. All currently available local anaesthetic agents have now been described for infant spinal anaesthesia with the choice of agent determined by institutional preference. Attempts to increase the duration of motor block by addition of α2 agonists, such as clonidine, have been hampered by a significant incidence of postoperative sedation and apnoeas. Despite strong opinions for and against awake regional

techniques, there are limited studies comparing spinal anaesthesia to general anaesthesia with modern agents such as desflurane or sevoflurane and no studies comparing awake caudal anaesthesia to awake spinal anaesthesia. On current evidence, there is no anaesthetic technique which reliably reduces the apnoeic risk in ex-premature infants to a level which would allow lower abdominal surgery day-case surgery in ex-premature infants.

Research agenda

A large controlled prospective study comparing differences in peri- and postoperative complications between regional anaesthesia and general anaesthesia with modern volatile agents in ex-premature infants is required.
A randomised controlled trial comparing apnoea outcome between awake caudal anaesthesia and awake spinal anaesthesia is required.
A suitable adjuvant to prolong the duration of intra-spinal local anaesthetics without inducing apnoea is required.

Practice points

Awake spinal anaesthesia without intravenous sedation produces the lowest incidence of postoperative apnoeas and bradycardias.
Spinal anaesthesia is most appropriate for neonatal inguinal hernia repair but many other surgical procedures have been described.
Bupivacaine, tetracaine, levobupivacaine and ropivacaine have all been described for neonatal spinal anaesthesia
Duration of spinal anaesthesia varies from 80 to 120 min depending on the agent and dose.
Postoperative monitoring is recommended for all infants currently <45 weeks PMA and ex-premature infants with ongoing apnoeas and complex medical histories.
There is no consensus on appropriate postconceptual age for day-case lower abdominal surgery in infants.

Conflict of interest statement

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Neonatal ventilation

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Preventing ventilation-induced lung injury and bronchopulmonary dysplasia is an important goal in the care of ventilated neonates. Recently, there have been tremendous efforts to improve ventilation strategies, which aim at ventilating with a 'protective' and 'open-lung' strategy. Several different ventilation modes are now available, but it is important to note that, with regard to the neonatal pulmonary and neural outcome, there is still no clear evidence as to the superiority of one ventilation mode over another. Clinicians should bear in mind that any ventilation mode used to ventilate a neonate should be accompanied by real-time pulmonary monitoring to continuously adapt the ventilation strategy to the sudden changes in the respiratory mechanical properties of the lung. This article will describe the different ventilation modes available for neonates and highlight the importance of using a protective and open-lung ventilation strategy, even in the operating room.

The past decade has seen a great increase in awareness of the potential harm of hyperventilation in neonates with large tidal volumes (V_t) leading to well-described ventilation-induced lung injury.[1,2] The mechanisms of this injury involve alveolar overdistension, the presence of shear forces and the release of pro-inflammatory cytokines. Moreover, inadvertent hyperventilation with consequent hypocapnia has been demonstrated to promote the development of cystic periventricular leukomalacia.[3] On the other hand, suboptimal V_t may result in inefficient gas exchange, hypercapnia, agitation and a potentially increased risk of intraventricular haemorrhage (IVH).[4] Thus, there have been extensive efforts to develop new ventilation strategies in neonates, based on non-invasive ventilation and the application of volume guarantee modes, to optimise V_t and to ventilate at optimal functional residual capacity

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(FRC). Besides descriptions of the different ventilation modes available for neonates, this article will highlight the importance of using a ventilation strategy including low V_t, recruitment manoeuvres and high positive end-expiratory pressure (PEEP), especially in critically ill neonates.

Ventilation modes

Advances in ventilator technology have led to the development of various ventilation modes the usefulness of which has not yet been adequately proved either because of the lack of randomised trials and/or because studies have been done in heterogeneous groups. Although the terminology for the different ventilation modes used in neonates is confusing, these modes can be distinguished on the basis of whether they are volumetric (e.g., flow generator), barometric (pressure generator) or dual modes (combining pressure and flow generators). In addition, these modes can be either totally or partially controlled, with the child being able to trigger the onset of the ventilator cycle.

Pressure-controlled ventilation

This mode is often promoted in neonates in clinical practice since it provides a lower peak inspiratory pressure as a consequence of a limited and constant inspiratory pressure and a decelerating flow. The combination of decelerating flow and maintenance of constant airway pressure over time improves ventilation distribution, particularly in a lung with heterogeneous mechanical properties (as in acute lung injury), and thereby improves gas exchange.[5] Moreover, this mode allows compensation for a potential leak around an uncuffed endotracheal tube. The basic and most frequently applied mode in neonatal intensive care is 'the time-cycled, pressure-limited ventilation' (also called intermittent positive-pressure ventilation: IPPV). In addition to the limitation of the peak inspiratory pressure (PIP) and the level of PEEP, the settings for this mode require adjustment of the inspiratory (T_i) and expiratory time (T_e) to determine the respiration rate, irrespective of the child's own breathing, but usually at a level close to that observed physiologically. While ventilating with a short or a long T_i does not affect the incidence of chronic pulmonary disease (CPD) in neonates, there is some evidence that a short T_i duration is accompanied with decreased risk of air leak and a decreased mortality.[6] Thus, T_i is set between 0.35 and 0.5 s with a longer T_e unless a higher mean airway pressure is required, which can be achieved by elevating the PEEP level and/or reversing T_i/T_e. Nevertheless, this mode of ventilation often leads to an asynchrony between the child and the ventilator[7] and may result in the use of heavy sedation and neuromuscular blocking agents. Thus, synchronised ventilation with the patient allowed to trigger the onset of the ventilation is nowadays the common mode used in neonatal intensive care. Among the different triggering techniques that have been developed, flow triggering via a flow sensor interposed between the endotracheal tube and the ventilator's connection has been shown to be the most sensitive[8] and is therefore routinely applied in clinical practice. 'Synchronised intermittent mandatory ventilation' (SIMV) pressure control mode was the first mode in which the ventilator was set so as to secure a fixed respiration rate synchronised with the child's breathing within the limit of the ventilator setting. The ventilator does not assist a child breathing above this limit, but delivers additional untriggered cycles if the child is not breathing sufficiently to meet the predefined setting. For this reason, 'the assist-control' (AC) mode was developed in order to 'assist' each breath on the basis of positive-pressure ventilation, but with a 'control' of a minimum number of ventilator cycles. Nevertheless, if the child breathes at a high rate, the ventilator assists all triggered breaths by applying the initially set T_i, which will result in a decreased T_e and may lead to air trapping by shortening the time necessary to achieve adequate expiration. Accordingly, 'pressure support ventilation' (PSV) may be superior since both the initiation and the termination of ventilator assistance are controlled by the child's breathing effort and the changes occurring in the airflow. Depending on the ventilator, the inflation will stop when the inspiratory flow level decreases and reaches a percentage of the peak flow that varies between 10% and 25% of the maximum inspiratory flow.[9] Although PSV is associated with a lower work of breathing (WOB) and counteracts inadequate spontaneous breathing and the high resistance due to small endotracheal tubes, a novel technique called proportional assist ventilation (PAV) has been developed to reduce the WOB even further. In this mode, the rate of lung inflation and thus the inspiratory pressure are controlled by the patient and are proportional to the child's effort.[10]

Since the pressure applied depends on the inspiratory flow generated by the child, this mode assumes that the child is not hypopnaeic and there is no leak around the endotracheal tube.[7] More interesting is the neurally adjusted ventilator assist (NAVA), which relies on the child's respiratory control and diaphragmatic activity.[11] The inspiratory effort is detected via bipolar electrodes mounted on a naso-gastric feeding tube, positioned at the level of the diaphragm. The level of ventilatory support is then proportional to the inspiratory effort. While this mode is not affected by the presence of a leak, its utility is still not defined in neonates, especially in premature babies with immature control of the ventilation. A very recent prospective crossover study demonstrated that NAVA is associated with improved patient–ventilator synchrony and a lower peak airway pressure in comparison with PSV.[12]

Volume-controlled ventilation

Volume-controlled ventilation (VCV) is based on the traditional delivery of a fixed preset V_t at a pre-established rate. The major disadvantage of pressure-limited ventilation lies in the variable V_t that results from changes in lung compliance and resistance, as VCV does not take into account the pressure needed to deliver the desired V_t. Thus, high tracheal pressures may be encountered during ventilation, especially in the event of decreases in lung compliance or increases in airway resistance. These high pressures may be limited either by setting the pressure pop-off valve or by determining the level of T_i to limit high peak pressures during the ventilation of neonates with sick lungs. Nevertheless, this mode of ventilation is impractical and unpopular, particularly in infants, since the preset V_t is lost due to the compression of the gas in the ventilator circuit and to the leak around the uncuffed endotracheal tube.

Volume-targeted ventilation

The increasing awareness of the usefulness of direct control of the PIP and the benefit of ventilation with a small constant V_t led to the development of dual modes that guarantee V_t with a limited pressure.[13] Different ventilators and modes have been developed to enable the physician to choose a target V_t and set a high pressure limit that allows the ventilator to autoregulate the inspiratory pressure (within the maximum limit set) or the T_i to guarantee the target V_t. All these modes are grouped under the same terminology, recognised as 'volume-targeted ventilation modes', and include all modes that guarantee V_t by adjusting the inflating pressure in response to the exhaled V_t, which is compared with the desired target V_t.[14] However, there is still no evidence that volume-targeted ventilation offers any advantage over pressure-limited ventilation with regard to the outcome (death or the risk of CPD).[15] Nevertheless, volume-targeted ventilation has been associated with a significantly shorter duration of ventilation, a lower rate of pneumothorax and a decreased incidence of severe (grade 3 or 4) IVH relative to pressure-limited ventilation.[15]

The 'volume guarantee' (VG) ventilation mode is in fact a pressure-limited, volume-targeted time- or flow-cycled ventilator. This mode can be combined with all the other standard modes used in neonates, such as SIMV, AC or PSV. Besides the maximum PIP, the desired V_t (exhaled V_t) is set and also T_i, which determines the duration of insufflations. The ventilator bases its working pressure on the difference between the exhaled V_t and the desired V_t. However, adjustments in the working pressure are limited between one breath and another to avoid overinflating with high V_t, which reduces the risk of both volutrauma and barotrauma. Moreover, when the child triggers ventilation and/or lung compliance changes, the ventilator analyses each breath separately to maintain constant values for V_t. These characteristics are interesting during the weaning period since the inspiratory pressure is adjusted in real time.[13] The VG mode is far superior to 'volume-limited ventilation', which consists in setting an upper volume limit; if the measured inspired V_t exceeds this limit, the pressure support of the ventilator will stop. With this volume-limited mode, there is no automatic adjustment of the inspiratory pressure. In contrast, in the 'pressure-regulated volume control' (PRVC) mode, the flow rate will vary to adjust the inspiratory pressure to deliver the targeted V_t.[16] Thus, this mode behaves similarly to pressure control modes with regard to the pressure and flow patterns, but delivers the set V_t by adjusting the PIP on the basis of the lung compliance. This mode has been demonstrated in one study to be very useful in premature babies with very low birth weight (LBW) with a shorter duration of mechanical ventilation and less haemodynamic impairment.[17] When this mode is combined with

other ventilator options that allow the patient to breathe spontaneously with a pressure support, it is called 'automode'. The PRVC mode is more flexible than volume-assured pressure support ventilation (VAPS), which combines volume and pressure-targeted ventilation. The ventilator delivers the targeted V_t, but with a pressure-limited action in a pressure support mode. Since the pressure is limited, this mode acts by increasing the T_i, which may lead to expiratory asynchrony.

High-frequency ventilation

High-frequency ventilation (HFV) has rapidly come to the focus of interest in neonates since it allows ventilation with small tidal volumes and the application of a mean airway pressure (MAP) higher than that obtained with conventional ventilation. This strategy is very effective in infants with severe respiratory failure because HFV improves the gas exchange by optimising the lung volume while ventilating at lower proximal airway pressures and avoiding damage to the lungs.[18] The principle is based on the natural 'resonant' frequency of the lung and the fact that less pressure is required to move the gas into and out of the lungs at this resonant frequency, which is around 10 Hz (1 Hz = 60 bpm) in neonates and is even higher in premature babies. In fact, HFV improves the gas exchange by enhancing both the convection and the diffusion of the respiratory gases. Different ventilators delivering HFV are available and, despite the fact that they are of great value as a feature of the available modes of mechanical ventilation in neonates, there is no clear evidence in the literature as to the superiority of one type of HFV ventilator versus another. The first mode to be promoted was high-frequency jet ventilation (HFJV), a very well-established technique in the field of anaesthesia. It consists of delivering short bursts of gas (with very short T_i) at very high frequency (up to 600 min^{-1}) on top of a constant flow that determines a PEEP level. This technique necessitated a specific endotracheal tube, however, and failed to prove its usefulness in clinical practice, with conflicting results on the neurological and respiratory outcomes in neonates treated with this modality.[19–21] Another modality for the provision of HFV is high-frequency flow interruption (HFFI), which consists of interrupting at a high frequency (up to 20 Hz) a continuous flow delivered by a high-pressure gas source.[22] However, this technique failed to demonstrate any beneficial advantage as regards the pulmonary outcome, and some studies have even highlighted the higher incidence of air leaks in premature babies treated with HFFI.[23,24] The most frequently used modality nowadays is high-frequency oscillatory ventilation (HFOV). This modality is based on the presence of an electromagnetically driven piston or vibrating diaphragms that generate biphasic pressure waveforms at very high frequency (up to 15 Hz). Thus, HFOV has both an active inspiratory phase and an active expiratory phase (by inducing a negative proximal airway pressure during exhalation). When using HFOV, it is important to adjust the inspiration/expiration (I/E) ratio to avoid any gas trapping that may occur as a consequence of the active exhalation part.[9] HFOV provides very small oscillatory tidal volumes that are superimposed on an adjustable MAP. HFOV is, in theory, particularly beneficial when a high-volume strategy is required to maintain FRC as HFOV maintains FRC with a lower MAP than with other modes of ventilation. Nevertheless, a recent meta-analysis failed to demonstrate any evidence of a greater benefit of HFOV over conventional ventilation when used as a primary or rescue mode to ventilate infants with an acute pulmonary dysfunction.[25,26] There may be a lower incidence of chronic lung disease in premature babies ventilated with HFOV[26,27] but this finding needs to be confirmed in future trials.

Continuous positive airway pressure and non-invasive ventilation

The high incidence of complications following endotracheal intubation[28] and the concern about the potential harm of conventional ventilation led to the development of non-invasive respiratory support that allows the application of a continuous positive airway pressure (CPAP) and/or the delivery of non-invasive ventilation (NIV). Note that at least some CPAP is essential for recruiting, and maintaining airway patency and lung expansion.[29] The aim of nasal CPAP is to maintain FRC, decrease the WOB and reduce the frequency of apnoea of prematurity.[30] It is therefore routinely used in clinical practice to support recently extubated pre-term infants and, as an alternative to intubation and ventilation, to support those experiencing significant apnoea of prematurity and those with respiratory distress soon after birth. Some systems also allow the provision of a phasic positive increase in pressure (pressure

support or pressure-controlled) on top of the CPAP and can be synchronised (SNIMV, synchronised nasal intermittent mandatory ventilation) or not (NIMV). During the past decade, the use of NIV for acute respiratory failure in neonates has been expanding, and predictive factors for the successful use of NIV have recently been identified.[31] However, there are still no clear guidelines for the initiation of NIV. The main disadvantages of NIV are mainly based on the inability of NIV to oxygenate and ventilate the patient in a satisfactory manner despite the fact that NIV is well tolerated by the child. While meta-analyses have failed to demonstrate the benefit of NIV in the presence of respiratory distress syndrome,[32] its ability to prevent extubation failure in neonates is beyond doubt.[33] Accordingly, the use of NIV to protect against the risk of re-intubation during the first 72 h is the current evidence-based indication for NIV in neonates.[29] For this purpose, NIV is started after the minimal PEEP level is set to around 6-cm H_2O and the PIP to between 10- and 12-cm H_2O.

CPAP can be delivered essentially by two means: (1) a continuous flow and a device that varies the exhalation either by modifying the expiratory orifice size or by immersing the distal end under water to a certain level, which determines the desired CPAP. This latter is called 'bubble CPAP', the bubbles creating pressure oscillations that are transmitted to the airway opening, and it has been suggested that this phenomenon may improve gas exchange by facilitating diffusion.[34] (2) a variable flow that allows change of the CPAP level, but needs nasal prongs, which redirect the exhaled gas out of the expiratory limb. The WOB with the variable-flow CPAP has been shown to be less than that with the bubble CPAP.[35] Another system that is based on the variable-flow setting is the bilevel CPAP or BiPAP. The BiPAP allows the child to trigger the inspiratory phase and to breathe between two levels of positive pressure, with some systems including an abdominal wall sensor to help synchronisation with the child's inspiratory efforts. The BiPAP system seems to be better in improving oxygenation and ventilation than the CPAP system in LBW infants.[36]

The application and successful use of CPAP and NIV rely on the airway interfaces and their ability to guarantee comfort and optimise the delivery of pressure. Of all the interfaces that are available to provide CPAP, the binasal prongs have been demonstrated to be superior.[37] While prongs may be associated with a high incidence of nasal trauma in infants,[9] leaks remain a major concern in NIV. Such leaks may lead to reduced alveolar ventilation, child-ventilator asynchrony and increased nasal resistance.

Extracorporal membrane oxygenation (ECMO)

With the exception of heart failure, the use of ECMO in neonates is indicated when all modes of conventional ventilation (including HFOV and nitric oxide) have failed to maintain adequate oxygenation in the presence of reversible respiratory failure. Persistent pulmonary hypertension is a characteristic of nearly all diseases treated by ECMO (meconium aspiration, severe hyaline membrane disease, idiopathic persistent pulmonary hypertension, sepsis and congenital diaphragmatic hernia). The use of neonatal ECMO requires an experienced team that is at ease with the technique and can face all the complications related to its use in neonates. Due to the size of the cannula and the risk of IVH with heparinisation in the premature brain, neonatal ECMO can be considered only in neonates older than 34 weeks post-menstrual age and/or greater than 2 kg body weight. Under these conditions, the survival rate for neonates appears to be much higher than for either paediatric or adult patients.[38] However, intracranial injury continues to be a major complication associated with ECMO-treated neonates.[39] There are two potential ways to perform neonatal ECMO: veno-arterial or veno-venous ECMO. A total bypass, particularly in cases of associated heart failure, requires a veno-arterial technique where the venous cannula is inserted into the internal jugular vein and advanced through the superior vena cava, while the arterial cannula is placed into the right common carotid artery with the tip of the cannula advanced up to the innominate artery. In veno-venous ECMO, a double-lumen cannula is often used so that only one vessel is cannulated and the blood is drained from the right atrium, is oxygenated and is returned to the right atrium. Recent meta-analyses, including the four available trials in which ECMO was compared with conventional ventilatory support for severe respiratory failure, demonstrated the strong benefit of ECMO as concerns mortality (relative risk (RR) 0.44; 95% confidence interval (CI) 0.31–0.61), especially for babies without congenital diaphragmatic hernia (RR 0.33, 95% CI 0.21–0.53).[40] Nevertheless, further studies are needed to determine the criteria

for the introduction of ECMO, and long-term follow-ups are needed in view of the high incidence of severely disabled children.

Application of ventilation modes in the operating theatre

Despite the great advances in the development of new anaesthetic ventilators, which include a variety of modes of ventilation widely used in the intensive care setting, there is still no evidence as to the benefit of these modes of ventilation under general anaesthesia in improving the clinical outcome. However, the application of these modes to neonates helps the clinician to apply ventilation strategies that are part of the 'lung protective ventilation' and optimise the ventilation distribution. Since most of the neonates admitted to the operating theatre receive neuromuscular blocking drugs, mandatory ventilation is often used, while the synchronised ventilation mode is applied during induction or weaning from the ventilator (Table 1).

As stated above, the traditional mandatory VCV is inappropriate in the paediatric anaesthesia setting because it implies the use of a constant flow and it does not take into account the compressible volume and the potential air leak around the endotracheal tube. The constant flow characterising the VCV mode induces high PIP with less time for equilibrium to be attained between the airway (P_{aw}) and the alveolar pressure (P_{alv}), this being known as the time constant. Moreover, the compressible volume is an important issue in the neonate and it is crucial to know if the ventilator corrects for this compressible volume in the case of a fixed V_t setting. Most modern ventilators available in the anaesthesia setting do correct for this compressible volume when the ventilator is checked during the first use. If there is a change of circuits between patients, it is important to recheck the ventilator to correct for the compressible volume. In the event of an old ventilator or limited compensation if the pressure exceeds 30 cmH_2O,[41] it is important to take the compressible volume into account when

Table 1
Summary of different available modes of ventilation with their particular settings.

Mode of ventilation	Abbreviation	Settings
Pressure controlled ventilation	PCV	Set PIP and PEEP Set Rate independently from T_i and T_e
Intermittent positive-pressure ventilation	IPPV or time-cycled, pressure-limited ventilation	Limitation of PIP and PEEP Set T_i at 0.35 s. Rate depends on T_i and T_e
Synchronized intermittent mandatory ventilation	SIMV	Fixed respiration rate synchronized with child's breathing within limit of ventilator setting.
Assist-control	AC	Assist each breath on the basis of PCV Set minimum cycles and short T_i
Pressure support ventilation	PSV	Set variables for support based on PCV Set minimum rate and trigger threshold ± pressure slope
Neurally adjusted ventilator assist	NAVA	Set trigger to pick up the electrical diaphragmatic activity Adapt NAVA level to regulate pressure support
Volume-controlled ventilation	VCV	Fixed preset V_t and rate Limit high pressures with pop-off valve or T_i
Volume guarantee ventilation mode	VG or pressure-limited, volume-targeted time	Set the maximum PIP and PEEP, the desired exhaled V_t and T_i
Volume-limited ventilation	VLV	Set upper volume limit And Pressure support variables
Pressure-regulated volume control	PRVC or autoflow	Flow rate will vary to adjust PIP to deliver target V_t
Volume-assured pressure support	VAPS	Combines volume and pressure-target ventilation Set target V_t and Pressure limit as in PSV
High-frequency jet ventilation	HFJV	Short bursts with short T_i High frequency (600/min) constant flow determines PEEP level
High-frequency flow interruption	HFFI	Interrupts at high frequency (20 Hz) continuous flow
High-frequency oscillatory ventilation	HFOV	Adjust MAP, I/E ratio, Rate

PIP, peak inspiratory pressure; T_i, inspiratory time; T_e, expiratory time; MAP, mean airway pressure; V_t, tidal volume.

setting the V_t. For instance, if the compressible volume reaches 1 ml cmH_2O, and the delivered V_t is set at 7 ml kg^{-1} in a 3 kg neonate, the ventilator may generate a PIP of 25 cm H_2O during ventilation and thus have 25 ml of compressible volume. The preset V_t should be adjusted to almost 15 ml kg^{-1} because 50% or more may be lost in the delivery system (not taking into account the dead space and the potential leak). In any case, use of the VCV mode requires that the overpressure valve be set to protect the lung from any dangerous increase in peak pressure that may be induced by changes in lung compliance during the surgery. In neonates, therefore, particularly with a less compliant lung, the PCV is the mode of choice for ventilation.

The decelerating flow that characterises the PCV mode offers a limited and constant inspiratory pressure with a plateau pressure that is reached much more quickly, but at a lower PIP. This mode has been demonstrated to improve the ventilation distribution, decrease the intrapulmonary shunt and thus improve oxygenation. In addition, the PCV mode allows any compensation in the presence of a leak around the endotracheal tube. Nevertheless, while PCV better meets the criteria required by the protective ventilation strategy, V_t will be variable in this mode, particularly if there is a decrease in lung compliance or an increase in respiratory resistances during the surgery. During PCV, V_t is variable and depends on three components: (i) the time constant, (ii) the pressure gradient between the maximal set peak pressure and the PEEP level, and (iii) T_i, which is determined by the respiration rate and the ratio I/E. The time constant is characterised by the mechanical properties of the respiratory system, which include the total respiratory system compliance (Crs) and resistance (Rrs). Application of the time constant concept to the inspiratory phase implies that T_i is set to allow enough time for the achievement of pressure equilibrium between the airways and the alveoli. Accordingly, if Rrs increases and/or Crs decreases, the equilibrium time will increase. Further, it is important to allow sufficient time for complete deflation, considering that the expiratory flow presents an exponential decelerating profile and thus, almost three to four time constants of the respiratory system are needed for complete deflation. Finally, it is important to note that the available anaesthetic ventilators are not equal in generating a maximal insufflation flow, and the V_t generated by a given pressure level may vary from one ventilator to another.[42]

Given the benefit of maintaining diaphragmatic activity to decrease a ventilation perfusion mismatch during general anaesthesia, use of the PSV mode in routine practice is becoming very popular in paediatric anaesthesia. The new ventilators include a flow trigger highly sensitive to minimal flow variations (similar to those observed with intensive care ventilators) and can therefore be applied in neonates since minimal WOB is required to activate the beginning of the inspiratory phase.[43] The pressure support is based on a decelerating flow, which generates a fixed insufflation pressure; thus, V_t may vary with the patient's inspiratory efforts, the level of pressure support and also the mechanical characteristics of the lung. Currently, it is not possible to vary the cycling (transition from inspiration and expiration) on anaesthetic machines. In most ventilators, the insufflation stops when the flow is less than 25% of the maximal inspiratory flow. This limitation may have a negative impact in the presence of a neonate with an obstructive disease, where the cycling should occur later.[44] Although there have been no studies on use of the PSV mode in neonates, it can be applied during anaesthesia in clinical practice to compensate the increase in the WOB, which is particularly high in neonates. For instance, application of a pressure support of 5 cmH_2O in addition to a PEEP level at induction will help keep the airways patent, compensating the WOB; and it may ease inhalation induction by optimising the gas exchange. During the maintenance of anaesthesia, a higher level of pressure support may be necessary (up to 10 cmH_2O) to counteract the resistances due to the endotracheal tube and the circuit and to guarantee an optimal V_t for gas exchange.[45] At the end of an anaesthetic procedure, PSV allows a smoother recovery and weaning from the ventilator. In all cases, it is important to set a minimal security respiration rate to deliver in a pressure control mode in the event of apnoea. Finally, some anaesthetic ventilators allow changes in the pressure slope (the time to achieve pressure support). By increasing this time (and thereby decreasing the pressure slope), we can limit the auto-trigger activated by the cardiac activity, which is frequently observed in neonates at low trigger threshold.[46] To avoid this phenomenon, it is also possible to increase the trigger threshold with the risk of increasing the WOB.

Recently, the PRVC mode with automode (auto-flow) has become part of the new anaesthetic ventilators introduced in the operating theatre. VCV with decelerating flow in combination with synchronisation with a pressure support of the spontaneous ventilation offers the advantages of pressure modes, but with the guarantee of a minimal V_t. Theoretically, this mode overcomes the inconvenience of

both PCV and VCV and may have tremendous advantage in neonates under anaesthesia, particularly when abrupt changes in lung compliance occur during surgery (i.e., laparoscopy, or abdominal or thoracic surgery). Nevertheless, there are still no data concerning the use of this mode in the operating theatre and hence its use is still anecdotal and based on the experience of different clinicians.

'Open lung' and 'protective' ventilation strategy in the operating theatre

The open-lung strategy that is applied in the intensive care unit (ICU) should also be considered when a neonate is ventilated in the operating theatre. This strategy primarily targets the atelectasis and the consequent ventilation inhomogeneity observed under general anaesthesia, which can significantly impair the pulmonary gas exchange. First of all, the physiological characteristics of the chest wall (high compliance) and the lung (increased static elastic recoil pressure) in neonates promote airway closure and a decrease in FRC. The decrease in ventilation induced by general anaesthetics and the inactivation of the intercostal muscle activity associated with the cranial shift of the diaphragm are also responsible for the lung collapse and atelectasis formation. This latter is enhanced by the resorption of alveolar gas in the event of inhalation of a high FiO_2 concentration. Thus, this 'open-lung strategy' requires that recruitment manoeuvres should be regularly performed, such as application of a vital capacity manoeuvre (or twice the V_t) after induction, after disconnection and suction, and thereafter every 30 min during the anaesthetic procedure.[47] However, and in all cases, a minimum PEEP level of 5 cmH_2O is required to maintain recruitment of the distal airways[48] and the use of high concentrations of oxygen should be avoided. Nevertheless, a higher PEEP may be required in the presence of poorly compliant and atelectatic lungs to maintain adequate alveolar recruitment.

In addition to this open-lung strategy, it is crucial to apply 'protective ventilation' in an attempt to protect against ventilator-induced lung injury.[49] Ventilation with low V_t at optimal FRC is therefore also essential in the operating theatre. Optimisation of the PEEP level will increase the lung volume while adapting T_i and T_e, will guarantee adequate lung inflation and deflation, respectively, especially if T_i/T_e is adjustable on the basis of estimations of the time constants.

This ventilation strategy may lead to mild hypercapnia, which can be regarded as safe if maintained at around 6–7 kPa in the absence of high intracerebral pressure and pulmonary hypertension. It has also been demonstrated that mild hypercapnia at this level improves both the cerebral oxygen saturation and the subcutaneous tissue oxygenation.[50] Paediatric anaesthetists should be more aware of the importance of the position of the oxygen–haemoglobin dissociation curve. The large affinity for oxygen of foetal haemoglobin in comparison with that in the adult explains the shift of the curve to the left with a very low P_{50}, which can be aggravated in cases of hyperventilation (Bohr effect) with a subsequent decrease in tissue oxygen delivery.[51]

Monitoring of ventilation

It is inconceivable today to ventilate a neonate without having access to real-time pulmonary monitoring. Almost all ventilators available in the anaesthesia setting display some waveforms, and it is vital that these should meet the criteria of a protective open-lung ventilation strategy. The classical pulmonary waveforms are represented by pressure, volume and flow displayed versus time. While the pressure and flow curves are specific for the ventilation mode used, it is crucial to focus on the flow versus time curve, which allows detection of the following features: (i) an interruption in the inspiratory waveform indicating a lack of time for equilibrium to be reached between the alveolar and the airway pressure, with the risk of inadequate lung inflation, and (ii) an incomplete deflation of the lung with the risk of auto-PEEP with overdistension of the lung and an enhanced risk of barotrauma. Thus, as regards the flow curve, it is essential to adjust both T_i and T_e, (either by changing the ratio or by decreasing the respiratory rate) to let the waveform reach the zero flow state before the transition to the next insufflation or exsufflation.[52]

The pressure–volume and the flow–volume loops afford an insight into the lung mechanics. The flow–volume loop is very useful for the detection of any change in the inspiratory or expiratory resistances. For instance, increases in airway resistance will be obvious in the flow–volume curve, with a concave expiration loop. The pressure–volume loop provides information on the dynamic

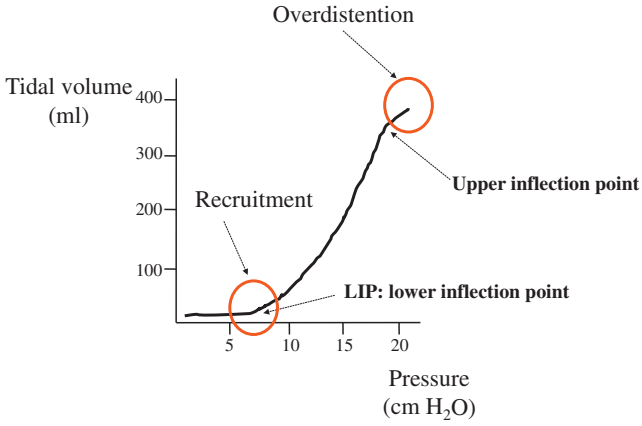

Fig. 1. Information provided by the pressure-volume loop.

compliance of the lung (defined by the slope of the loop), and also on the tidal volume, and facilitates establishment of the best PEEP level. Two inflection points characterise the loop. The first is at the lower part of the loop and corresponds to the beginning of alveolar recruitment. The lower flatter part can help in optimisation of the PEEP level, while the upper inflection point may occur at the end of the inspiration limb in cases of lung overinflation. In this situation, it is important to adjust V_t or the PIP to avoid any flattening of the upper end (Fig. 1).

Ventilation in transport

Transferring sick and unstable neonates between the ICU setting to the operating theatre is very hazardous. Transfer involves a higher risk of extubation, hypothermia, equipment and monitoring disconnection and also a risk of interruption to ideal ventilation modes and/or vital treatments such as nitric oxide. For sick neonates there should be a multidisciplinary discussion to decide whether the surgery can adequately be done in the ICU to prevent risk of transfer. This concept of surgery in the neonatal unit is no longer a novel one, for many studies have highlighted the beneficial effect of such practice on neonatal morbidity and mortality.[53] There are still some controversies surrounding the kind of procedures that can be performed in the ICU but a recent survey in the UK demonstrated that surgeons are becoming increasingly comfortable with performing laparotomy in very sick infants with necrotising enterocolitis in the ICU.[54] While the mortality following surgery for necrotising enterocolitis is more closely related to the severity of illness than to the location of the laparotomy, the transport of neonates weighing less than 1500 g to the operating theatre for laparotomy has been demonstrated to be associated with significant deterioration in a number of physiological parameters including oxygenation, which, in theory, may well impact on morbidity.[55] Thus, avoidance of the transfer of neonates weighing less than 1500 g in an unstable condition is nowadays encouraged. Surgery in the neonatal ICU maintains a continuity of care, but does require a surgical, neonatal and anaesthesia team that are comfortable with working together in that environment.

In other circumstances, transfer of a neonate with nasal CPAP is possible, especially as such devices are battery-powered. Regional anaesthesia for hernia repair for instance, can be performed while the child is under nasal CPAP, while more complex surgery may require that the trachea of the child be intubated with controlled ventilation.

Conclusion

The advances in technology over the last 20 years have led to the development of a variety of ventilation modes with confusing terminology, but which have undoubtedly contributed to the

advances in neonatal ventilation. It is important to note, however, that there is still no clear evidence as to the superiority of one ventilation mode over another with regard to the neonatal pulmonary and neural outcome. When applying the different available devices based on the newborn and premature respiratory physiology, clinicians should bear in mind that ventilation with a 'protective' and 'open-lung' strategy is essential to reduce the prevalence of bronchopulmonary dysplasia.

Practice points

- Match the characteristics of the ventilation with the pathophysiology of the patient.
- The choice of the ventilation mode should meet the criteria of protective open-lung ventilation strategy: 'Open the lung and keep it open'.
- Allow permissive mild hypercapnia.
- Real-time pulmonary monitoring should always guide the ventilation parameters.

Research agenda

- There is still a need for large studies to define the relevance of various ventilation modes;
- Utility of modern ventilation modes (such as the NAVA) in neonates;
- Establish evidence for the use of HFO ventilation and the reduction in the incidence of chronic lung diseases; and
- Better define the indications for non-invasive ventilation in the presence of respiratory distress syndrome.

Conflict of interest statement

None.

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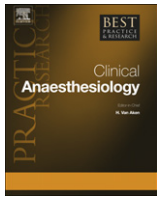

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Neonatal fluid management

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Perioperative fluid management in paediatrics has been the subject of many controversies in recent years, but fluid management in the neonatal period has not been considered in most reviews and guidelines.[1–3] The literature regarding neonatal fluid management mainly appears in the paediatric textbooks and few recent data are available, except for resuscitation and fluid loading during shock and major surgery. In the context of anaesthesia, many neonates requiring surgery within the first month of life have organ malformation and/or dysfunction. This article aims at reviewing basic physiological considerations important for neonatal fluid management and mainly focusses on fluid maintenance and replacement during surgery.

Physiological considerations: neonates are not just small adults

Major physiological changes occur within the first days and months of life. They mainly concern body composition, renal function and changes in the cardiovascular system.[4]

Body composition

Throughout foetal life and during the first 2 years of life the distribution of body fluid undergoes a gradual but significant change.[5] Total body water (TBW) represents as much as 80% of body weight in premature infants, 78% in full-term newborns and 65% in infants of 12 months of age compared to 60% in adults (Table 1). These age-related changes in TBW mainly reflect changes in extracellular fluid (ECF) with growth. As the body cells proliferate and organ development progresses, the ECF volume

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Table 1
Body composition and morphometric data in children (ICF: intracellular fluid; ECF: extracellular fluid).

	Premature	Full-term	1 yr	3 yr	9 yr	Adult
Body weight (BW kg)	1.5	3	10	15	30	70
Body surface area (BSA m^2)	0.15	0.2	0.5	0.6	1	1.7
BSA/BW	0.1	0.07	0.05	0.04	0.03	0.02
Total body water (% BW)	80	78	65	60		
ECF (% BW)	50	45	25	20		
ICF (% BW)	30	33	40	40		

decreases proportionally. It represents 50% of body weight in premature infants, 45% in full-term newborns and 25% in infants of 12 months of age compared to 20% in adults. The intracellular fluid compartment increases only moderately during the first year of life, representing 33% of body weight at birth and 40% of body weight by the end of the first year, and does not change substantially after that.

Renal maturation

Maturation of renal function is basically achieved by the end of the first month of life. Glomerular filtration increases rapidly from 34 weeks gestational age when kidneys have completed their nephronic structure.[6–8] After birth, renal vascular resistances decrease abruptly while systemic vascular resistances and arterial pressure increase. As a consequence, renal blood flow increases dramatically. This explains why glomerular filtration rate, still low during the first 24 h of life, rises very rapidly thereafter. During the first 6 weeks after birth, the area of cortical and juxtaglomerular nephrons, as well as the volume of glomerular capillaries and the size of glomerular membrane pores also increase. Tubular function is less mature than glomerular function at birth. Renal threshold for glucose is low explaining the high incidence of glycosuria even after moderate hyperglycaemia. The tubular capacity to reabsorb sodium is low in premature infants.[9] At term, the neonatal nephron begins to reabsorb sodium more actively in response to growth requirements. Sodium excretion in response to parenteral sodium load is also reduced. Careful control of sodium balance is essential in premature surgical neonates, as both hypernatraemia and hyponatraemia may have detrimental effects on the brain.

At birth, the newborn is unable to effectively concentrate urine. Clearance of free water is lower than that of adults thus explaining the impaired ability of newborn infants to cope with excessive water loading or water deprivation.

Finally, the renin–angiotensin–aldosterone system is functional in neonates[10] but feedback mechanisms are immature, especially in premature infants.[11]

Developmental cardiovascular changes

Newborns and premature infants have limited cardiovascular reserves in response to increased preload or afterload.[12–14] Any reduction in preload is also poorly tolerated owing to reduced compliance of the right ventricle and is rapidly followed by a reduction of systolic ejection volume. Cardiac output is high to compensate for the high oxygen affinity of foetal haemoglobin and to match the high oxygen consumption.[15] Cardiac output is highly dependent on heart rate in the neonatal period.[13] However, by the end of the first month of life, the capacity of the cardiovascular system to adapt is close to that of adults. In premature infants, excess of fluid will promote the persistence of patent ductus arteriosus.[16,17]

Maintenance requirements

Calorie requirement

The metabolic rate of a full-term newborn in a neutral environment is 32 kcal kg^{-1} per day during the first hours of life. Requirements increase rapidly during the first week of life, and then at a slower rate, increasing linearly with growth.[18]

In 1957, Holliday and Segar[19] estimated metabolic requirements for children at bed rest, and this estimation is still used in daily practice. The calculated calorie expenditure was 100 kcal kg^{-1} for infants weighing 3–10 kg, (1000 + 50) kcal kg^{-1} for each kilogram more for children between 10 and 20 kg, and 1 (500 + 20) kcal kg^{-1} for each kilogram over 20 kg. Half of those calories were thought to be required for basic metabolic needs and the remainder for growth. General anaesthesia essentially mimics calorie requirements at closer to basal metabolic rate.[20] As the maintenance needs for water paralleled energy metabolism, the estimated caloric expenditure was used to determine the maintenance fluid therapy (known as the 4–2–1 rule). Since the publication of this article, hypotonic solutions have had widespread use for decades until the danger of induced hyponatraemia was demonstrated in clinical practice.[21–25]

Water requirement

Under normal conditions, 1 ml of water is required to metabolise 1 kcal. This takes into account insensible water losses across the skin and respiratory tract, and urinary water loss. Therefore, in the awake child, calorie and water consumption are considered equal (Table 2). In anaesthetised children, Lindahl[20] calculated that 166 ml of water were required to metabolise 100 calories. Using indirect calorimetry, he calculated hourly maintenance fluid to be equal to the following expression 2.5× kg + 10 (ml h^{-1}). In term neonates, water intake is progressively increased during the first days of life from 60 ml kg^{-1} per day the first day and subsequently increased by 20 ml kg^{-1} per day to achieve 150 ml kg^{-1} per day at the end of the first week of life. Insensible water loss increases with decreasing body weight in premature infants, especially when they are cared under radiant warmer.[26] Several factors contribute to this large insensible water loss in premature infants: small size, an increased body-surface-area-to-body-weight ratio, increased thermal conductance, thinner more permeable and vascularised skin and a higher respiratory rate.

Electrolytes requirements

Daily sodium and potassium requirements were calculated by Holliday and Segar from the amount of electrolyte delivered by the same volume of human milk.[19] The daily needs were 3 mmol kg^{-1} per day sodium and 1–2 mmol kg^{-1} per day potassium. The combination of maintenance-fluid and electrolyte requirements results in a hypotonic electrolyte solution (0.2% saline equivalent). In premature infants, sodium and potassium requirements are higher than later in life, 3–5 mmol kg^{-1} per day for sodium and 2–4 mmol kg^{-1} per day for potassium mainly because of the immaturity of renal tubular function. Calcium requirements range between 0.8 and 1 mmol kg^{-1} per day.

Preoperative assessment

The preoperative assessment of fluid volume and state of hydration varies from elective surgery patients with no or slowly developing fluid deficit such as those scheduled for hernia repair to the severely sick premature infant with necrotising enterocolitis who is undergoing a dynamic deficit in blood and interstitial volume and in whom it is more difficult to evaluate fluid balance.

Vascular volume

The ultimate goal of perioperative fluid therapy is to maintain a correct fluid and electrolyte balance and, as a consequence, normal cardiovascular stability.[27] Indeed, dehydration and some medical conditions associated with third-space sequestration of fluids (e.g., intestinal occlusion) will in turn

Table 2
Fasting guidelines for elective surgery in neonates.

Ingested material	Minimum fasting period (h)
Clear liquids	2
Breast milk	4
Infant formula	4

affect vascular fluid volume. Restoration of an adequate vascular fluid volume is essential to maintain cardiovascular stability, organ perfusion and adequate tissue oxygenation. Isotonic transfer of fluid from the extracellular compartment to a non-functional interstitial space forms third-space volume. Replacement of intravascular volume loss should be performed by administration of normotonic and normo-osmolar solution. Crystalloid solutions such as Ringer lactate or normal saline, or even a colloid solution such as albumin can be used (see below). The prognosis of some medical conditions such as septic shock depends on the quantity and the rapidity of vascular loading; the younger the child, the greater the quantity of fluid loading related to body weight.[28–30] The fluid challenge is usually 10–20 ml kg^{-1} in children, but no clear recommendations can be found in the literature for the neonatal period even in the most recent published guidelines.[31]

Preoperative management of pyloric stenosis is much more codified. Pyloric stenosis is a medical emergency and not a surgical emergency. Preoperative correction of fluid and electrolyte deficits may require several hours or even days. The targets of preoperative fluid management is to correct dehydration and to obtain serum chloride $\geq$106 mmol l^{-1}, serum Na^+ $\geq$135 mmol l^{-1}, serum bicarbonate (HCO_3^-) $\leq$26 mmol l^{-1}, urine chloride (Cl^-) >20 mmol l^{-1} and urine output >1 ml kg^{-1} per hour. The most severe cases usually require an initial fluid challenge of 20 ml kg^{-1} of crystalloids to restore vascular fluid volume.

Fasting guidelines

There is now a large body of evidence that free intake of clear fluids up to 2 h preoperatively does not affect the pH or volume of gastric contents at induction of anaesthesia in children. While there have been relatively few studies in infants, these suggest that infants may be allowed clear fluids up to 2 h and breast milk 4 h preoperatively.[32,33] It was demonstrated >25 years ago that the gastric emptying of 110–200 ml of human milk was 82 ± 11% after 2 h in neonates and infants of <1 year of age, 84 ± 21% after whey-hydrosylated formula, 74 ± 19% after whey-predominant formula, 61 ± 17% after casein-predominant formula and 45 ± 19% after cow's milk.[34] Thus human milk and whey-predominant formula emptied faster than casein-predominant formula and cow's milk. Two other studies performed prior to anaesthesia demonstrated also that breast milk empties from the stomach faster than most formulas in infants and both require more than 2 h to ensure complete gastric emptying.[32,33] According to these data, the American guidelines recommended 4 h fasting time for breast milk and 6 h for infant formula and non-human milk.[35] These recommendations were also endorsed by The Royal College of Nursing that considered that there was insufficient evidence to change contemporary best practice (i.e., breast milk up to 4 h and formula and cows' milk up to 6 h).[36] However, recent Scandinavian guidelines recommended 4-h fasting for breast milk but also for formula milk in infants of <6 months of age.[37] Thus, it may be recommended to stop breast feeding and infant formula 4 h prior to anaesthesia in neonates (Table 2). This is our practice for otherwise healthy surgical neonates.

Intra-operative fluid management

Quantity of intra-operative fluids

Intra-operative fluid therapy is aimed at providing basal metabolic requirements (e.g., maintenance fluids), compensating for the preoperative fasting deficit and replacing losses from the surgical field.

When following modern more liberal nil per os (NPO) guidelines, fasting fluid deficit is expected to be minimal even in small infants and the sicker babies usually already have a functional intravenous line placed prior to surgery, and thus are expected to be correctly hydrated. Third-space losses may vary from 1 ml kg^{-1} per hour for a minor surgical procedure to as much as 15–20 ml kg^{-1} per hour for major abdominal procedures, or even up to 50 ml kg^{-1} per hour for surgery of necrotising enterocolitis in premature infants. Blood losses are replaced with either 1:1 ratio of blood or colloid, or 3:1 ratio for crystalloid. Third-space losses should be replaced with crystalloid (e.g., normal saline or Ringer lactate), but maintenance fluids are basically hypotonic as discussed above. Thus, intra-operative fluid administration requires two different types of fluids administered at different rates: one with maintenance fluids at a set rate (Table 2) and the other for replacement fluids.

Glucose: necessary or harmful?

The next question is whether or not administration of dextrose is necessary during surgery. In the last several years, there has been a complete re-evaluation of the place of glucose in routine intra-operative solutions. As already discussed above, energy requirements during anaesthesia are close to the basal metabolic rate. Administration of dextrose was previously deemed mandatory in children to avoid perioperative hypoglycaemia which may be difficult to diagnose in an anaesthetised child, but the risk of hyperglycaemia was, at that time, underestimated.

The risk of hypoglycaemia is a legitimate concern in neonates and small infants, especially in those on total parenteral nutrition. There is, however, no agreement in the literature regarding the definition of hypoglycaemia.[38] The value of 2.4 mmol l^{-1} is often proposed as the acceptable level in infants and children. In neonates, hypoglycaemia during fasting or illness is well known and results from several factors.[39] Whole-body glucose metabolism corrected for body mass in neonates is up to twice as high as in adults. Hepatic glycogen stores corrected for body mass are less in neonates than in adults. Gluconeogenic enzymes to convert amino acids to glucose are also inefficient. Prior to cardiopulmonary bypass, the incidence of hypoglycaemia is as high as 9% in neonates receiving glucose-free solutions.[40] In 1990, Larsson et al.[41] studied blood glucose concentrations in neonates undergoing major surgery during the first week of life. Intra-operative blood glucose levels were maintained by most neonates who did not receive intra- and preoperative glucose. However, hypoglycaemia occurred when a preoperative glucose infusion was interrupted during surgery or in neonates younger than 48 h of age.

Prolonged and severe hypoglycaemia is associated with extensive and widespread neuronal injury involving predominantly gray matter structures.[42,43] However, transient hypoglycaemia has also been associated with neurologic injury in neonates.[44,45] Thus, in neonates, preventing hypoglycaemia is essential, especially in asphyxiated neonates and those undergoing cardiac surgery.[39] Certain neonates are at increased risk of hypoglycaemia such as infants of diabetic mothers and those with the Wiedemann–Beckwith syndrome.

The danger of hyperglycaemia in the perioperative period is a real clinical issue that has been extensively reviewed.[46–48] Hyperglycaemia can induce osmotic diuresis and, consequently, dehydration and electrolyte disturbances. In the early 1980s, animal studies in adult animals clearly demonstrated that glucose worsens outcome from both global and focal ischaemia. The proposed mechanism of this injury is that, in the presence of an ischaemic or hypoxic insult, oxidative metabolism of glucose fails, and glycolysis, with its end-product of lactate, increases. With sufficient intracellular lactate accumulation, intracellular pH falls, which may lead to compromised cellular function or cell death.

In contrast to the adult, moderate hyperglycaemia in the neonate seems to protect the brain from ischaemic damage.[39] Indeed, hyperglycaemia increases cerebral high-energy reserves and glycogen stores.[49–52] Glucose uptake and metabolism is slower and lactate accumulates slower in the neonatal brain compared with the adult brain. Finally, lactate clearance is enhanced, thereby avoiding the toxicity of lactacidosis. In young infants, glucose infusion at a rate of 120 mg kg^{-1} per hour is sufficient to maintain an acceptable blood glucose level and to prevent lipid mobilisation.[53,54]

Clinical guidelines

To avoid both hyper- and hypoglycaemia in the neonates, usually two distinct intravenous lines are useful: one for providing glucose and metabolic requirements, the second for fluid replacement. Our practice is to use polyionique B66 (balanced isotonic hydrating solution containing sodium chloride (NaCl)120 mmol l^{-1} plus 0.9% dextrose) for maintenance fluid therapy and replacement of most of third-space-compartment losses and to monitor closely blood glucose levels during surgery.[55] As the volume of fluid administered is usually quite large, the amount of glucose is sufficient to avoid hypoglycaemia and usually does not induce hyperglycaemia. A glucose-infusion rate between 120 and 250 mg kg^{-1} per hour is sufficient to avoid hypoglycaemia and to prevent lipid mobilisation in neonates and infants.[56] In paediatric cardiac surgery, glucose administration decreases the incidence of hypoglycaemia, without significantly affecting the incidence of hyperglycaemia. Moderate intra-operative glucose administration (150 mg kg^{-1} per hour) may be recommended to achieve this goal.[57,58]

Volume replacement during infancy: indications and choice of crystalloids and colloids

Crystalloids (e.g., normal saline or Ringer lactate) are first administered to treat absolute or relative blood-volume deficits frequently observed during surgery in children. Their advantages include their low cost, their lack of effect on coagulation, the absence of risk of anaphylactic reaction and of risk of transmission of any known or unknown infectious agent. This practice should also apply to premature and newborn infants. Indeed, studies performed in hypotensive premature infants or polycythaemic newborns have demonstrated that normal saline is as effective as albumin to restore and maintain arterial pressure or to treat neonatal polycythaemia.[59–62] In addition, in premature infants, crystalloid administration was causing less fluid retention in the first 48 h than 5% albumin. However, volume replacement with crystalloids in neonates on veno-arterial membrane oxygenation aggravated the oedema in a pre-existing situation of capillary-leakage syndrome, whereas volume replacement with colloids had lesser effects on oedema.[63]

The rate of fluid administration will be indicated by the cardiovascular condition. Normally, 15–20 ml kg^{-1} of Ringer lactate solution over 15–20 min will re-establish cardiovascular stability. After administration of a total of 30–50 ml kg^{-1} of crystalloid solution, the administration of a colloid solution (albumin or synthetic colloid) to maintain intravascular osmotic pressure is indicated.[64]

Hydroxyethylstarch (HES) preparations are becoming very popular for vascular loading in adults and children.[65] However, the number of paediatric studies aimed at evaluating HES efficacy and tolerance is limited and, within years, available HES solutions have changed with reduced molecular weight and molar substitution ratio. The third generation of HES (130/0.4) has reduced adverse effects on coagulation and renal function than older solutions while maintaining efficacy.[66] Only studies performed with this third-generation HES (130/0.4) are discussed, as HES of first and second generations are no longer available in most countries. The European prospective multicentre observational post-authorisation safety study enrolled 300 paediatric patients who received a third-generation HES.[67] Among the paediatric patients, ~10% were neonates. Whatever the age group, no serious adverse event were reported while the mean volume infused was 11 ± 4.8 ml kg^{-1}. However, only children with normal renal function and intact coagulation system were included in this prospective study. Chong Sung et al.[68] showed that the administration of 10 ml kg^{-1} HES 130/0.4 to children undergoing cardiac surgery does not cause more bleeding or a higher transfusion requirement than fresh frozen plasma, but no neonates were included in this randomised clinical trial. Using a higher infusion volume of 15 ml kg^{-1}, Haas et al.[69] found that activated modified thromboelastography values were significantly more impaired after HES 130/0.4 than after albumin or gelatine in children with weight range of 3–15 kg. They concluded that, from a haemostatic point of view, it might be preferable to use gelatine solutions as an alternative to albumin rather than HES 130/0.4. The most recent study randomised 119 children to receive 50 ml kg^{-1} of either 4% albumin or 6% HES 130/0.4 for intra-operative fluid-loading replacement in children undergoing cardiac surgery.[70] They found similar blood loss between the two groups but a higher number of children in the albumin group required allogenic transfusion whereas intra-operative fluid balance was lower in the HES group. Although many infants were enrolled in this study, neonates (<28 days) were excluded. To summarise, the new generation of HES seems to be safer than the older generation, but sufficient safety data are lacking to recommend its use in neonates owing to their immature renal and coagulation functions.

Gelatines have been used for many years in children but also in early infancy to treat intravascular fluid deficits. Haemaccel™ is no longer used in many countries owing to its high risk of anaphylactic reaction. Haemaccel™ was demonstrated to be as effective as 4.5% albumin to maintain blood pressure during major surgery in neonates, but less effective to maintain plasma colloid osmotic pressure and plasma albumin concentration.[71]

Although the use of albumin has been challenged owing to its high cost and to its uncertain risk of transmission of non-conventional agents, it remains the main colloid used in the neonatal period and early infancy for volume expansion.[72,73] In hypotensive premature infants, 4.5% albumin was demonstrated to be as effective as fresh frozen plasma to restore blood pressure, but more effective than 20% albumin.[74] This suggests that the volume of albumin administered is more important that its concentration to maintain or restore cardiovascular stability. Thus, 5% albumin is still the preferred

Table 3
Transfusion thresholds for infants under 4 months of age.

Anaemia in the first 24 h	Haemoglobin 12 g/dl (Hct ~ 0.36)
Neonates receiving intensive care	Haemoglobin 12 g/dl
Chronic oxygen dependency	Haemoglobin 11 g/dl
Late anaemia, stable patients	Haemoglobin 7 g/dl
Acute blood loss	10% of blood volume

colloid in newborn infants as it is iso-oncotic to plasma and very effective to maintain blood pressure and plasma colloid perfusion pressure.[71]

The use of fresh frozen plasma should be restricted to neonates and children with proven coagulation disorders.

Guidelines for neonatal blood transfusion

Blood-transfusion safety has dramatically improved in recent years, but unnecessary transfusion still carries some risks that justify reasonable indication prior to administering blood products. The clinical indication for the administration of erythrocytes to a patient during the course of surgery should be dictated only by the necessity to maintain oxygen-carrying capacity and oxygen delivery to peripheral tissues.

Appropriate transfusion thresholds for the first 4 months of age are higher than for older children due to physiological differences between this age group and adults. Indeed, neonates and infants have higher oxygen consumption per kilogram and a higher cardiac-output-to-blood-volume ratio than adults. Normal haemoglobin values are significantly higher at birth and decrease gradually over the first few months of life. In addition, at birth, foetal haemoglobin is the main haemoglobin and has a higher affinity for oxygen than adult haemoglobin. Suggested transfusion threshold according to clinical status and haemoglobin levels have been published for infants of <4 months of age[75] and are summarised on Table 3. These were not published with special reference to the surgical patient.

Accurate monitoring of blood loss in neonates is vital to any replacement regimen. It can be achieved by weighing sponges and observing small, calibrated, suction bottles but visual estimation is also essential in the practice of neonatal anaesthesia. The concept of measuring *a priori* the allowable red cell loss based on the starting blood volume, haemoglobin and haematocrit combined with proper cardiovascular monitoring (e.g., heart rate, blood pressure and urine output) and haemoglobin measurements may help to guide blood replacement.

Blood-volume estimates are based on the age of the patient. The estimated blood volume (EBV) is 90–100 ml kg^{-1} in premature infants, 80–90 ml kg^{-1} in term neonates and then decreases to achieve 70–75 ml kg^{-1} in infants >3 months of age. EBV should be calculated and indicated on anaesthesia chart when haemorrhagic surgery is performed. Allowable blood loss (ABL) is calculated as follows:

$$ABL = weight \times EBV \times \left[\frac{(H_o - H_1)}{H_{mean}}\right]$$

where H_o = initial haematocrit, H_1 = target haematocrit and H_{mean} is the average haematocrit.

Losses below the maximum allowable can be replaced with crystalloids or colloids as discussed previously. In the absence of ongoing blood loss, ~4 ml kg^{-1} of packed red cells will be required to raise the haemoglobin level by 1 g dl^{-1}.

Conclusion

Neonates are not small adults. The large extracellular space explains why the amount of fluid required to maintain or to restore blood volume is considerably higher in neonates compared to older children and adults. Avoiding hypoglycaemia is essential in the neonatal period. The rationale for fluid loading and blood transfusion is, however, close to that recommended in adults.

Practice points

- The ECF compartment represents 45% of body weight in full-term neonates explaining why large volumes of isotonic fluids may be required during major surgery associated with intravascular volume depletion
- Both hypoglycaemia and hyperglycaemia have to be avoided. In young infants, glucose infusion at a rate of 120 mg kg^{-1} per hour is sufficient to maintain an acceptable blood glucose level and to prevent lipid mobilisation
- Blood glucose levels should be closely monitored during surgery
- The new generation of hydroxyethylstarch preparation seems to be safer than the older generation preparation, but sufficient safety data are lacking to recommend its use in neonates owing to their immature renal and coagulation functions
- 5% albumin is the preferred colloid in newborn infants as it is iso-oncotic to plasma and very effective to maintain blood pressure and plasma colloid perfusion pressure
- In the absence of ongoing blood loss, ~4 ml kg^{-1} of packed red cells will be required to raise the haemoglobin level by ~1 g dl^{-1} in neonates

Research agenda

- Short- and long-term safety data after administration of hydroxyethylstarches in the neonatal period
- The paradoxical neuroprotection associated with moderate hyperglycaemia in newborn infants
- Non-invasive monitoring of vascular volume in newborn infants

Conflict of interest statement

None declared.

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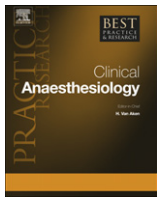

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Pulmonary hypertension of the newborn

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Pulmonary hypertension presenting in the neonatal period can be due to congenital heart malformations (most commonly associated with obstruction to pulmonary venous drainage), high output cardiac failure from large arteriovenous malformations and persistent pulmonary hypertension of the newborn (PPHN). Of these, the most common cause is PPHN. PPHN develops when pulmonary vascular resistance (PVR) remains elevated after birth, resulting in right-to-left shunting of blood through foetal circulatory pathways. The PVR may remain elevated due to pulmonary hypoplasia, like that seen with congenital diaphragmatic hernia; maldevelopment of the pulmonary arteries, seen in meconium aspiration syndrome; and maladaption of the pulmonary vascular bed as occurs with perinatal asphyxia. These newborn patients typically require mechanical ventilatory support and those with underlying lung disease may benefit from high-frequency oscillatory ventilation or extra-corporeal membrane oxygenation (ECMO). Direct pulmonary vasodilators, such as inhaled nitric oxide, have been shown to improve the outcome and reduce the need for ECMO. However, there is very limited experience with other pulmonary vasodilators. The goals for anaesthetic management are (1) to provide an adequate depth of anaesthesia to ablate the rise in PVR associated with surgical stimuli; (2) to maintain adequate ventilation and oxygenation; and (3) to be prepared to treat a pulmonary hypertensive crisis – an acute rise in PVR with associated cardiovascular collapse.

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Persistent pulmonary hypertension of the newborn (PPHN) is a cardiopulmonary disorder characterised by marked pulmonary hypertension resulting in a severe reduction in pulmonary blood flow and shunting from the pulmonary circulation to the systemic circulation. PPHN typically affects full-term and near-term neonates shortly after birth and occurs in 1–2 newborns per 1000 live births. Neonates with PPHN develop severe respiratory distress, refractory hypoxaemia and acidosis. Despite significant improvements in treatment, this disorder causes substantial morbidity in newborns, with a mortality rate of about 10–20%.[1,2]

Physiology

In the normal foetal circulation, most of the cardiac output bypasses the lungs because hypoxia maintains intensive pulmonary arteriolar constriction. After birth, the combination of rhythmic ventilation of the lung and increased alveolar oxygen tension alters the balance between vasoconstrictors and vasodilators, resulting in a dramatic decrease in pulmonary vascular resistance (PVR). Pulmonary blood flow significantly increases as the lungs assume the function of gas exchange. Three endothelial-derived mediators, nitric oxide (NO), prostacyclin and endothelin, play important roles in the regulation of pulmonary vascular resistance during the transitional period.[3,4] NO is thought to be the most important endogenous regulator of vascular tone, and, therefore, endothelial nitric oxide synthase, the enzyme that converts L-arginine to L-citrulline and NO in the presence of oxygen, is a critical enzyme during the transition period. NO stimulates soluble guanylate cyclase in the vascular smooth muscle cell, resulting in increased levels of cyclic guanosine monophosphate (cGMP). cGMP then binds to the Ca^{++} channel and decreases Ca^{++} influx, producing relaxation of the vascular smooth muscle cell. Type 5 phosphodiesterase (PDE-5) in the vascular smooth muscle cell breaks down cGMP and limits the duration of vasodilation. Prostacyclin (PGI_2) is another important vasodilator for the vascular smooth muscle cell. PGI_2 activates the enzyme adenylate cyclase, which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Increased cAMP also decreases Ca^{++} influx resulting in vascular smooth muscle relaxation. Type 3 PDE breaks down cAMP and limits the duration of vasodilation induced by PGI_2 (Fig. 1).[5] Endothelin-1 (ET-1) mediates hypoxic pulmonary vasoconstriction through the endothelin-A receptor on vascular smooth muscle cells and vasodilation through the endothelin-B receptor on endothelial cells.[3]

Significant changes in the circulation occur at birth. Under normal circumstances, there is a progressive fall in pulmonary vascular resistance (PVR) and an immediate rise in systemic vascular resistance (SVR), and the decline in the PVR/SVR ratio results in an increase in pulmonary blood flow and oxygen uptake in the lung. Factors that contribute to the postnatal increase in SVR include the removal of the placenta, a catecholamine surge associated with birth and cutaneous vasoconstriction from the cold extrauterine environment. Factors that promote the decrease in PVR include expansion of the lung to normal resting volume, establishment of adequate alveolar ventilation and oxygenation and successful clearance of foetal lung fluid. When abnormal conditions develop before, during or after birth, the postnatal adaptation of the pulmonary vasculature from the high-resistance foetal state to the low-resistance adult state may be impaired and result in high pulmonary arterial pressure. When pulmonary pressure supersedes the systemic pressure, blood will shunt right to left across existing cardiovascular channels, such as the foramen ovale or ductus arteriosus, and result in intractable systemic hypoxaemia and cyanosis. Because hypoxaemia, hypercarbia and acidosis, all increase pulmonary vascular tone,[6,7] right-to-left shunting will further increase pulmonary vascular resistance resulting in a clinical downward spiral that leads to high mortality rate of these infants, if aggressive treatment is not applied or is ineffective.

Pathophysiology

PPHN is typically divided into three types of abnormalities of the pulmonary vasculature: underdevelopment, maldevelopment and maladaptation.[8–10]

Underdevelopment is characterised by a reduction in the cross-sectional area of the pulmonary vasculature from pulmonary hypoplasia, producing a relatively fixed elevation of PVR. Typical lesions

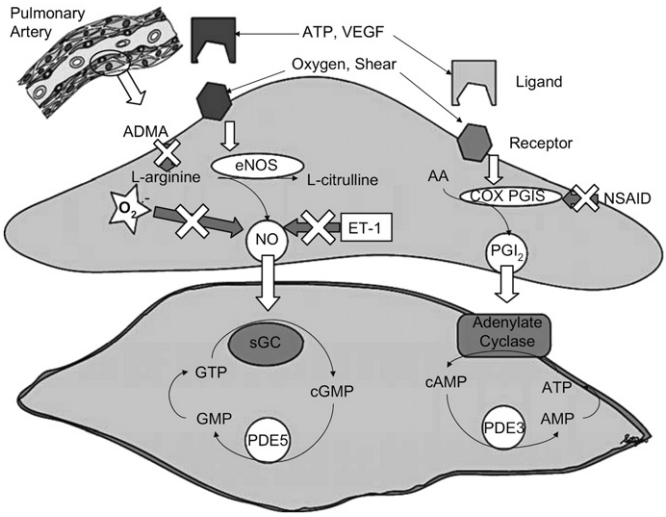

Fig. 1. Mechanism of endothelium-dependent vasodilation in the pulmonary artery. Endothelial nitric oxide synthase (eNOS) and cyclooxygenase (COX) are stimulated by physiologic agonists ATP and vascular endothelial growth factor (VEGF) and directly by oxygen and shear stress. Nitric oxide (NO) and prostacyclin (PGI_2) diffuse to vascular smooth muscle, where they activate soluble guanylate cyclase (sGC) and adenylate cyclase, respectively, to increase the levels of cGMP and cAMP. These cyclic nucleotides initiate smooth muscle relaxation. Specific phosphodiesterases (PDE) promote breakdown of the cyclic nucleotides. The arginine analogue, asymmetric dimethyl arginine (ADMA), superoxide (O_2-), and endothelin (ET-1) decrease NO release and cause vasoconstriction. NSAID, nonsteroidal anti-inflammatory drug; PGIS, prostacyclin synthase.

include congenital diaphragmatic hernia (CDH), cystic adenomatoid malformation of the lung, renal agenesis, oligohydramnios accompanying obstructive uropathy and intrauterine growth restriction. Although some degree of postnatal pulmonary vasodilatation can occur, this adaptive mechanism is limited, and therefore the mortality is greatest in this group of patients.

Maldevelopment refers to the situation in which the lungs develop normally; however, the muscle layer of the pulmonary arterioles is abnormally thick and extends into small vessels that normally have thin walls and no muscle cells.[10] Patients with this disorder will undergo remodelling of the pulmonary vascular bed during the first 7–14 days after birth with an associated reduction in PVR. It appears that vascular mediators stimulate maldevelopment of the pulmonary vasculature. When compared to healthy control patients, infants with severe PPHN have higher plasma concentrations of the vasoconstrictor ET-1 and lower concentrations of cGMP.[11] Conditions associated with PPHN caused by vascular maldevelopment include post-term delivery and meconium aspiration syndrome. In these disorders, the pulmonary vasculature responds poorly to oxygen and ventilation, which normally produce a decrease in PVR. Excessive perfusion of the foetal lung from constriction of the ductus arteriosus or pulmonary venous obstruction may also predispose to vascular maldevelopment. Nonsteroidal anti-inflammatory drugs (NSAIDs) produce ductal constriction and are associated with PPHN. Finally, one study found that the use of selective serotonin receptor inhibitors (SSRIs) during the second half of pregnancy produced a sixfold increased risk of PPHN compared with control infants.[12] Animal studies have shown that an accumulation of serotonin in the rat foetal lung may lead to vasoconstriction and proliferation of pulmonary smooth muscle cells.[13]

In maladaptation, the pulmonary vascular bed is normally developed. However, adverse perinatal conditions cause active vasoconstriction and interfere with the normal postnatal reduction in PVR. These conditions include perinatal depression, pulmonary parenchymal diseases and bacterial infections, especially those caused by group B *Streptococcus* (GBS). In newborn lambs, pulmonary hypertension can be induced by cardiolipin and phosphatidylglycerol, two phospholipids located primarily in the cell wall of GBS.[14]

Neonatal pulmonary hypertension is sometimes seen with high-output congestive heart failure among children born with large arteriovenous malformations, commonly, vein of Galen aneurismal

malformations.[15–17]These aneurismal malformations are rare congenital intracranial vascular malformations and 94% of patients present with systemic cardiac manifestations as the first clinical symptoms.[18] Emergency endovascular embolisation and then staged embolisations are usually essential for treatment, and to resolve the associated congestive heart failure, as well as pulmonary hypertension. Echocardiography typically reveals bi-ventricular dysfunction with some degree of mitral and tricuspid regurgitation. The lungs will manifest pulmonary congestion with reduced pulmonary compliance and impaired gas exchange. The associated hypoxaemia and hypercapnia will cause the reactive pulmonary vasculature of the neonate to develop systemic or supra-systemic pressures with bidirectional shunting through the ductus arteriosus. Inhaled NO is commonly administered during the perioperative period and is especially helpful as a bridge therapy to maintain adequate oxygenation by reducing right-to-left shunting until an emergency embolisation can be performed.

Pathophysiology summary

- Normally at birth there is a fall in PVR and rise in SVR resulting in an acute rise in pulmonary blood flow.
- This normal change in the circulation may be interrupted due to abnormaties of the pulmonary vasculature:
  - *Underdevelopment* from pulmonary hypoplasia associated with CDH and other congenital malformations of the lung produce a relatively fixed elevation in PVR with limited adaptability. This group has the highest mortality.
  - In *maldevelopment* the muscle layer of the pulmonary arterioles is thickened and extends into small vessels. Post-term delviery, meconium aspiration syndrome and prenatal exposure the NSAIDs or SSRIs are all associated with this condition.
  - In *maladaptation* the pulmanry vasculature is normal; however, PVR does not decline at birth and is associated with prenatal depression and bacterial infections such as Group B streptococcus.

Pulmonary hypertension associated with congenital heart disease

Pulmonary hypertension associated with congenital heart disease is most commonly seen among patients with large left-to-right shunts, such as a large ventricular septal defect (VSD), large patent ductus arteriosus (PDA), complete atrioventricular canal, truncus arteriosus, transposition of the great arteries with large VSD and specific types of single ventricle defects without obstruction to pulmonary blood flow. The size of the shunt, the blood flow through the shunt and the location of the shunt are the most important risk factors for the development of pulmonary arterial hypertension (PAH).[19] Nearly all patients with truncus arteriosus, about 50% of the patients with VSD and only 10% with atrial septal defect (ASD) will eventually develop Eisenmenger syndrome.[20] However, pulmonary hypertension is rarely seen in the neonatal period, with the exception of patients who have elevated pulmonary venous pressure caused by conditions such as mitral valve stenosis, total anomalous pulmonary venous connection with obstruction or single ventricle with mitral atrasia and intact atrial septum. Urgent decompression of pulmonary venous pressure is usually required for survival in these patients.

Cardiovascular effects of pulmonary hypertension

At birth, the size and mass are equal in the left ventricle and the right ventricle; therefore elevated pulmonary pressures are generally well tolerated. However, an acute, supra-systemic elevation in PVR produces a significant increase in the afterload of the right ventricle and has the potential to cause right ventricular dysfunction or failure. Left ventricular stroke volume is also decreased, as there is limited volume available for left ventricular filling and the intraventricular septum will bow to the left. A sudden increase in PVR that results in pulmonary pressure exceeding mean arterial pressure will

compromise cardiac output from right ventricle (RV) failure and lower arterial pressure, producing arterial and/or venous oxygen de-saturation. This phenomenon is termed a pulmonary hypertensive crisis.[21] Hypercarbia, hypoxia, acidosis and noxious stimuli from pain or airway manipulation can all cause a sudden increase in PVR, resulting in pulmonary hypertensive crisis and/or right heart failure.[22,23] Without rapid and effective treatment, a pulmonary hypertensive crisis can soon escalate to circulatory collapse and death.

Clinical presentation and investigation of pulmonary hypertension

PPHN should be suspected in any term or near-term newborn with respiratory distress, labile oxygenation and/or cyanosis shortly after delivery. Many infants with CDH and congenital lung lesions are diagnosed antenatally through routine ultrasound screening.

The primary findings on physical examination reveals tachypnoea, retractions, grunting, desaturation unresponsive to supplemental O_2 and cyanosis. Cardiac examination may have altered heart sounds, such as a loud P2, split S2, a systolic murmur secondary to tricuspid regurgitation or a diastolic murmur of pulmonary valve regurgitation and the signs of right heart failure, such as hepatomegaly. In infants with a right-to-left shunt via a patent ductus arteriosus, different O_2 saturation between the right upper extremity and lower extremities is expected due to higher oxygenation in the right brachial artery than in the descending aorta.[24]

The next step of diagnostic evaluation of suspected patients is to determine if the patient's symptoms are due to PPHN and to rule out other possible disease. The initial assessments include chest X-ray, electrocardiogram (ECG) and echocardiography. The chest X-ray may be normal or may demonstrate changes of underlying disease, such as meconium aspiration syndrome, neonatal pneumonia and CDH. Radiographic signs of PPHN include RV enlargement and enlarged main and hilar pulmonary arterial shadows with peripheral attenuation of peripheral pulmonary vascular markings. The ECG commonly is normal for age, with right ventricular predominance. ST segment elevation is sometimes present in infants with perinatal asphyxia. When PPHN is suspected, transthoracic echocardiography will confirm the presence of pulmonary hypertension and provide additional information about the cause of PPHN. By measuring the systolic regurgitant tricuspid flow velocity, Doppler echocardiography is able to estimated pulmonary artery systolic pressure.[25] Pulmonary pressure obtained by Doppler echocardiography is correlated highly with the values directly measured during right heart catheterisation.[26] Echocardiography is also useful to rule out congenital heart disease and to directly assess ventricular systolic and diastolic function.

Medical management of PPHN

The treatment of pulmonary hypertension depends on the aetiology of the original disease, the degree of impairment of cardiac and respiratory function, the severity of pulmonary hypertension and the likelihood of response to treatment. The therapeutic management of pulmonary hypertension in infants includes treatment of the underlying disease, maintenance of adequate systemic arterial blood pressure and pulmonary perfusion, oxygen supplementation to optimise oxygenation and pharmacologic measures to produce pulmonary vasodilatation.

It is important to improve alveolar oxygenation with supplemental oxygen. Neonates with mild respiratory distress may respond well to oxygen alone delivered via nasal cannula or facemask. Neonates with moderate respiratory distress require mechanical ventilatory support, and patients with moderate-to-severe respiratory distress require multiple interventions to maintain oxygenation and cardiac function.

Typically, the strategy of mechanical ventilatory support depends on the degree of lung disease and the patient's response to treatment. In general, patients with less severe pulmonary impairment are treated with conventional mechanical ventilation, and ventilated to maintain normocapnia. If the infant is agitated and breathing out of synchrony with the ventilator, opioid analgesics such as morphine or fentanyl are administered; and if dyssynchronous breathing persists and a specific cause cannot be identified, neuromuscular blockers are indicated. Those infants with severe lung disease more commonly require high-frequency oscillatory ventilation (HFOV). A randomised trial of HFOV and

iNO among patients with severe PPHN found 23% of patients who initially were assigned to HFOV, recovered without iNO.[27] Circulatory support usually is needed in severely affected patients. Adequate vascular volume should be maintained with intravenous fluids, and transfusion of packed red blood cells is commonly required to replace blood lost from sampling and to optimise tissue oxygen delivery. Dopamine, dobutamine or epinephrine is frequently used to improve cardiac output and systemic blood pressure.[28]

The application of surfactant therapy facilitates alveolar expansion in patients with parenchymal lung disease, especially in neonates with respiratory distress syndrome. Surfactant has also been shown to improve alveolar recruitment in patients with pneumonia, sepsis and meconium aspiration syndrome.[29]

Inhaled nitric oxide therapy has brought the treatment of PPHN into a new era. iNO decreases the pulmonary artery pressure and pulmonary-to-systemic arterial pressure ratio.[30] Oxygenation improves as pulmonary vessels are dilated in well-ventilated parts of the lung, thereby redistributing blood flow from regions with decreased ventilation and reducing intrapulmonary shunting. In the circulation, iNO has an ultrashort half-life. It combines with haemoglobin and is rapidly converted to methaemoglobin and nitrate and therefore produces little effect on SVR and systemic blood pressure. iNO improves oxygenation and reduces the need for ECMO in term and late preterm infants with severe PPHN and does not appear to have toxicity.[24,27,31] In a Cochrane review, iNO improved oxygenation in approximately one-half of infants who received the drug.[32] The outcome was not affected by presence or absence of echocardiographic evidence of PPHN; however, no benefit was noted among infants with CDH.

Other vasodilators, such as sildenafil, milrinone and calcium channel blockers are also used in PPHN.[33] Sildenafil is selective PDE type-5 inhibitor, which blocks the hydrolysis of cyclic GMP. They provide relatively selective pulmonary vasodilation, produce rapid onset of action and act synergistically with NO.[34,35] One randomised controlled study of 13 infants with severe PPHN (oxygen index ≥ 40) demonstrated improved oxygen index in patients who received sildenafil; six of seven infants treated with sildenafil survived compared with one of six placebo-treated controls.[36]

ECMO, a form of cardiopulmonary bypass, may be considered in critically ill infants with persistent pulmonary hypertension, CDH, severe pneumonia and those with severe hypoxic respiratory failure that cannot be oxygenated adequately with conventional ventilators and/or high-frequency oscillatory ventilation.[37]

Medical management of PPHN

- Oxygen
- Conventional mechanical ventilation to produce normocapnia or mild hypocapnia
- HFOV when high pressures or rates are required with conventional mechanical ventilation
- Maintain the Hct 35–45%
- Inhaled Nitric Oxide
- Catecholamines and/or milrinone as indicated for circulatory support
- ECMO for patients who are unresponsive to above therapeutic measures

Further research is needed

- To determine the efficacy of ECMO in the treatment of PPHN or PPHN associated with CDH.
- To determine the safety and effectiveness of newer pulmonary vasodilators such as calcium channel blockers such as verapamil; phosphodiesterase type 5 inhibitors such as sildenafil; prostanoids such as epoprostenol; and endothelin inhibitors such as bosentan.

Congenital diaphragmatic hernia (CDH)

The optimal mode of mechanical ventilation for CDH patients is not defined. However, it is clear that barotrauma from the use of high ventilatory rates and high inspiratory pressures is a significant contributor to morbidity and mortality.[38,39] The term 'gentle' ventilation is applied to conventional ventilation and refers to controlling the peak inflation pressure (18–22 cmH_2O) while tolerating an oxygen saturation of 85% and hypercapnia, and allowing spontaneous ventilation.[40–42]

Even though there are limited data, it appears that iNO has no long-term benefit in infants with CDH.[32,43] In one study evaluating the value of iNO, 53 infants were randomly assigned to receive iNO or control. Death or the need for ECMO was not significantly different and ECMO was used more often in the iNO group. In addition, there were no significant changes in PaO_2 detected 30 min after starting iNO. However, a transitory improvement occurred in approximately one-half of the infants treated with iNO.

Anaesthetic consideration for patient with PPHN

Children with pulmonary hypertension undergoing anaesthesia have a higher morbidity and mortality from cardiovascular complications.[22,44,45] The management of a neonate with pulmonary hypertension is a challenge for the anaesthesiologist because of the potential for developing a pulmonary hypertensive crisis with either right-to-left shunting or right-sided heart failure or even cardiac arrest.

The goals of anaesthetic management in patient with PPHN are (1) to provide an adequate depth of anaesthesia and analgesia to minimise the autonomic response to surgical stimulation and airway manipulation that may produce an acute increase in PVR; (2) to optimise myocardial function; (3) to choose a ventilation strategy that produces pulmonary vasodilation; and (4) to be prepared to treat a pulmonary hypertensive crisis and cardiac collapse.

Anaesthetic agents

No single anaesthetic agent or technique has proven ideal for patients with PPHN, and most studies of anaesthetics are from older children, adults or animal models. In children, Carmsoino and colleagues were unable to show an outcome difference between patients who were sedated versus those undergoing general anaesthesia.[22] A balanced anaesthetic technique combining volatile agents, opoids and muscle relaxants is commonly used to provide adequate anaesthesia and analgesia.

The volatile anaesthetics exert differing effects on the pulmonary vasculature. Some of the effects are conflicting and not fully understood.[46–49] For example, desflurane may potentiate pulmonary vasoconstriction in response to adrenoceptor activation.[50] Isoflurane and sevoflurane are generally associated with pulmonary vasodilatation and are commonly used in patients with pulmonary hypertension. However, any of the volatile agents can reduce systemic vascular resistance and cardiac contractility at doses greater than 1 minimum alveolar concentration (MAC). The use of these agents among patients with limited cardiac output and pulmonary hypertension may lead to systemic hypotension and decrease coronary perfusion.[51] Nitrous oxide has been shown to moderately attenuate hypoxic pulmonary vasoconstriction.[52,53] Although increasing pulmonary vascular resistance and pulmonary pressure has been observed in animal models[54] and in adult patients,[55] nitrous oxide does not increase PAP and PVR in infants.[56] Because all neonatal patients have potential intracardiac communications, nitrous oxide should probably be avoided in any surgical procedure with a potential risk of air embolism.

Propofol reduces both pulmonary and systemic vascular resistance, but has a greater effect on SVR.[57,58] The use of propofol should be limited among patients with severe PPHN and limited right heart function, in which maintenance of systemic blood pressure is critical.

The effect of ketamine in children with PAH is controversial. Both Morray and Wolfe demonstrated that ketamine significant increases in PVR and PAP in children undergoing cardiac catheterisation.[59,60] However, Hickey showed no significant effect of ketamine on PAP and PVR in infants with normal and elevated pulmonary vascular resistance.[61] Ketamine produces sympathetic nervous system activation

and increased epinephrine and norepinephrine levels,[62] which may change the reactivity of the pulmonary vascular bed. Therefore, ketamine is not commonly used in patients with PPHN.

Opioids are the mainstay of anaesthetic management for patients with PPHN. Fentanyl has minimal pulmonary and systemic haemodynamic effects and has been shown to attenuate the increase in pulmonary vascular resistance in response to noxious stimuli.[63] In addition, studies of children with congenital heart disease demonstrate that fentanyl, in combination with midazolam, preserves myocardial performance and does not alter pulmonary-to-systemic blood flow among patients with intracardiac shunting.[64,65]

Anaesthetic management

CDH patients represent the largest group of patients with PPHN who require surgery in the neonatal period. Other patients include those with congenital cystic adenomatous malformations of the lung, and patients with severe PPHN requiring ECMO as a rescue therapy. Although some newborns with CDH do not require mechanical ventilatory support before surgery, all of those with PPHN will be mechanically ventilated.

All medications to treat pulmonary hypertension and heart failure should be continued before, during and after procedure,[66] and specific medications for the treatment of pulmonary hypertensive crisis such as iNO should be immediately available.

Induction of anaesthesia is most commonly accomplished with fentanyl in those patients who are mechanically ventilated prior to surgery; however, carefully titrated propofol or sevoflurane can be used to facilitate tracheal intubation. The level of induction should be deep enough to block autonomic response from airway instrumentation that can increase pulmonary artery resistance. At the same time, induction agents should be administered carefully to avoid hypotension, which can decrease coronary perfusion pressure, thereby avoiding right ventricular ischaemia.[67] Hypotension caused by induction agents should be treated promptly with fluid administration and phenylephrine or norepinephrine.

Maintaining adequate intravascular volume is critically important because hypovolaemia will reduce preload to the right ventricle leading to decrease in stroke volume and cardiac output. On the other hand, an over-distended right ventricle from hypervolaemia or an acute rise in PVR will cause the intraventricular septum to shift to the left compromising filling of the left ventricle, and leading to decreased stroke volume and cardiac output. Invasive monitoring of arterial pressure and central venous pressure are useful for monitoring haemodynamic changes and optimising volume. Since many of these patients are hypoxaemic, blood transfusion may be necessary with a target haematocrit of 35–45%. Many infants also require inotropic support of the circulation to maintain adequate blood pressure and perfusion during surgery. Dopamine is the first-line agent used in our institution when a patient is hypotensive with dobutamine or epinephrine added as needed. Milrinone, a PDE-3 inhibitor, is also commonly used during the perioperative period because of its combined effect of decreasing PVR, increasing myocardial contractility and improving cardiac output.[68] Milrinone usually is used once blood pressure is adequate.

Neonatal patients with vein of Galen malformations undergoing endovascular therapy pose unique challenges to the anaesthesiologist. These patients typically must be transported to a radiology suite away from the intensive care unit and operating theatres, yet maintain iNO therapy, invasive monitoring and other vasoactive infusions used to treat congestive heart failure. The anaesthesiologists must pay special attention during the injection of embolic agents (glue). We have observed acute desaturation with slow recovery that responds to hyperventilation and treatment with sodium bicarbonate, suggestive of pulmonary hypertensive crisis. To our knowledge, this phenomenon of pulmonary hypertensive crisis has not been described in the medical literature; however, we have observed this finding repeatedly among the most severely affected patients with very large arteriovenous malformations.

Vigilant postoperative monitoring is also critical for patients with PPHN and all patients will require intensive care during the postoperative period. Mortality is high in the first postoperative day due to increased pulmonary pressure, cardiac arrhythmias or fluid shifts.[69] As mentioned before, hypoxaemia, pain, noxious stimuli and acidosis can all increase pulmonary hypertension, and these risk factors

should be controlled to avoid increasing PVR in the postoperative period.[70] Inhaled nitric oxide, if used during the procedure, should be weaned progressively in the postoperative period to avoid rebound pulmonary hypertension.[71–73]

Pulmonary hypertensive crisis and cardiac arrest

A pulmonary hypertensive crisis is characterised by a rapid increase in PVR resulting when the pulmonary artery pressure exceeds systemic blood pressure and right heart failure ensues. Several risk factors may contribute to a pulmonary hypertensive crisis, and include hypoxaemia, hypotension, hypoventilation, inadequate preload of the right ventricle and noxious stimulation. The management of a pulmonary hypertensive crisis consists of eliminating noxious stimuli that cause the increase of PVR, administration of a pulmonary vasodilator, providing adequate preload and supporting cardiac output. Treatment includes the following: (1) The administration of 100% oxygen.[23] (2) Correct metabolic and respiratory acidosis. PVR is directly related to H^+ concentration and PCO_2 level. Metabolic acidosis should be corrected with sodium bicarbonate and hyperventilation to produce a respiratory alkalosis that will help reduce PVR. (3) Increase the depth of anaesthesia with a bolus of fentanyl that will suppress endogenous catecholamines that can increase PAP.[63] (4) Administer pulmonary vasodilators; iNO provides selective pulmonary vasodilatation and is the first line of medication used intra-operatively because of its rapid onset and effectiveness. (5) Support cardiac output with adequate preload and inotropic support with dopamine and/or milrinone. For the acute management of increased PVR, there are limited data about the use of other pulmonary vasodilators, such as calcium channel blockers, sildenafil and prostacyclin.

Pulmonary hypertensive crisis

- Rapid, acute rise in PVR in excess of SVR
- Caused by noxious stimulation, hypoxaemia, hypoventilation, and hypotension
- Treatment
  - 100% oxygen
  - Correct respiratory and metabolic acidosis
  - Fentanyl to suppress endogenous catecholamine release
  - Rapid acting pulmonary vasodilator like nitric oxide
  - Circulatory support with preload bolus and cathecholamines and/or milrinone

Summary

PPHN remains an important cause of mortality and morbidity in neonates and is a major challenge to the anaesthesiologist during surgical intervention. It is crucial for the anaesthesiologist to know the aetiology of the disease, to understand the pathophysiology of PPHN, to be aware the potential risk during perioperative period, and to be familiar with the treatment of a pulmonary hypertensive crisis and associated cardiac collapse.

Conflict of interest statement

None.

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Tracheo-oesophageal fistula (TOF) and oesophageal atresia (OA)

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Tracheo-oesophageal fistula (TOF) and oesophageal atresia (OA) represent a series of anatomical abnormalities presenting for emergency surgery in the neonatal period. They present the anaesthetist with cardio-respiratory challenges in the preoperative, intra-operative and postoperative phases. In addition to the consequences of the pathology itself, co-morbidities are very common, which superimpose further considerations. The basic science, anatomy and genetics are discussed as well as the clinical presentation, perioperative management, controversies and complications. The evidence for optimum management is based mostly on expert opinion; there are very few large randomised controlled trials concerning many areas of perioperative management.

Tracheo-oesophageal fistula (TOF)and oesophageal atresia (OA)is a relatively common congenital malformation occurring in 1:3000–4500 live births.[1–3] In 80–85% of patients, the lesion consists of an oesophageal atresia with a distal oesophageal pouch and a proximal TOF.[4] The other 15–20% comprise variations of anatomical abnormalities, including isolated OA and isolated TOF. Neonates with TOF/OA are often born prematurely and are of low birth weight. Approximately 50% of neonates with TOF/OA have associated abnormalities, with cardiac anomalies being the most common. The perioperative management of TOF/OA continues to be a challenge for surgical, anaesthetic and neonatal teams.

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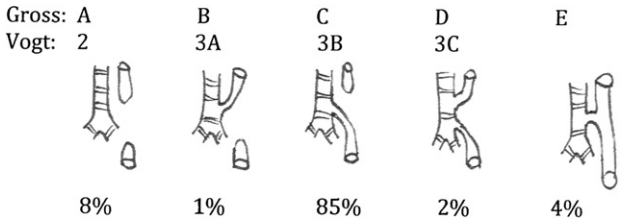

Fig. 1. Anatomical Gross and Vogt classifications of anomalies of the oesophagus and trachea, with approximate incidences. Please note the Gross type E is frequently referred to as 'H' type due to its anatomical shape resembling the letter H.

Embryology and genetics

The intimate relationship between the oesophagus and trachea is evident from early embryonic life. In normal development, respiratory and digestive tubes originate from a diverticulum of the primitive foregut. This endodermal structure separates to form the oesophagus and trachea. There is disagreement as to the exact mechanism by which this happens[5]; however, TOF/OA occurs when this process fails to complete. A communication (fistula) therefore remains.

The genetics of TOF/OA is incompletely understood; certain syndromes such as Trisomy 18, which appears to be a higher risk than the more common trisomy 21, are associated in 6–10% of cases. Three separate genes associated with syndromic TOF/OA in humans have now been identified as being associated with oesophageal atresia.[5–8] Twins are more likely to have the condition, with a relative risk of 2.54 compared with singletons.[9] Non-twin siblings appear to have a low recurrence rate.[8] Where chromosome cases are excluded, there is no link with maternal age. In terms of environmental teratogens, a few cases have been reported where the mother was exposed to methimazole in the first trimester of pregnancy.[10]

Anatomical pathology

Various anatomical classifications exist. Most commonly described are the Gross[11] and Vogt[12] classification; others include the Ladd and Kluth classifications. Anatomic variations are well described (Fig. 1). The most common lesion is OA with distal TOF (type C) occurring in 85% of neonates.[13] In a series of patients, it was found that TOF was at or below the carina in 11% of cases, within 1 cm of the carina in 22%, and above this in 67%.[14] This has marked practical implications for the anaesthetist in that the ideal aim after induction is to place the tip of the tracheal tube below the fistula and above the carina. The exact anatomy is usually unknown before surgery; therefore, these figures suggest that the ideal position of the endotracheal tube is frequently difficult to achieve. Most commonly, the upper oesophageal segment ends blindly in the mediastinum at the level of the second to third thoracic vertebra.[15]

Isolated OA (type A), where there is no communication with the trachea, occurs in approximately 8% of cases, and isolated TOF (type E or H-type) occurs in 4%. A proximal TOF with OA (type B) occurs in approximately 2% of cases, and, rarely, OA can occur with proximal and distal TOFs (type D) in 1% of cases. Multiple fistulas can also occur.

Co-morbidity and associated abnormalities

OA/TOF is linked with other clinical defects in more than 50% of babies, and 20–30% will be preterm weighing <2000 g.[1,2,16] A number of associated conditions and syndromes are presented in Table 1. Cardiovascular defects occur in 30% of TOF/OA, most commonly ventriculoseptal defects and tetralogy of Fallot.[19] Cardiac pathology has been found to be an independent predictor of mortality and intra-operative critical events in infants with TOF/OA.[20,21]

Clinical presentation

The diagnosis of TOF/OA can be suspected prenatally by the presence of polyhydramnios and finding an absent stomach bubble on ultrasound.[22] Passing a nasogastric tube (NGT) soon after birth

Table 1
Table of associated conditions with TOF/OA. Some are weak associations. Please note the initial description of "VACTERL" was named "VATER" syndrome, where 'R' refers to radial anomaly, and did not include the renal and cardiac abnormalities. As many as 20–30% of infants with TOF/OA have at least three of the VACTERL lesions included.[18]

Association	Composition	Comment
VACTERL	Vertebral anorectal, cardiac tracheo-oesophageal, renal limb defects[17]	Overlaps with other syndromes or conditions e.g. CHARGE, Feingold syndrome, 22q11 deletion syndrome. Occurs sporadically.
CHARGE	Coloboma, heart defects, anal atresia, retarded growth, genital hypoplasia, ear anomalies	Can be diagnostically difficult if only few of the features are present. Genetic defect is CHD7 mutation.
SCHISIS	Omphalocele, cleft lip, cleft palate, genital hypoplasia	
POTTER's syndrome	Renal agenesis, pulmonary hypoplasia, typical dysmorphic features.	
VACTERL-H	As with VACTERL with the addition of hydrocephalus	Rare, X-linked
22q11 deletion	Also called "CATCH": cardiac abnormality, abnormal facies, thymic aplasia, cleft palate, hypocalcaemia	Weak association with OA, features include recurrent infections, hypocalcaemia (hypoparathyroidism)
Chromosome 17q22q23.3 deletion	Associated congenital heart defect	Case report – suggested link
Trisomy conditions	Associated with trisomy 18, 21, 13	Strongest association with trisomy 1 8 (Edward's syndrome)
Feingold syndrome	Similar to VACTERL, with the addition of microcephaly and learning difficulty	Dominant inheritance
Multiple gastro-intestinal atresias (MGIA)	Multiple atresias of oesophagus, small intestine and biliary system.	Several reports. Lethal condition

Adapted from Shaw-Smith.[5]

will not advance beyond 9–10 cm in OA and plain chest X-ray (CXR) will show the NGT arrested in the superior mediastinum at the level of T2–T4. Although a contrast oesophagogram can confirm the diagnosis of OA and define the presence of a fistula, this is generally not undertaken unless defining the extent of the oesophageal defect or for isolated fistulas, as this may result in contrast aspiration.[23] With OA, the presence of gas in the stomach signifies a distal TOF. If not spotted at birth, the baby may present with respiratory distress and choking with feeds. Urgent diagnosis and treatment are necessary to avoid aspiration of acidic gastric contents and saliva. Isolated TOF (H-type- TOF; H-TOF) can present later with recurrent pneumonia and aspiration.

Clinical management of neonates with TOF/OA

Preoperative assessment and management

Once the diagnosis has been made, infants are transferred to a tertiary paediatric centre for further management and investigation. The patient is nursed 30° head-up or in a prone position to reduce the risk of pulmonary aspiration. A Replogle tube is often placed in the upper oesophagus and placed on continuous suction to reduce the volume of saliva secretions. Usually, a 10-F tube is used if the neonate is above 1500 g in weight and 8F if below. The main goal is to prevent aspiration of acidic gastric contents (via the TOF) and saliva (as a result of accumulation in the upper oesophageal pouch); however, the use of a Replogle tube is by no means universal, as Replogle tubes occasionally block with significant risk of aspiration if not recognised. Some centres advocate regular intermittent conventional naso-oesophageal tube suction and emphasise nursing vigilance.

Preoperative echocardiography is mandatory to exclude both associated cardiac defects and a right-sided aortic arch that occurs in 2.5% of cases.[24,25] An identified congenital heart defect may need to be managed preoperatively following consultation with a paediatric cardiologist, although surgical correction is almost always performed after the TOF/OA surgery. In the case of a right-sided aortic arch,

surgical access to the oesophagus and TOF via the typical right thoracotomy would be rendered more hazardous, so the surgeon may elect to perform a left thoracotomy.

The respiratory function needs to be assessed, particularly in the presence of low birth weight, prematurity and co-morbidity where preoperative intubation may be required. If there is significant respiratory compromise in the premature infant, consideration should be given to performing an emergency fistula ligation. Fluid, electrolyte and glucose balance needs to be maintained preoperatively via an intravenous cannula as large amounts of suctioned secretions may require replacement. Blood tests need to be taken for full blood count, electrolytes and cross-match, although transfusion is usually not required intra-operatively.

A 'babygram' (Fig. 2) or separate chest and abdominal X-rays are used to initially diagnose the OA based on the upper mediastinal position of the inserted naso- or orogastric tube. The CXR is inspected for the presence of pulmonary infiltrates indicating aspiration pneumonitis and for signs of congenital heart disease. Air in the stomach confirms the presence of a tracheo-oesophageal fistula, and an air-

Fig. 2. Babygram showing coiled nasogastric tube and gas in stomach.

filled connection between the trachea and the stomach can occasionally be seen. Available X-rays are further examined for bony vertebral anomalies. If present, the position of umbilical arterial and venous catheters and of an endotracheal tube can be verified. Ultrasound examination of the neonate with OA and TOF will evaluate the presence of intracranial haemorrhage in premature babies, the renal anatomy, and the spinal cord as part of the VACTERL workup.

Operative considerations

TOF/OA (gross types C, D and B) surgery is urgent to prevent aspiration and respiratory compromise. Surgery is generally done on the first or second day of life after echocardiography and evaluation of co-morbidities. The procedure involves ligation of the fistula and anastomosis of oesophagus.

Left-lateral positioning is required with a roll placed under the lower left chest to elevate the thorax and expose the surgical site. The standard technique involves a right posterolateral thoracotomy through the 4–5th intercostal spaces, approximately 5–6 cm long. In the case of a right-sided aortic arch, the surgeon may elect to perform a left thoracotomy, which would render the surgery more technically challenging. Muscles are split or divided and the trachea and oesophagus are exposed via extrapleural blunt dissection. Extrapleural dissection offers the benefit of protecting against anastomotic leak, but some surgeons may use the transpleural route.

Good communication between surgeon and anaesthetist throughout the procedure is imperative. In particular, the following issues require careful collaboration:

- Surgical manipulation of the lungs may cause significant disturbance of haemodynamics and gas exchange.
- Retraction may occlude the trachea or bronchi, impairing ventilation.
- The azygous vein needs to be tied off to aid exposure to the oesophagus; rarely the inferior vena cava drains into the right atrium via the azygous vein. Therefore, before division, it is important that the surgeon performs a test occlusion, making sure that this does not affect blood pressure.
- When the fistula is ligated and divided, the anaesthetist may be asked to perform positive pressure hand-ventilation to assess the integrity of the fistula ligation while the surgeon instils saline around the suture line and looks for bubbles.
- Identification of the blind proximal oesophagus is aided by the anaesthetist gently advancing the oro-oesophageal tube to the end of the pouch.[15]
- During surgery, the anaesthetist will be asked to insert an NGT, which the surgeon will place into the stomach before the oesophageal anastomosis is completed over the catheter. The NGT is fixed firmly at the nose (often with a suture) to avoid inadvertent removal postoperatively.

The thoracotomy is then closed. There is generally no need for an intercostal drain with an extrapleural technique.

Long-gap OA (more than two vertebral segments) type C may require a staged procedure, involving early ligation of TOF and gastrostomy for feeding. In this case, the oesophageal anastomosis is generally performed at 6–12 weeks to reduce the postoperative tension on the oesophagus.[26]

Isolated OA (type A) is rare and bronchoscopy is important to exclude an upper pouch TOF.[27] A gastrostomy is performed and the extent of the gap measured with the help of contrast. Primary or delayed correction is then performed.

H-TOF (type E) generally presents later with recurrent pneumonia or coughing on feeding. The diagnosis is established on contrast oesophagogram and confirmed at bronchoscopy and oesophagoscopy. Surgery is most frequently performed through a low cervical neck approach in the supine position.

Thoracoscopic surgery

Recent advances in thoracoscopic surgery have shown comparable outcomes compared with open thoracotomy but thoracoscopic TOF/OA repair requires advanced skill in minimally invasive surgery.[28] It is performed with the patient in 45° prone or left-lateral positions to allow the lung to fall away from the posterior mediastinum. Typically, three to four port sites are employed. Lung isolation with left

mainstem intubation is preferred, with or without additional insufflation of CO_2, to achieve lung collapse. Surgical access to the atresia and fistula is typically good.

Monitoring

Standard anaesthetic monitoring should be employed from the beginning of the anaesthetic. In addition, pre- and post-ductal oxygen saturation monitoring is commonly used in neonatal anaesthesia, and the use of a precordial stethoscope taped to the left chest could be considered. Secure peripheral venous catheters should be placed. Debate exists as to whether to insert an arterial catheter, although most would believe it is advisable because of the potential haemodynamic instability during surgical lung retraction and for blood gas analysis. An umbilical arterial line may be a good alternative to radial or femoral lines. Central venous catheterisation is not usually required[29] unless there is cardiac pathology or difficult venous access; blood loss and fluid shifts during surgery should be minimal. Temperature monitoring is important and all measures to maintain normothermia during neonatal surgery should be available and employed (warmed operating room, forced warm air mattress, fluid warmer and patient covers).

Induction and intubation

Despite considerable anaesthetic risks, controversy still exists as to how the patient should be induced and intubated so as to minimise ventilatory difficulties. Many different anaesthetic techniques have been used with good effect. The anaesthetist needs to plan for potential difficulties in advance of the procedure.

Anaesthesia for bronchoscopy, intubation and TOF repair can be induced intravenously, by inhalation, or by a combination of inhalation and intravenous techniques with additional utilisation of local anaesthetics and opioids. Inhalation induction with sevoflurane or halothane allows spontaneous respirations and adequate anaesthetic depth but may be associated with hypotension, hypoventilation and coughing. Ketamine maintains spontaneous respirations; although may not ablate the response to airway manipulation, may increase airway secretions, and has been associated with neurodevelopmental concerns. The use of opioids may suppress response to airway or surgical stimulation but may be associated with apnoea.

Awake intubation

Awake intubation using topical anaesthesia has been advocated in the past, although this has been shown to be more traumatic, more difficult and associated with more desaturation, increased intracranial pressure and potential intracranial haemorrhage.[30]

Maintaining spontaneous ventilation

Intubation of the anesthetised, spontaneously breathing neonate with TOF is the seemingly optimal management as it avoids the need for positive pressure ventilation whilst providing appropriate stress protection. The negative intrathoracic pressure generated during spontaneous ventilation causes gas to enter the lungs rather than the TOF. It also allows the option of wake-up if there is some difficulty. The main disadvantage of spontaneous ventilation is that the severely compromised neonate may already have poorly compliant lungs and thus adequate gas exchange may not be achievable without positive pressure support. Suboptimal laryngeal view and coughing may also compromise intubation and gas exchange.

Apnoeic intubation

Pre-intubation neuromuscular blockade offers the benefit of optimal airway conditions without coughing or straining. Textbooks and authors advocate 'gentle bagging' with a facemask, although gases will still pass through the path of least resistance regardless of ventilation pressure. Usually, 'gentle bagging' will ventilate the lungs[31], although this will not be the case if the TOF is large or the lung compliance very low. These factors would increase stomach inflation to the detriment of lung

ventilation. Subsequent endotracheal intubation could result in direct intubation of the fistula itself, or preferential gas flow down the fistula.[32]

Regardless of how the patients are induced, they will need intubation and may need positive pressure ventilation for the thoracotomy. Without knowing exactly the size of fistula or its relation to the carina, precise and accurate placement of an endotracheal tube (ETT) within the trachea is essentially a blind technique. There are a number of proposed methods of estimating the correct endotracheal tube position: manipulating the ETT during auscultation; placing the tracheal tube into the bronchus and withdrawing until air entry is heard bilaterally; and rotating the endotracheal tube so the bevel faces anteriorly away from the fistula in an attempt to occlude the fistula.[2] A cuffed endotracheal tube may also provide assistance in occluding the fistula. Despite these ideas, three particular problems can still occur:

- A large fistula may be preferentially intubated.
- A fistula at or near the carina can still make precise placement that makes exclusive lung ventilation extremely difficult.
- Surgical manipulation intra-operatively or patient positioning may occlude or displace the endotracheal tube.

Use of bronchoscopy

In view of the unknown features and potential problems with airway management of patients with TOF/OA, some authors advocate performing bronchoscopy intra-operatively before intubation and thoracotomy.[27,31,33] Bronchoscopy has been used effectively to assess the presence, type, number, size and location of fistula[14,33–35], as well as to determine or exclude additional fistulas that may otherwise be missed and leave the patient with an ongoing source of aspiration. Fig. 3 shows a carinal fistula, illustrating the difficulty one would have in optimally placing an endotracheal tube and exclusively ventilating the lungs. Fig. 4 shows the presence of an H-TOF or type E fistula. Examination of the airways may also reveal tracheomalacia or bronchial abnormality and influence the decision of when to extubate postoperatively.[34,36] A flexible or rigid bronchoscope can be used. A Karl–Storz rigid scope has the advantage of ventilating though the scope or insufflating gases during spontaneous ventilation.

Bronchoscopy can also be used to visualise the placement of a Fogarty embolectomy catheter[37], bronchial blocker or Foley catheter[38] to occlude the fistula. Placement of a catheter can aid the surgeon in identifying the TOF.

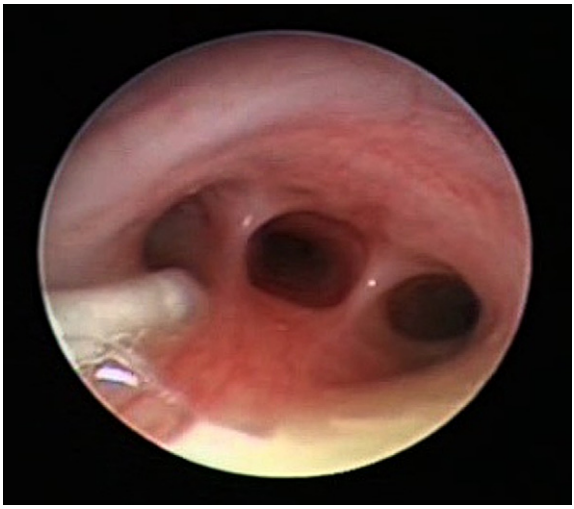

Fig. 3. Bronchoscopic view of tracheo-oesophageal fistula at the carina.

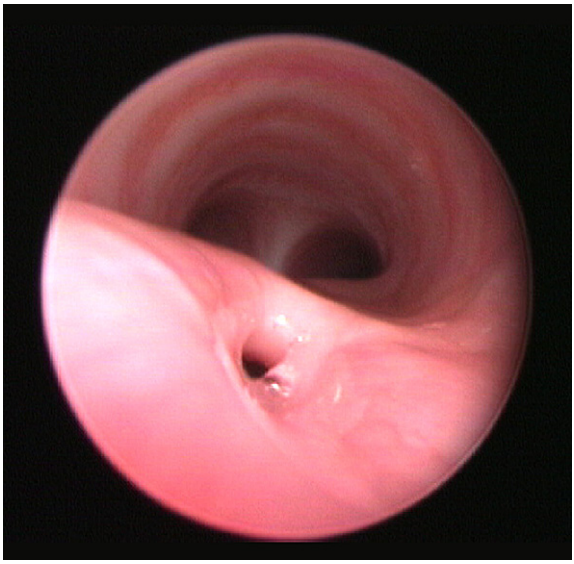

Fig. 4. Bronchoscopic view of H-TOF or Type E tracheo-oesophageal fistula.

A recent study by Atzori, et al.[27] concluded that tracheobronchoscopy "is a useful and safe procedure and should be recommended in tertiary centers for babies with oesophageal atresia before surgical repair." In their study, bronchoscopy was clinically useful in 45% of patients, including 24% in whom it was crucial in modifying surgical approach. In these cases, a cervical approach was used instead of thoracotomy as some patients thought to have isolated atresias were found to have an unsuspected proximal fistula (type B), and some patients were found to have H-TOFs (type E). All carinal fistulas were occluded in this series with a Fogarty catheter and found to improve ventilation. Other authors have also found that bronchoscopic findings have changed their surgical approach or modified surgical technique in up to 31% of patients.[33,38]

Performing flexible bronchoscopy through the ETT will also confirm placement below the TOF and above the carina, as well as exclude multiple fistulas and confirm tube positioning after manipulation or movement. Practically, bronchoscopes may be too large in the low birth weight children who require small (2.5 mm or 3 mm internal diameter) endotracheal tubes.

The main disadvantage of bronchoscopy is that the pre-term neonate and patients with respiratory compromise may not tolerate spontaneous ventilation for bronchoscopy or that the airway may be too small to allow bronchoscopy. Complications such as oxygen desaturation, inadequate ventilation, trauma to the airway, coughing, laryngospasm and bronchospasm have been known to occur both with rigid and flexible bronchoscopy.[39,40]

Ventilation

Ventilatory management in patients with OA and TOF is a significant challenge for the paediatric anaesthetist. The patient may already have respiratory compromise from aspiration and will undergo thoracotomy in the lateral position with lung retraction, all of which will result in lung compliance changes and additional difficulty with ventilation and oxygenation. Intubation followed by positive pressure ventilation has been cited as causing a number of deaths due to direct intubation of the TOF or preferential ventilation through a low-resistance TOF into the stomach.[41]

Ventilatory difficulties are common during the repair of OA and TOF and were found in 16% in one series.[31] They include hypercarbia, desaturation and inability to ventilate. Hypercarbia is common and may be tolerated except in patients with congenital heart disease sensitive to changes in pulmonary vascular resistance, and it may also result in return to foetal circulation in otherwise healthy babies and

needs to be considered and identified. While neonatologists support the use of low inspiratory oxygen concentrations in premature babies and advocate a target saturation of 85–95% to minimise oxidative stress in premature neonates, most term neonates will be maintained at increased inspiratory oxygen concentrations intra-operatively to reduce the incidence of oxygen desaturations related to intra-operative hypoventilation and surgical manipulations. Typical reasons for acute changes in ventilation include accidental intubation of the fistula, accidental mainstem intubation or extubation, kinking of the airway during surgical retraction and lung compression by the surgeon. Whenever acute changes occur, the surgeon needs to be notified and the cause needs to be identified.

Several suggested approaches to managing the fistula and ventilation difficulties are summarised in Table 2.

In general, a combination of techniques can be employed depending on the patient's condition, the position of the fistula and the progress of the surgery. While spontaneous respirations may be maintained during line placement and bronchoscopy, gentle positive pressure ventilation may be required during thoracotomy and isolation of the fistula. Once the fistula is ligated, regular positive pressure ventilation and possibly positive end expiratory pressure can be used.

Emergency ligation of fistula

The pre-term infant with TOF/OA and severe respiratory distress syndrome (or hyaline membrane disease) is particularly problematic (in particular, if the fistula is large and in close proximity to the carina). Low lung compliance will favour ventilatory gases down the low-resistance fistula causing inadequate ventilation of the lungs and distention of the stomach. Gastric distention will further compromise ventilation and can also cause gastric rupture and pneumoperitonium.[44] Emergency gastrostomy was traditionally performed but this is not advocated due to worsening gas flow to the lungs.[41,45] Bronchoscopy and Fogarty catheter occlusion may not be possible either as the smallest bronchoscope may not permit ventilation while manipulating the catheter.[46] It is now recommended that emergency transpleural ligation of the TOF is the procedure of choice in infants with the combination of these problems.[15,45] This involves ligation, but generally not division, of the TOF. The aim in this instance is to re-operate in 8–10 days to divide the fistula and repair the atresia. Another potential solution is to ligate the gastro-oesophageal junction trans-abdominally.[47]

Analgesic management

The use and timing of analgesia depend on a number of factors, including the type of ventilation used and the plan for early or late extubation. Intra-operative and postoperative analgesic management

Table 2
Techniques, advantages and disadvantages of managing the fistula and difficult ventilation in TOF/OA patients.

Technique	Advantage	Disadvantage
Maintain spontaneous ventilation	Avoids positive pressure ventilation down fistula	Inadequate ventilation or apnoea during thoracotomy
Placement of endotracheal tube below fistula	Simple procedure	May not be possible for fistulas at or near carina
Gastrostomy to decompress stomach	Reduces gastric distension and atelectasis	May increase oxygen flow 'egress' through the fistula[42]
Electively intubating the left main bronchus	Bypasses fistula effectively. Surgical retraction of the right lung may be easier	Hypoxia, difficult to place in left side correctly, can be dislodged during surgical retraction
Occlude TOF with a Fogarty embolectomy catheter or bronchial blocker via trachea[37,38]	Effective in improving ventilation and reducing aspiration	Very little published experience. Equipment often not immediately available
Occlude TOF with Fogarty catheter via gastroscopy[43]		
Emergency TOF ligation[15]	Effective	Time required to perform
Emergency ligation of gastro-oesophageal junction	Can keep patient supine	Invasive, time required to perform

is by intravenous opioid analgesia, by epidural, by anaesthetic, by other routes of local anaesthetics or by a combination of analgesic administration.

Systemic analgesics

Although continuous infusion of morphine has been used safely and with good effect in many institutions, fentanyl-based opioids are sometimes preferred by neonatologists due to concerns for accumulation of morphine and its metabolites in neonates. Fentanyl may be used intra-operatively and as continuous infusion for postoperative analgesia as well. Paracetamol may be given enterally or intravenously for postoperative analgesia.

Regional anaesthesia

Epidural catheters in neonates can be inserted via caudal[48], lumbar or thoracic spaces and can be advanced to position the catheter tip in the mid- to high thoracic region. Epidural analgesia can obviate the need for intra- and postoperative opioid analgesia and avoid opioid-related hypoventilation and apnoea. Ideally placed preoperatively to be used during the surgery, postoperative placement can be considered in tenuous patients. Verification of successful tip positioning is recommended and can be performed by electrical stimulation, ultrasound or radiologically. A standard epidural catheter can be difficult to image with ultrasound; however, new catheters (FlexTip Plus™) have incorporated a wire coil to improve ultrasound visualisation. It must be remembered that local anaesthetic clearance is reduced in the neonate.[49] Both maximum dose [50–52] and duration should be reduced; most would limit the infusion for 48 h postoperatively.

As an alternative to epidural anaesthetics, local infiltration, intercostal blocks, paravertebral blockade or intrapleural infusion of local anaesthetic can be considered.

Although case series have suggested that regional techniques can reduce opioid requirements and days of ventilator use, the evidence for improved outcome measures in these patients is lacking. A careful risk–benefit analysis needs to be considered, (including co-morbidity and postoperative facilities to manage neonatal epidurals) before undertaking a particular technique.

Postoperative management

Neonates should return to the neonatal intensive care unit (NICU) postoperatively for respiratory monitoring and pain control. Decision regarding postoperative extubation takes into account patient prematurity and size, associated co-morbidity, patient preoperative and intra-operative status, ease and duration of surgery, tension of oesophageal anastomosis, ease of intra-operative ventilation and quality of postoperative pain control. Consequently, an otherwise healthy term neonate with efficient epidural analgesia may be extubated in the operating room following uncomplicated repair. On the other hand, small premature babies, patients with significant co-morbidities, patients with significant intra-operative instabilities or following long or difficult surgeries and requiring intravenous opioid analgesia may benefit from a period of postoperative ventilation. Typically, early extubation within 24 h should be possible, thus minimising the time that the repair site is exposed to the pressure of the endotracheal tube. If the oesophageal repair was performed under tension, patients may need to be paralysed and ventilated for a number of days[53], although there is disagreement between centres with regard to precise timing. The H-type repairs via the cervical technique are often also extubated

Table 3
Results of study correlating oesophageal gap length with morbidity. Please note the mortality also correlated with length of gap, with Group A having an 80% mortality, 50% in Group B, 22% in Group C and 15.6% in group D. (Figures derived from Upadhyaya et al.[58] These mortality figures are considerably higher than contemporaneous studies; it is suggested this is because of late presentation and a high incidence of low birth weight and pneumonitis.

Group	Gap length	Anastomotic leak (%)	Oesophageal stricture (%)
A	>3.5 cm (ultralong)	80	100
B	2.1–3.5 cm (long)	50	75
C	>1 cm < 2 cm	28	22.5
D	<1 cm	10.5	19

Table 4
Spitz Prognostic Classification [55] related to birth weight and survival.

Group	Cardiac anormality	Birth weight	Survival %
I	No	>1500 g	97%
II	No	<1500 g	59%
III	Yes	<1500 g	22%

early; however, one must be mindful of the potential for upper airway oedema causing airway compromise.

Regular pharyngeal suction is necessary for a few days postoperatively. Importantly, the suction catheter should be clearly marked so that it is not passed as far as the anastomosis where it can cause trauma. Broad-spectrum prophylactic antibiotics are given. Trans-anastomotic feeding by NST is usually started 48 h after surgery. Typically, radiographic studies (barium swallow) are performed 5 days postoperatively to confirm integrity of the anastomosis before oral feeds are re-introduced.

Mortality and prognosis

The overall survival of infants with TOF/OA has improved. A retrospective analysis of 147 infants from 1986 to 2005 showed mortality improving from 87% in 1986–95 to 94% in 1996–2005. This is despite an increased incidence of congenital cardiac disease (23% to 29%).[54] Early diagnosis, improved surgical technique, sophisticated ventilator support, advanced intensive care management and early treatment of associated congenital anomalies have been cited for these improvements.[15]

Most prognostic indicators are based heavily on co-morbidity. For example, major congenital heart disease (cyanotic lesions requiring surgical correction or acyanotic lesions requiring medical or surgical treatment for cardiac failure) and low birth weight (<1500 g) have been shown to be independent predictors of mortality in infants undergoing TOF/OA repair.[20,21,55] Infants >1500 g with no cardiac abnormality have a survival of 97–98%; infants either with cardiac abnormality or with low birth weight have a survival of 59–82%; and infants with both major cardiac abnormality and <1500 g a survival of 22–50%.[55,56] Respiratory compromise with ventilator dependence and severe associated anomalies also have prognostic significance.[57]

Recently, the length of oesophageal gap has been cited as a prognostic indicator. Upadhyaya et al.[58] studied 50 patients and divided them into groups based on the measurement of oesophageal gap (Table 3).

Although the Spitz prognostic classification[55] is the most widely accepted (Table 4), a recent study by Okamoto et al. has suggested a revision, based on 121 consecutive infants from 1981 to 2005.[59] The authors proposed a four-part classification (Table 5):

Complications and morbidity

Early

Even after repair, most patients will have structural and functional abnormalities of the trachea and oesophagus as a result of defective embryological development.[60,61] Severe tracheomalacia and bronchomalacia occur in 10–20% of infants. Tracheomalacia can be severe enough to be life threatening

Table 5
Table of new proposed prognostic classification. Survival is based on 121 infants in the series. (Adapted from Okamoto et al 2009).

Class	Risk	Cardiac anomaly	Birth weight	Survival %
I	Low	No	>2000 g	100%
II	Moderate	No	<2000 g	81%
III	Relatively high	Yes	>2000 g	72%
IV	High	Yes	<2000 g	27%

Adapted from Okamoto et al., 2009.

and, if so, may require urgent aortopexy. The presence of tracheomalacia may be a cause for early re-intubation postoperatively.

Anastomotic leaks occur in 15–20% of patients, the majority being small leaks that will seal spontaneously.[62] Major disruptions manifest as early pneumothorax and salivary drainage from chest drain. Anastomotic strictures develop in 30–50%[54,63] requiring dilatation in nearly half of these patients. Recurrent fistula occurs in 10% of patients post-repair.

Late

Gastro-oesophageal reflux (GOR) is common, occurring in almost all patients after TOF/OA repair, and is probably due to intrinsic motility and sphincter abnormality. Significant reflux occurs in approximately 40% of cases, about half of whom will require surgical management[64] and half will be managed medically. Recurrent chest infections occur in up to two-thirds of patients in early childhood[65,66] and can be attributed to recurrent aspiration from GOR or abnormal tracheal epithelium. Generally, this will improve with age.[67]

Summary

The newborn who presents with TOF/OA provides difficult challenges to the paediatric anaesthetist, surgeon and neonatal teams. The neonate is pre-term in up to 30% of cases, may have respiratory compromise, and 50% will have other existing co-morbidities, especially cardiac anomalies. The particular challenge in anaesthetising a neonate with TOF is managing lung ventilation in the presence of a communication between the airway and the oesophagus. Added to this, the surgery involves thoracotomy with the inherent potential haemodynamic, ventilatory and analgesic problems.

There are many strategies and techniques to manage the neonate with TOF/OA. Most evidence is based on expert opinion and retrospective analysis of case series. Prognosis appears to be improving; however, certain subgroups pose a particularly difficult challenge, such as prematurity, low birth weight, associated congenital heart disease, chronic lung disease and large peri-carinal fistulae. The key to management is good preoperative assessment and preparation, together with communication with cardiology and surgical colleagues. Some authors propose preoperative bronchoscopy to define the anatomy, although this is not without some practical difficulty. Emergency procedures in the event of ventilation difficulty should be discussed and prepared in advance of the anaesthetic. Options for analgesia depend on the proposed plan for postoperative ventilation; a careful risk–benefit analysis should guide the use of systemic versus regional techniques on an individual case-by-case basis.

Practice points

1. Surgery is relatively urgent due to risk of pulmonary aspiration.
2. Preoperative cardiac echocardiography is mandatory.
3. There is a frequent association with congenital anomalities, especially cardiac and VACTERL.
4. Premature neonates <1500 g, major cardiac lesions, syndromes and pulmonary problems increase mortality risk.
5. There is the potential for significant difficulty with ventilation, primarily from fistula intubation, ventilation and gastric distension.
6. There is evidence that performing bronchoscopy is valuable, although some patients may be too compromised to tolerate it.
7. Ventilatory difficulties can occur during induction, surgery or postoperatively. There are a variety of options to manage ventilation difficulty.
8. Surgery is generally done through right-sided thoracotomy and dissection is usually extrapleural.
9. In some cases delayed anastomosis is necessary (long-gap OA).
10. Early and long-term complications are common and are likely to require further surgery and anaesthetic input.

Research agenda

Further outcome-based clinical studies are needed with regard to:

1 The incidence and cause of ventilatory difficulty and the effectiveness of different management strategies.
2 The use and complications of bronchoscopy pre-intubation.
3 Defining in which cases blocking the fistula may be beneficial and comparing the various methods of blocking device with regard to practicality, efficacy and complications.
4 The outcomes and complications of thoracoscopic surgery compared to open procedures.
5 The safety and effectiveness of the various analgesic modalities, defining the incidence of complications and comparing the different regional and systemic modalities.

Conflict of interest

None.

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Vascular access in the neonate

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Up to recently, inserting venous or arterial 'lines' in the neonate was essentially based on clinical skill and experience. The recent advent of portable ultrasound (US) machines with paediatric probes has resulted in the development of new approaches that, if correctly learned and used, should allow quicker and safer vascular access in this population. Both classic and new techniques are reviewed on the basis of literature and authors' experience. Live illustrations are freely available at www.

Obtaining vascular access in the neonate is a challenging and important aspect of their care. Some of the challenges are unique to the neonatal population. New equipment such as ultrasound (US) and newer types of catheter, such as peripherally inserted central catheters (PICCs), have produced substantial changes and opportunities, and increasingly the choice of access and management of the lines is becoming evidence based.

Ultrasound for vascular access in the neonate

The use of US has greatly increased the efficiency of gaining intravenous access in the neonate. The advantages are greatest when using the correct equipment. In the neonate, the structures are small and room for the US probe is limited; the equipment should include Doppler (screening for occlusion and thrombosis) and zoom functions, and a high-frequency (>10 MHz) 'small' (<30 mm width) linear US probe. Sterile gel and probe covers should be used for US guidance (Video 1).

US visualisation of vessels can be done

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- in the short-axis view (SAX), where the probe is placed transversally to the direction of the vessel, which is seen in cross section; and
- in the longitudinal view or long-axis view (LAX), where the probe follows the direction of the vessel, which is seen in its length.

Research is underway to develop multiplanar US imaging, allowing simultaneous SAX and LAX views of the vessels.[3]

The needle can be advanced under the probe using two approaches:

- out-of-plane (OOP) where the needle crosses the US beam perpendicularly and
- in-plane (IP) where the needle stays in the US beam.

The most common combinations are the SAX view with OOP approach for the internal jugular vein (IJV), femoral vein (FV) and femoral artery (FA), and the LAX view with IP approach for the subclavian vein (SCV). The keys for success and safety include following the basic rules (Table 1) and obtaining adequate training in US-guided vascular access on phantoms and adults before using it in neonates and infants[1,2] (Video 2).

Peripheral venous access

The upper limb

Any visible vein in the upper limb can be used. Puncture of a deep humeral vein should not be attempted blindly at the antecubital fossa to avoid arterial or median nerve injury. The small vein at the anterior aspect of the wrist can be used for transient venous access in infants and children but is seldom usable in neonates. Transillumination can be used to locate small veins; a variety of portable light sources using light-emitting diodes are now available.[4]

The axillary vein

This is an alternative route for central venous catheterisation. In the child, in the head-down position with the arm abducted, the course of the axillary artery is determined by palpation. The skin is then punctured just below it, proximal to the humeral head.[5] The catheter is directed parallel and inferior to the artery until blood is obtained. In neonates, the puncture site could be above the axillary pulse.[6] As this technique carries a risk of arterial puncture and nerve damage, it should not be attempted without US guidance.

The lower limb

The most used veins are the internal saphenous vein, the small veins at the dorsum of the foot and the external saphenous vein. PICCs are often inserted at the ankle or at the antero-lateral aspect of the leg.

Intraosseous access

The intraosseous access is a true central venous access. It is usually a last-resort vascular access used in life-saving circumstances when no other venous access is quickly possible. It is usually only

Table 1
Basic rules for efficient use of ultrasound for vascular access.

• adequate orientation of the probe
• careful identification of the vascular target: as a rule, veins are collapsible and arteries pulsatile; but the difference is often subtle in neonates: little pressure on the probe can make a vein disappear and an artery collapsible!
• placing the target in the center of the screen: so, "middle of the probe = middle of the screen"
• continuous visualization of needle tip during the procedure

a temporary measure.[7] The preferred insertion sites are the proximal or distal end of the tibia, and the distal end of the femur. Any bone-marrow aspiration needle can be used but special needles with a luer-lock connection are better and easier to secure. They are available with different lengths (2.5, 3.0 or 4.0 cm) and needle design (lancet, trocart, screw needle, side ports or pencil-point end). Electric drills and other devices are available to aid insertion.

Possible complications of this route are cellulitis, osteomyelitis, bone fracture, fat or bone marrow embolism and extravasation of fluid into the extraosseous tissue leading to compartment syndrome. To avoid extravasation, the intraosseous route should not be attempted in a broken bone or after previous intraosseous access in the same bone. The needle should be properly secured and its insertion site regularly inspected.

Neck and scalp

Branches of the temporal vein are often prominent on the fronto-parietal aspect of the neonate's head. Care must be taken to avoid accidental catheterisation of a branch of the superficial temporal artery.

The external jugular vein is easy to see in a crying baby. To gain access, place the neonate head-down with a rolled towel under the shoulders and the head turned slightly away from the puncture site. In the awake neonate, a skin wheel with local anaesthesia is useful to anesthetise the skin entry site. To facilitate cannulation, it is useful to ask a helper to press on the lower end of the vein, just above the clavicle. This avoids its collapse during inspiration.

Technical tips

Strict asepsis should be observed. The inner needle of the catheter being slightly longer than the cannula, it should be advanced a few millimetre further after blood appears in the needle hub to make sure the cannula has also entered the vessel. The needle is then slightly withdrawn and kept immobile, while the cannula is gently advanced over it. Venous flashback is sometimes not immediate. Experience is required to recognise entering the vein by feeling a 'click' when its wall is pierced. Waiting a few seconds instead of advancing the catheter further allows blood to appear at the needle hub.

Complications

Phlebitis is caused by mechanical and chemical irritation of the venous endothelium. Contributing factors include the material of the cannula (polyurethane is less phlebogenic than Teflon), duration of catheterisation, nature (pH, tonicity and composition) of the solution and site of insertion (upper limb veins are less prone to phlebitis).

Extravasation can have significant consequences such as skin necrosis, compartment syndrome and delayed limb deformation. It should be prevented by a careful insertion technique and surveillance. In the absence of blood return, correct cannulation of the vein must be confirmed by manual injection of a few millilitres of saline.

Some teams add a small dose of heparin to the IV solution to prolong catheter patency. However, in one study performed in neonates, adding 0.5 IU of heparin ml^{-1} of solution prolonged catheter (24 or 26 G) patency by a mean of only 7.4 h: 33.8 h $\pm$ 23.1 with heparin versus 26.4 h $\pm$ 16.4 without ($p < 0.0001$).[8]

Central venous access

Equipment

Central venous catheters are inserted using the Seldinger technique. They are made of polyurethane or silicone and should be radiopaque, making X-ray visualisation easier. Length marks help diagnose ongoing decannulation or partial embolisation. Polyurethane softens at body temperature and becomes more flexible, which reduces the risk of perforation. The guide wire should be

atraumatic and equipped with a J tip. In neonates and infants, the radius of curvature of the J tip is close to, or larger than, the vein.[9] This can produce difficulties when introducing the guide wire.[10] Recommended catheter sizes are 22 G (or 2 Fr) if the neonate is less than 2 kg and 20 G (or 3 or 4 Fr) above 2 kg.

Position of catheter tip

Whatever the site of insertion, verifying catheter tip position with X-ray is mandatory. For catheters placed in the superior vena cava (SVC), the tip should be (1) outside the pericardial sac, which ascends alongside the medial wall of the SVC (to avoid perforation and tamponade), and (2) parallel to the vessel wall (to avoid perforation). The ideal position therefore varies according to the side of insertion. For right-sided catheters, being in the upper SVC outside the cardiac silhouette is safe, while for left-sided catheters, the angle the catheter tip makes with the vessel or cardiac wall is crucial; the more perpendicular it is, the greater the risk of perforation. Therefore, for left-sided catheters the tip is placed lower, that is, in the lower third of the SVC or in the upper part of right atrium (RA).

Placement inside the RA increases the risk of dysrhythmias, thrombosis and perforation.

In cadaver studies, the pericardial reflection is 0.5 ± 0.04 cm below the carina in infants and children[11] but can extend up to 5 mm above it in neonates. The level of carina on X-ray is thus not a good landmark in neonates.[12] Oesophageal echocardiographic studies in infants have shown large inter-individual distance variability between the carina and the junction of SVC with RA.[13] A persistent left SVC is present in 0.3–4.3% of patients; whether the vessel catheterised is a persistent left SVC and drains in the RA or LA (rare) should be confirmed radiologically with dye.[14]

In case of femoral access, the ideal position of the tip of catheter is either in the ipsilateral iliac vein or in the inferior vena cava (IVC) below the level of the renal veins (L1) to avoid blocking their drainage. Catheter tip at the level of L3 is satisfactory.

Internal jugular vein (IJV)

Landmark approach

The neonate is placed 15–30° head-down with a rolled towel under the shoulders. Whether the head should be in neutral position or moderately turned away from the puncture site is an unsolved issue. In neonates and infants, US screening shows that the relationship between the carotid artery (CA) and the IJV is highly variable and unpredictable. When US scanning is performed at the level of the cricoid cartilage or apex of the sternomastoid muscle triangle with the head in neutral position, the IJV covers CA in 25 (R)–44% (L) of the cases, and is internal to it on the right side in 6%.[15] When the head is progressively turned away up to 45°, the incidence of overlapping of the IJV to the CA increases.[16] In contrast to older infants and children, a simulated Valsalva manoeuvre, liver compression and/or Trendelenburg position increase only marginally (by a mean of 12–15%), the cross-sectional area of the IJV in infants less than 6 months of age.[17] This is probably due to the shorter distance between the RA and the IJV and to the high compliance of the venous system at that age. The head-down position is nevertheless used to increase venous pressure and reduce the risk of air embolism. Simultaneous palpation of CA, needle progression into tissue and full neck extension reduces the surface area of the IJV.[17] However, stretching the skin over the IJV with tape lifts it up, increases its anterio-posterior diameter and decreases the occurrence of vein collapse during needle progression.[18] This taping manoeuvre probably has the same effect as stretching the skin with the non-dominant hand when no US guidance is used. During spontaneous ventilation, IJV diameter decreases during inspiration. The exploratory needle should thus be advanced only during expiration; moreover, this keeps the apex of the lung farther from needle tip.

Many approaches to the IJV have been described; the most used are

- The anterior approach: The needle-entry site is the convergence of the sternal and clavicular heads of the sternomastoid muscle. The needle is inserted 30–45° into the skin aiming initially at the ipsilateral nipple.

- The posterior approach: The needle-entry site is on the lateral border of the clavicular head of the sternomastoid muscle, at a point situated 1/2 to 2/3 on the line joining the mastoid process to the clavicle. The needle is advanced underneath the muscle toward a point just beneath the ipsilateral sternoclavicular joint.

Using another approach, the needle entry site is at the level of the cricoid cartilage, midway between the carotid pulse and the sternomastoid muscle. The child's head is turned $<30^{\circ}$ away and the needle is directed toward the ipsilateral nipple at an angle of 30° with the skin. With this technique, a reduced incidence of carotid puncture has been claimed.[19]

Prior IJV localisation with a small (24-G) pilot needle before inserting the IV needle is controversial; it carries a risk of venous haematoma or arterial puncture but, when left in place, seems to facilitate IJV cannulation in infants less than 6 months.[20]

US guidance

'US screening' of the neck area determines the position, size and patency of the IJV. If the IJV is collapsing during inspiration, (relative) hypovolaemia is possible and administration of an IV fluid bolus may make the procedure easier. Only 'real-time US guidance' has been shown to increase the safety and efficacy of IJV catheterisation in neonates and infants compared with use of classical landmarks. With US use, fewer attempts are needed and the incidence of CA puncture is decreased, but the results are less impressive than in older children.[21,22] To access the IJV, the US probe is placed transversally to the neck to obtain a cross section, or SAX view, of the IJV and CA. In neonates, the US is best used for the anterior approach. The probe is placed above the clavicle with the IJV in the middle of the screen. The needle tip is tracked OOP. By tilting the probe cranially, the needle tip can be seen progressing in the subcutaneous tissue and progressive tilting it toward the chest follows needle tip progression into IJV (Video 3). The increased risk of accidental subclavian artery or pleural puncture is explained by their proximity to the distal part of the IJV.

Difficulties may be encountered in small pre-term neonates. The size of the needle is often close to the IJV diameter and the vein is very mobile, slipping away from the needle tip. Vein transfixion without flashback of blood is frequent, with blood flow usually obtained during slow needle withdrawal.[23]

Subclavian vein (SCV)

The SCV is extrathoracic up to approximately 1 year of age.[24] The initial direction of the exploring needle is therefore more cephalad in that age group. To access the SCV, place a rolled towel under the shoulders, and keep the head in a neutral position or moderately turned away from the puncture site with the arms are along the body and the table tilted 15–30° head-down. In children, the classic position (placing a towel between the scapula to arch the shoulders) decreases the vein cross-section area and is no longer recommended[25], although no data are available in neonates. With US, it can be seen that in the spontaneously breathing neonate/infant, the intrathoracic SCV diameter decreases dramatically during inspiration; therefore, the exploratory needle should be advanced only during expiration. Although changes in vein diameter are less important during intermittent positive pressure ventilation (IPPV), the exploratory needle should also be advanced only during expiration to decrease the risk of pleural puncture. Lastly, slight downward traction on the arm increases the visibility of SCV in the periclavicular area, facilitating its identification and cannulation. The left SCV is often preferred because it continues into the innominate vein in a smoother way to the SVC than the right SVC that enters it at an acute angle.

Landmark approach

The puncture site is below the clavicle, in the deltopectoral groove, between the first rib and clavicle, approximately where the latter is crossed by the external jugular vein. The skin should be entered 5 mm below the lower border of the clavicle so that the pathway of the needle stays altogether parallel to and just under it. The needle should be slightly bent in its middle to make it progress

upwards and away from the pleura when passing under the clavicle. In neonates, the needle should initially be directed toward the cricoid as soon as it passes under the clavicle. The attached syringe is then lowered to make sure the needle remains just beneath it. The vein is usually found close to the skin. If no blood is aspirated during slow insertion or removal during expiration, then the needle should be redirected from beneath the clavicle aiming at a point midway between the cricoid and the suprasternal notch. When inserting the guide wire into the vein, tilting the head toward the catheterisation side helps prevent catheter malposition into the ipsilateral IJV.[26]

US-guided approach[27]

For the beginner, it is useful to start in the neck obtaining an SAX view of the IJV and to follow it caudally until it joins the SCV. The probe is then placed at the supraclavicular level to obtain a LAX view of the SCV. The 2.5 mm 'Hockey-Stick' probe is placed with its foot on the clavicle and stick directed medially and slightly cranially to allow simultaneous visualisation of the needle passing under the clavicle and the entire SCV up to its fusion with the ipsilateral IJV. The vascular structures pass between two bony structures: the superficial and lateral one is the clavicle, the deep and medial is the first rib just above the lung. It is critical to distinguish the SCV from the subclavian artery. The former is more anterior, more superficial, not pulsating and its size varies with respiration, and valves may be seen in it. The external jugular vein usually reaches the SCV close to the IJV, coming from above the clavicle. The SCV is short in small neonates. Its length can be increased by slightly pulling the arm downwards.

Using the IP approach, the needle is passed under the clavicle and the probe, taking care to maintain the LAX view of the SCV. When the needle tip has passed the anterior wall of the SCV, it may be advanced up to junction with the IJV. The correct path of the guide wire can be checked by US. If it goes into the ipsilateral IJV, it can be withdrawn and redirected under US guidance by compressing the distal IJV with the probe (Video 4).

Femoral vein (FV)

This vein is often used during resuscitation; being far from the neck and chest, it allows managing the airway, lungs and circulation without interruption. Even though it is safe, with easy landmarks and few complications, the use of the FV for vascular access has traditionally been discouraged in neonates, being used only for cardiovascular resuscitation. It should, however, be considered when other sites are unavailable.[28] In infants and children, FV catheterisation shows the same incidence of infection and mechanical complications as subclavian or jugular central venous access.[29]

In a recent study, US examination at the level of the inguinal ligament in 14 neonates with the hips slightly externally rotated showed wide variation in the relationship between the FV and the femoral artery (FA). In 11 neonates, the FV was medial to the FA, in two neonates the FV was completely below the FA, while, in one, the FV was partially overlapped by the FA.[30] Moreover, mean FV diameter increased slightly when normovolaemic babies were moved from the supine to the reverse Trendelenburg position.[30,31] Given this variability in relation to the FA, US screening before puncture or US guidance is recommended.

Lastly, firm inguinal compression 1–2 cm above the inguinal ligament with two or three fingers at the point of arterial pulsation increases the FV cross-sectional area by an average of 60% in infants.[32]

Landmark approach

The femoral pulse below the inguinal ligament is the key landmark with the FV usually running medially to the FA. If there is no palpable pulse, the vessel position usually corresponds to the junction between the internal and medial third of the inguinal crease. To access the FV, place the child in the reverse Trendelenburg position with the hip slightly rotated externally, in straight position. The puncture is made 1 cm below the inguinal crease, using a 30–45° angle and pointing the needle to the head of the child. The first attempt should start 5 mm medial to the arterial pulse. Following attempts should be made 6 mm medial, then 4 mm medial.[33]

Because of anatomical variations among patients, a few failed attempts or difficulties in pulse palpation should prompt an US-guided localisation of the vessels.

In one study in pre-term infants weighing less than 1000 g, a 79.6% success rate was obtained by placing a small 5 cm-thick pad under the infant's buttocks to expose the groin, but the incidence of arterial puncture was 10.2%.[34]

US guidance

'US screening' of the inguinal area determines the size (usually 3–5 mm), patency and position of the FV. Iliac vein thrombosis is suspected if the FV diameter does not increase after abdominal compression. 'Real-time US guidance' lowers the incidence of accidental FA puncture[35] and should increase success rate and lower procedural time but studies are still needed in infants and neonates.

The US probe is placed just below and parallel to the inguinal ligament to obtain a SAX view of the vessels. If the FV is located below the FA, external leg rotation or even knee flexion can reposition it medially to the FA. With an OOP approach, the needle tip is directed towards the centre of the FV. A helper is needed to apply low abdominal compression and increase the lumen size. Transfixion of the FV occurs frequently but can be reduced by experience (Video 5).

Peripherally inserted central venous catheter (PICC or epicutaneo-cave catheter)

Peripherally inserted central venous catheter is a semi-invasive way to provide intermediate to long-term central venous access in neonates for parenteral nutrition, antibiotic treatment or inotropic support. It combines the advantages of peripheral and central access: bedside insertion, relatively low cost, safety and compatibility with a wide variety of medications and long-term use. Its main disadvantages are hazardous venous progression after initial cannulation and a small-calibre catheter that may preclude blood sampling, transfusion and rapid fluid rates. A Cochrane review suggested that PICC use improves nutrition in the newborn without evidence of increased adverse events, including systemic infection.[36]

Equipment

PICCs are provided in different sizes (28–23 G) and lengths (15–50 cm). Single and double lumen catheters made of silicone or polyurethane are available. Silicone catheters are easier to insert but are associated with an increased risk of technical problems and bacterial colonisation upon removal.[37] Polyurethane catheters seem to be less likely to burst or rupture.[38]

Technique

Preferred sites include the cephalic, basilic, median antibrachial and accessory cephalic veins for the upper limb, and the internal and external saphenous veins for the lower limb. The occipital, metopic and temporal veins can also be used. If a vein from the upper extremity is selected, the head should be turned toward the arm of insertion. A local anaesthesia with an eutectic mixture of lidocaine and prilocaine (EMLA®) and/or sucrose by mouth must be provided for analgesia.

Catheter length of insertion is estimated from the insertion point to the midline of the sternum if inserted from an upper extremity or to at least 2 cm above the umbilicus if inserted from a lower extremity.[39] After selection of a suitable vein, helped by US guidance if necessary, the skin is carefully cleaned and draped. The vein is cannulated using a removable needle, peelable cannula or semi-Seldinger technique. The PICC is then inserted into the vein and slowly advanced up to the desired length. Correct catheter tip location must be verified radiologically, using contrast if necessary. In experienced hands, US can be used to check the position of the catheter tip.[40]The catheter should be repositioned if required and carefully secured. Cardiac dysrhythmias[41], myocardial perforation and tamponade have been described with PICCs because movements of the limb affect the tip position. Abduction of the arm moves the catheter tip toward the heart when it is inserted in the cephalic vein, whereas adduction causes the same displacement when the basilic or axillary vein is used.[42] The catheter tip should be positioned outside the pericardal reflection line, that is, above the second thoracic vertebra on the chest X-ray, while the arm is in the position that leads to maximum migration toward the heart. Cases

of pleural effusion or catheter rupture with migration into a pulmonary artery with subsequent haemorrhage have been reported.[43]

Complications of central venous access[44]

Perforation, infection and thrombosis are the three major complications of central venous access. As a rule, in a neonate with a central venous line, and whatever its insertion site, sudden haemodynamic or respiratory degradation should prompt immediate X-ray to exclude tamponade or pleural effusion.[45,46] In the presence of signs of sepsis, blood cultures should be taken to exclude catheter infection or contamination. In the absence of blood on aspiration, the central and intravascular position of the catheter should be confirmed and the absence of thrombosis confirmed by US.

Complications common to all sites

Immediate

- Arterial puncture. Depending on the puncture site, any artery close to the vein can be injured; the smaller the child, the greater the risk. It can produce a haematoma (mass effect, displacement of vein) but also an arteriovenous fistula later.
- Haematoma. This can occur from venous or arterial puncture.
- Air embolism. This occurs mainly at the time of insertion in the spontaneously breathing neonate.

Immediate or late

- Tamponade. The clinical presentation is often atypical in neonates. It should be suspected in case of sudden haemodynamic deterioration.[45] Although the catheter itself can be used, the pericardium is usually drained by subxyphoidal pericardiocentesis.
- Vessel perforation. Consequences depend on the structure involved, size of the hole and fluid infusion rate. Risk factors for vessel wall perforation are repeated contact of the vessel wall and catheter tip (see Section titled 'Position of catheter tip'), occlusive thrombosis and local septic or chemical phlebitis. For central catheters inserted from a limb (PICC, femoral), limb movement can favour vessel erosion.
- Thrombosis. Although clinical signs are sometimes obvious (collateral circulation and limb oedema), it is often subclinical. The risk is increased in the neonatal period because of the small size of the vessels and the patient's critical condition (sepsis, shock and vasopressors). Duration of catheter placement is not a risk factor. Thrombosis and catheter occlusion is the most frequent mechanical complication of PICCs, with a risk of 10%[47], being more frequent with lower extremity catheterisation. Prophylactic continuous heparin infusion or administration of heparin in the infused solution have been proposed, but without beneficial evidence.[48,49] In cases where thrombosis is suspected, the diagnosis should be confirmed by US or Doppler and, if needed, angiography. The treatment can include heparin, streptokinase or alteplase. The catheter can be removed or left in place to provide local thrombolysis.
- Infection. The incidence varies from 3.7 to 10 per 1000 catheter days. One study reported similar infection rate for PICCs as for peripheral venous access.[50] The risk of catheter-related septicaemia is inversely proportional to gestational age and weight, and directly proportional to duration of catheterisation, use of parenteral nutrition or mechanical ventilation.[51] Differentiation between catheter infection and contamination is often difficult; catheter tip culture, and peripheral and central blood cultures may clarify the diagnosis. Coagulase-negative *Staphylococcus* is the most common organism, which can usually be treated with IV antibiotics (vancomycin) without removing the catheter. In case of Gram- negative infection, the catheter should be removed and the antiotherapy adapted accordingly. If fever persists despite catheter change and antibiotics, endocarditis should be excluded.

- Rupture of catheter. This complication is almost unique to PICCs. There is a risk of rupture and intravascular migration of the distal part of the catheter. In one series, 11 cases were observed in 1650 PICCs. A forceful attempt to flush a blocked line carries a recognised risk of rupture.[52]

Complications of access to the SVC

Immediate

- Pneumothorax
- Haemothorax
- Malposition. The catheter can be misplaced directly or migrate later into branches of the brachiocephalic veins such as a thymic vein or the first superior intercostal vein, into the azygos vein or abnormal vessels in the presence of congenital heart disease. This can lead to local thrombosis or perforation (see Section titled 'Late complications') and should thus be corrected as soon as possible. The diagnosis of malposition in the azygos vein is not easy on an antero-posterior chest X-ray; a lateral view is necessary to detect the aberrant catheter position.[14] As a rule of thumb, a lateral X-ray or opacification is necessary in any case in which the catheter path on an antero-posterior X-ray is atypical. A few cases of initial misplacement of the catheter in the epidural or subarachnoid space have been described.[53,54] In these cases, no blood could be aspirated from the catheter.

Late

Chylothorax: In an infant with a history of central venous catheterisation, it can be caused either by direct trauma to the thoracic duct (left) or great lymphatic vein (right) at the time of catheter insertion (needle or dilator) or by venous thrombosis in the area where those lymphatic vessels drain into the SVC.[55,56]

Complications of access to IVC

These include extravasation of fluids in the retroperitoneal space and migration of the catheter tip into the perimedullar space via the left lumbar and epidural veins. The right FV seems better to avoid this because of the increased angulation between the FV and lumbar vein on the right side.[57–59] Radiologic confirmation of the correct position of the catheter tip is necessary to avoid these complications.

Peripheral arterial access

Despite non-invasive monitoring techniques such as transcutaneous PO_2, PCO_2 and SpO_2, indwelling arterial catheters are often required in the management of critically ill neonates for continuous haemodynamic monitoring and blood sampling. The temporal artery site is no longer recommended because of the risk of cerebral embolisation when flushing the line. The radial and femoral arteries are the most commonly used. The ulnar artery is the largest terminal branch of the brachial artery.[60] Its catheterisation is associated with two major concerns: (1) ischaemic complications due to abnormal collateral supply of the arterial vascularisation of the hand; and (2) ulnar nerve injury. Cannulation of the ulnar artery should be avoided when cannulation of the radial artery has already been attempted on the same wrist because this could result in total occlusion of the arterial supply to the hand.

It is usually recommended that the brachial (humeral) artery should be used with caution due to the absence of collateral blood flow at its level and the proximity of the median nerve. However, in a large series of neonates and infants with congenital heart disease blind catheterisation of the brachial artery was not associated with more complications than the radial artery.[61] The axillary artery must be used with caution. There is some collateral flow at its level but the artery is surrounded by branches of the brachial plexus, which may be injured. The posterior tibial artery runs posterior to the internal

malleolus. It is best palpated with the foot in dorsiflexion. The dorsalis pedis artery runs on the dorsal aspect of the foot, usually between the first and second toes. It is best palpated with the foot in plantar extension.

These two arteries can be cannulated without major complications but measured peak systolic pressure may exceed aortic values due to pressure-wave amplification in the vascular tree.

The femoral artery is usually easy to locate and cannulate. Although there is a theoretical increased risk of contamination due to the proximity of the perineum, the incidence of infection is no greater than with radial catheters but the incidence of perfusion-related complications is greater.[62]

Technique

Performing the modified Allen's test to check the collateral circulation to the hand is recommended before radial or ulnar artery puncture[63]; however, its ability to predict ischaemia has recently been questioned in adults [64] and it is not validated in neonates. In case of doubt regarding collateral circulation, another site should be considered. Slight extension of the wrist or ankle helps locate and fix the artery. Its course can be identified by palpation, transillumination[65] (Video 6) or US. Results regarding US guidance are controversial and are probably experience dependent.[66,67] Neonates' radial arteries are very small (around 1 mm). A higher success rate is achieved if a very high frequency US probe (>13 MHz) and a zoom function are used. A SAX view of the artery is usually used with an OOP approach. Correct visualisation of the artery is obtained by using the zoom function. To ensure successful catheterisation, the needle tip should be seen progressing into the arterial lumen over a few millimetres by translating the probe slowly cephalad (Video 7).

Using a sterile technique is mandatory. A 24-G cannula is used for preterm and term newborn.

Nicking the skin with a 22-G needle can prevent damaging the cannula when it pierces the skin. The cannula is slowly inserted through the skin, with a 20–30° angle, watching for blood return in its hub. Whether the cannula is used alone or mounted on a syringe is a matter of preference. Slow insertion of the cannula prevents vasospasm and arterial trauma. Once into the artery, the cannula is carefully fixed to avoid both accidental removal and kinking at the puncture site. Connections should be secured to avoid blood loss by disconnection. The dressing should allow visual inspection of the skin proximal and distal to the catheter to detect early signs of a thrombotic complication (skin blanching or cyanotic discolouration). Before inserting an arterial catheter, the tubing and transducer are carefully flushed with the heparinised solution, taking care to eliminate any bubble of air. The pressure transducer is placed at a level with the child's mid-axillary line and zeroed.

The stopcocks of the arterial line should be clearly identified to avoid the accidental intra-arterial injection of anaesthetic agents, antibiotics, etc.

Maintenance of the catheter

The fluid used to maintain arterial line patency is a heparinised solution of 0.9% saline, 0.45% saline or 5% dextrose. The saline solutions have the advantage of allowing blood-glucose measurements and to be less favourable to bacterial growth. The recommended concentration of heparin is 0.5 IU ml^{-1}. The heparinised solution is flushed at a constant rate (1 ml h^{-1}) through an automatic disposable pressurised system, usually a syringe pump, in neonates.

Blood sampling should be performed slowly to avoid collapsing the vessel and damaging its endothelium. After blood sampling, the tubing should be flushed gently. Too rapid or forceful flushing results in blanching of the skin proximal to the cannula, and transmission of the iatrogenic pressure wave to distal sites such as the cerebral or the splanchnic circulation. Flushing no more than 0.5 ml with a 1 ml syringe over a period of 5 sec recommended. In case of damping of the arterial waveform, the tubing and stopcocks should be inspected to eliminate bubbles of air; however, gentle flushing is sometimes necessary to obtain a satisfactory waveform from a partially blocked cannula.

Complications

Ischaemia

Aetiologies of ischaemia are multiple, including thrombosis, vasospasm and emboli. Vasospasm can occur within minutes or hours after insertion. The first sign is skin mottling distal to the insertion site. Pallor, loss or reduced pulse and, sometimes, gangrene follow. Either injecting a small dose of lidocaine into the catheter or warming the contralateral limb to produce reflex vasodilation can be used. If it does not succeed, the catheter should be removed.

The incidence of arterial thrombosis varies according to the child's age. In one prospective study in which the radial artery was cannulated with a Teflon cannula, complete occlusion of the artery was diagnosed by Doppler flow examination in 20 out of 32 infants (median weight 1935 g), but arterial blood flow resumed within 1–29 days after cannula removal. The duration of occlusion was directly related to the duration of cannulation and inversely related to birth weight.[63] Although permanent ischaemic damage following arterial catheterisation is rare, removal of the cannula is recommended in case of increasing difficulties with blood sampling or appearance of cyanotic discolouration of the skin distal to the entry site. Ischaemic damage is more likely in case of low cardiac output and/or of use of vasopressors and can lead to dramatic consequences such as amputation.[68,69]

Embolisation can occur distally or proximally. Distal embolisation results from propagation of a thrombus formed near the cannula; proximal embolisation of air or debris occurs in case of aggressive flushing. Careful inspection of the skin proximal and distal to the cannula entry site and gentle flushing by hand are mandatory to avoid these complications.

In case of an ischaemic complication, local warming and systemic anticoagulation can be useful. Topical vasodilatation using a nitroglycerin ointment or patch[70], or a brachial plexus block[71] have been proposed.

Infection

Local infection is rare if the rules of asepsis are observed and if the cannula is left in place for less than 4 days. However, colonisation of the cannula is more frequent when multiple attempts have been required for its insertion. This is probably due to breaks in the rules of asepsis when dealing with technical difficulties.

Other complications

These include nerve damage by the needle or by a compressive haematoma, tendon sheath injury, accidental intra-arterial injection of anaesthetic drugs, formation of an arteriovenous fistula and compartment syndrome.[72]

Umbilical access

The umbilical vein and arteries can easily be accessed during the first few days of life, sometimes up to the end of the first week. The umbilical vein is the recommended emergency access for neonatal resuscitation. It can be used as any other central line to sample blood or to administer fluids, parenteral nutrition and blood.[73] The umbilical cord contains two arteries and one vein. It emerges from the baby's body with a short skin-covered portion, the future umbilicus and a distal membranous part. The vessels are buried within Warthon's jelly.

Within the body, the umbilical vein goes cephalad, enters into the liver and divides. One division joins the left branch of the portal vein and directs 20% of the blood to the liver. The other division, called the ductus arteriosus, bypasses the liver and carries remaining blood flow into the IVC via the left suprahepatic vein. After entering the abdomen, the umbilical arteries turn inferiorly and enter the pelvis to connect with the internal iliac arteries. There are some contraindications to umbilical vein and artery catheterisation. These include omphalitis, omphalocele, gastroschisis and peritonitis. Necrotising enterocolitis is a relative contraindication to the use of the umbilical artery.[74]

Umbilical vein

Catheter tip position

There are high and low positions for the tip of the catheter. The high position is ideal and is when the catheter is advanced through the ductus venosus into the IVC. On a chest X-ray, the tip should be above the diaphragm. The insertion length from the base of the cord can be estimated according to birth weight by using the formula: $1.5\times$ kg $+ 5.5$ cm[75] or by using standardised graphs.[74]

The low position is used for emergency venous access to avoid placement of the catheter in the liver. The tip is between 3 cm (pre-term) and 5 cm (full term) from the base of the cord.

Technique (Video 8)

The umbilical cord is cut 0.5–1 cm above its skinny part. The stump is gently tied using a tissue lace. The vein is a wide, thin-walled and gaping vessel. Before catheterisation, it is cautiously opened and clots may need to be removed. The catheter is then slowly inserted aiming for the upper part of the body.

Recommended catheter size for neonates less than 1500 g is a 3.5 Fr and for greater than 1500 g is a 5 Fr. Single- or double-lumen catheters are available. If an umbilical catheter is not available, a sterile 6 to 8 Ch feeding tube may be used.[76]

Umbilical artery

Ideal catheter tip position

The high position is ideal with the tip being in the descending aorta, above the diaphragm at the Th7–Th9 level. The insertion length from the base of the cord can be calculated according to birth weight using the formula: $3\times$ kg $+ 9$ cm, or using standardised graphs.[74] The less ideal low position is above the aortic bifurcation and below the renal vessels, usually corresponding to L3–L4.

Technique (Video 9)

The arteries are thick walled and usually have a degree of spasm. To be catheterised, they need to be carefully dilated using small forceps. The catheter is then carefully inserted aiming for the lower part of the body. The ideal catheter size for babies less than 1200 g is 3.5 Fr and for babies greater than 1200 g is a 5 Fr.

Complications of umbilical access

There are a number of possible complications with umbilical access including:

- infection;
- thrombo-embolism with clot, Wharton's jelly or even cotton swabs;
- vessel trauma such as perforation and aneurysm formation;
- umbilical vein catheter tip malposition resulting in fluid accumulation in the pleura, pericardial space, or peritoneum, pulmonary venous return obstruction, arrythmias and hepatic haematoma[77];
- umbilical artery catheters may lead to renal artery obstruction and hence systemic hypertension;
- vasospam and ischaemia[78,79];
- blood flow obstruction resulting in enterocolitis or hepatic necrosis;
- portal vein thrombosis[80];
- nerve lesions resulting from arterial umbilical catheter have also been described.

Different strategies have been evaluated to minimise the risk of thrombo-embolic complications. Heparin use does not show any significant impact on aortic thrombosis but decreases the incidence of

catheter occlusion.[81] The use of end-hole versus side-hole arterial umbilical catheters appears to decrease the incidence of thromboses.[82]

Summary

Vascular access in neonates and small infants is often challenging. US screening and guidance improves its safety and efficacy. However, safe use of US needs education and training to interpret correctly the images and achieve eye–hand coordination. Moreover, vigilance remains necessary during insertion and maintenance and also following a recent failed insertion or the removal of a central venous catheter.[46] Lastly, whether venous and arterial lines should be heparinised or not to prevent thrombotic complications remains controversial.[83]

Practice points

(1) Adequate training in US-guided vascular access on phantoms and adults to acquire eye–hand coordination is mandatory before using it in neonates and infants.
(2) US-guided vessel puncture requires the meticulous application of basic rules.
(3) Vigilance is necessary to detect complications of central venous catheterisation early during insertion and maintenance but also following recent failed insertion or removal of the catheter.
(4) Sudden haemodynamic or respiratory degradation in a neonate with a central venous catheter requires immediate X-ray to exclude tamponade or pleural effusion.

Research agenda

(1) Education and training in US should become part of the neonatologist's and paediatric anaesthesiologist's curriculum;
(2) What is the risk/benefit ratio of using heparin to maintain patency of venous and arterial catheters?[83]
(3) Incidence of asymptomatic vessel thrombosis after central venous access or PICC in neonates and small infants;
(4) Development of multi-planar probes to provide simultaneous SAX and LAX views.

Conflict of interest statement

None.

AppendixSupplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.bpa.2010.02.017.

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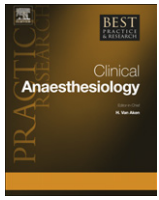

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The pharmacology of anaesthetics in the neonate

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Keywords:
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Neonatal anaesthesia dosing needs to be based on physiological characteristics of the newborn, pharmacokinetic/pharmacodynamic considerations and the adverse effects profile. Disease processes and treatments in this group are distinct from adults. Absorption, distribution and clearance are altered because of immaturity of enzyme, anatomical or physiological systems resulting in extensive variability of drug disposition in neonates. This is further compounded by pharmacogenomic influences. Population and physiological-based pharmacokinetic modelling have improved understanding of maturation and subsequent dose approximation. Postmenstrual age is a reasonable measure for maturation, although postnatal age may also have an impact. The neonatal response to drugs is also altered. Although neuromuscular monitoring is robust, there remains a need for other clinically applicable tools to assess pharmacodynamics that can provide effect feedback. In neonatal anaesthesia, a specific focus of interest is tools to assess depth of anaesthesia, sedation and pain. These tools have potential to improve effectiveness and safety.

Neonates are a heterogeneous population. They are the group of children from birth up to the age of 28 days of life and include both preterm (i.e., born before 37 weeks of gestational age) and term neonates. In practice, the word 'neonate' also extends to include former preterm neonates, who may be older than 28 days of life. Consequently, the postmenstrual age (PMA) of a neonate may range from extreme preterm birth at 22 weeks up to 50 weeks, whereas weight ranges from 0.5 to 5 kg; an entire order of magnitude. Age, size, co-morbidity, co-administration of drugs and genetic polymorphisms contribute to the extensive

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between-individual pharmacokinetic (PK) and pharmacodynamic (PD) variability in this population. These phenomena distinguish neonates as a specific population with major pharmacological differences from their older counterparts.

Neonatal PK differences

Absorption

Anaesthetic drugs are mainly administered intravenously or through inhalation, but premedication and postoperative pain relief are commonly administered enterally. Absorption after oral administration is slower in neonates than in older children due to delayed gastric emptying. Adult rates may not be reached until 6–8 months.[1,2] Congenital malformations (e.g., duodenal atresia), co-administration of drugs (e.g., opioids) or disease characteristics (e.g., necrotising enterocolitis) may further contribute to absorption variability. Slow gastric emptying and reduced clearance may dictate reduced doses and frequency of administration. For example, a mean steady state target paracetamol concentration above 10 mg l^{-1} at trough can be achieved by an oral dose of 25 mg kg^{-1} day^{-1} in premature neonates at 30 weeks, 45 mg kg^{-1} day^{-1} at 34 weeks and 60 mg kg^{-1} day^{-1} at 40 weeks PMA.[3] Because gastric emptying is slow in premature neonates, dosing may only be required twice a day.[3]

In some circumstances, rectal administration (e.g., thiopentone and methohexitone) may be speedier for neonates. However, the between-individual absorption and relative bioavailability variability may be more extensive than oral administration, making rectal administration less suitable for repeated administration.[4]

The larger relative skin surface area, increased cutaneous perfusion and thinner stratum corneum in a neonate increases systemic exposure of topical drugs (e.g., corticosteroids, local anaesthetic creams and antiseptics). Neonates have a tendency to form methaemoglobin because they have reduced methaemoglobin reductase activity and foetal haemoglobin is more readily oxidised than adult haemoglobin. This, combined with increased percutaneous absorption, resulted in reluctance to use repeat lidocaine–prilocaine cream in this age group.[5] Similarly, cutaneous application of iodine antiseptics can result in transient hypothyroidism.

Inhalational anaesthetic delivery is determined largely by alveolar ventilation and functional residual capacity (FRC). Neonates have increased alveolar ventilation and a smaller FRC than do adults because of increased chest wall compliance. Consequently, pulmonary absorption is generally more rapid in neonates.[6] The higher cardiac output and greater fraction of the cardiac output distributed to vessel-rich tissues (i.e., a clearance factor) and the lower tissue/blood solubility (i.e., a volume factor) further contribute to the more rapid wash-in of inhalational anaesthetics in early life.[7,8] Disease characteristics further contribute to the variability in inhalational absorption. Induction of anaesthesia may be slowed by right-to-left shunting of blood in neonates suffering cyanotic congenital cardiac disease or intrapulmonary conditions. This slowing is greatest with the least soluble anaesthetics (e.g., nitrous oxide, sevoflurane). Left-to-right shunts usually have minimal impact on uptake because cardiac output is increased so that systemic tissue perfusion is maintained at normal levels. The flow of mixed venous blood returning to the right heart ready for anaesthetic uptake is normal. If cardiac output is not increased, and peripheral perfusion is reduced, then there will be less anaesthetic uptake in the lung. Although alveolar anaesthetic partial pressure may be observed to rise rapidly, there is a slower rise in tissue partial pressure and anaesthetic effect is delayed.

Distribution

Distribution describes the movement from systemic circulation into various body compartments, tissues and cells. Distribution is influenced by body composition, protein binding, haemodynamics (e.g., regional blood flow) and membrane permeability. Disease processes also have an impact on distribution.

Body composition

Total body water and extracellular fluid (ECF)[9] are relatively increased in neonates and fall proportionately with postnatal age, whereas the percentage of body weight contributed by fat is 3% in a 1.5-kg premature neonate, 12% in a term neonate. The proportion of fat further doubles by 4–5 months of age.

These body component changes affect volumes of distribution of drugs. Polar drugs such as depolarising and non-depolarising neuromuscular blocking drugs (NMBDs) distribute rapidly into the ECF, but enter cells more slowly. The initial dose of such drugs is consequently higher in the neonate than in child or adult.

Fentanyl has an increased volume of distribution in neonates. The volume of distribution at steady state is 5.9 (standard deviation (SD) 1.5) l kg^{-1} in a neonate compared with 1.6 (SD 0.3) l kg^{-1} in an adult.[10] This may contribute to the reduced degree of respiratory depression seen after doses as high as 10 mcg kg^{-1} in term neonates. However, high doses of fentanyl result in prolonged effect in neonates due to reduced clearance. Reduction of propofol concentrations after induction is attributable to redistribution rather than rapid clearance. Neonates have low body fat and muscle content and so less propofol is apportioned to these 'deep' compartments. Delayed awakening occurs because central nervous system (CNS) concentration remains higher than that observed in older children as a consequence of this reduced redistribution.

Plasma proteins

Albumin and alpha-1 acid glycoprotein (AAG) concentrations are reduced in neonates, albeit with a broad range of scatter (0.32–0.92 g l^{-1}), but are similar to those in adults by 6 months.[11,12] AAG is an acute-phase reactant that increases after surgical stress. This causes an increase in total plasma concentrations for low-to-intermediate extraction drugs such as bupivacaine.[13] The unbound concentration, however, will not change because clearance of the unbound drug is affected only by the intrinsic metabolising capacity of the liver. Any increase in unbound concentrations observed during long-term epidural is attributable to reduced clearance rather than AAG concentration.[14] Total bupivacaine concentrations increase in the first 24 h after surgery in neonates given analgesia by continuous epidural infusion. This increase is attributable to an increase of AAG. This increase, combined with reports of seizures in infants given epidural bupivacaine infusion, has led to recommendations to stop epidural infusion at 24 h. However, it is the unbound bupivacaine that is responsible for effect and this unbound concentration may not change, implying that the infusion could be run for a longer duration.[15] Clearance is the key parameter and this is reduced in neonates. Unfortunately, clearance is associated with large between-subject variability and this means that unbound bupivacaine concentrations may continue to rise in individuals who have a very low clearance.

Plasma albumin concentrations approximate adult values by 5 months of age and are lowest in preterm neonates. Binding capacity approaches adult values by 1 year of age. In addition, free fatty acids and unconjugated bilirubin compete with acidic drugs for albumin binding (e.g., ibuprofen and ceftriaxone). Neonates also have a tendency to manifest a metabolic acidosis that alters ionisation and binding properties of plasma proteins. The induction dose of thiopentone is lower in neonates than in children. It is possible that this is related to decreased binding of thiopentone to plasma albumin; 13% of the drug is unbound in newborns compared with 7% in adults.[16]

Regional blood flows

The initial phase of distribution reflects regional blood flow. Consequently, the brain, heart and liver are first exposed. The drug is then redistributed to other relatively well-perfused tissues, such as skeletal muscle. There is a much slower tertiary distribution to relatively under-perfused tissues of the body that is noted with long-term drug infusions. There are maturational differences in relative organ mass and regional blood flow. In addition, perinatal circulatory changes (e.g., ductus venosus and ductus arteriosus) may also result in differences in distribution. Blood flow, relative to cardiac output, to the kidneys and brain increases, whereas that to the liver decreases through neonatal life.[17] Cerebral and hepatic mass as a proportion of body weight are also much higher in the infant than in the adult.[18] Reduced cardiac output and cerebral perfusion in neonates means that onset time after intravenous induction is slower in neonates. Offset time is also delayed because redistribution to well-perfused and deep under-perfused tissues is more limited.

Blood–brain barrier

The blood–brain barrier (BBB) is a network of tight junctions to restrict paracellular diffusion of compounds between blood and brain. There is confusion over the importance of this barrier in the

neonate; partly because of early studies on respiratory depression caused by pethidine or morphine. It was believed that pethidine caused less respiratory depression than morphine because the poorly developed BBB in the newborn resulted in higher brain morphine concentrations and subsequent respiratory depression.[19] It was postulated that BBB permeability to water-soluble drugs such as morphine changes with maturation.[19] However, the neonatal respiratory depression observed after morphine could be due to PK age-related changes. For example, the volume of distribution of morphine is reduced in term neonates 1–4 days ($1.3\ l\ kg^{-1}$) than those at 8–60 days ($1.8\ l\ kg^{-1}$) or adults ($2.8\ l\ kg^{-1}$).[20] Consequently, we might expect initial higher concentrations of morphine in neonates, resulting in more pronounced respiratory depression. Respiratory depression, measured by carbon dioxide response curves or by arterial oxygen tension, is similar from 2 to 570 days of age at the same morphine concentration.[21] The BBB theory in this particular circumstance lacks conviction. It is more likely that the increased neonatal respiratory depression after morphine is due to PK age-related changes.

The BBB may have an impact in other ways. Small molecules access foetal and neonatal brains more readily.[22] BBB function improves gradually, possibly reaching maturity at term.[22] Kernicterus, for example, is more common in premature neonates. Drugs bound to plasma proteins will not normally cross the BBB. However, the unbound lipophilic drugs passively diffuse across the BBB to achieve equilibrium very quickly. This may contribute to bupivacaine's propensity for seizures in neonates.

Besides passive diffusion, there are specific transport systems that mediate active transport. Pathological CNS conditions can cause BBB breakdown and alterations in these transport systems. Fentanyl is actively transported across the BBB by a saturable ATP-dependent process, whereas ATP-binding cassette proteins such as P-glycoprotein actively pump out opioids such as fentanyl and morphine.[23] P-glycoprotein modulation significantly influences opioid brain distribution, and onset time, magnitude and duration of analgesic response.[24] Modulation may occur due to disease processes, fever or presence of other substances (e.g., verapamil and magnesium).[23] The genetic polymorphisms affecting P-glycoprotein-related genes may explain differences in CNS-active drug sensitivity.[25]

Elimination

The main routes by which drugs and their metabolites leave the body are the hepatobiliary system, the kidneys and the lungs. The liver is the primary organ for clearance of most drugs, although the lungs have a major role for anaesthetic vapours. Drug-metabolizing enzymes are generally divided into phase I and phase II reactions. Phase I reactions are non-synthetic reactions like oxidation, reduction and hydrolysis. The most important group of enzymes involved in phase I processes are the cytochrome P450 (CYP) iso-enzymes. The liver is the primary organ for metabolic clearance, converting lipid-soluble drugs to water-soluble compounds. Although the metabolism of a given drug most frequently results in water-soluble inactive compounds, metabolism may also result in transformation to a more potent drug (e.g., codeine to morphine by CYP2D6, propacetamol to paracetamol by esterase, morphine to morphine-6-glucuronide by UGT2B7) or into a toxic compound (e.g., halothane to trifluoroacetyl chloride by CYP2E1 causing halothane hepatitis).

Hepatic metabolic clearance

In general, iso-enzyme-specific phenotypic metabolic clearance is based on constitutional, environmental and genetic factors, but in early neonatal life, mainly reflects ontogeny, that is, age-dependent activity. Most CYP iso-enzymes, except for CYP3A7, have a low phenotypic activity until birth. Some appear to be switched on by birth, whereas in others birth is necessary but not sufficient for the onset of activity.[26,27] CYP2E1 activity surges after birth[28], CYP2D6 becomes detectable soon thereafter, CYP3A4 and CYP2C appear during the first week, whereas CYP1A2 is the last to appear.[29] Neonates depend on the immature CYP3A4 for levobupivacaine or midazolam clearance and on CYP1A2 for ropivacaine clearance, hence the need for reduced epidural infusion rates in this age group.[30–32] Formation of the M1 metabolite of tramadol, reflecting CYP2D6 activity[33], appears rapidly around term and reaches 84% of mature values by 44 weeks PMA. Besides age and size, it is to be anticipated that other covariates such as genetic polymorphisms or disease characteristics also contribute to the phenotypic inter-individual variability observed.

Pharmacogenomics (PG) investigates variations of DNA and RNA characteristics as related to drug response that incorporates both PK and PD. There is large between-individual PK variability that is contributed to by polymorphisms of the genes encoding for metabolic enzymes.[34] Genetic variability influencing plasma cholinesterase activity and its influence on succinylcholine is a well-known example. Another example is the CYP2D6 single nuclear polymorphism (SNP), inherited as an autosomal recessive trait. The impact of genetic polymorphisms on drug metabolism in neonates were previously unknown, but have recently been documented for CYP2D6-mediated tramadol metabolism; both PMA and CYP2D6 activity score explained the between-individual variability in tramadol metabolism observed (Fig. 1). The interplay amomg maturation of tramadol clearance, M1 metabolite formation and developing GFR on M1 concentration (and subsequent analgesia) is shown in Fig. 2. This observation illustrates the potential relevance of polymorphisms in neonatal pharmacology.

Some phase II iso-enyzmes are mature in term neonates at birth (sulphate conjugation), whereas others are not (acetylation, glycination, glucuronidation).[35] Glucuronidation is of relevance in the metabolic clearance of several drugs (e.g., paracetamol, morphine and propofol) frequently administered by anaesthetists. Allometric body-size scaling complimented by maturation models[36,37] have been used to unravel the maturation of clearance of morphine[38,39] and paracetamol.[40,41] Paracetamol and morphine are cleared by specific isoforms (UGT1A6 and UGT2B7). Clearance of both drugs is immature in the premature 24-week PMA neonate and matures to reach adult rates by the first year of life (Fig. 3). Dexmedetomidine is also cleared predominantly by the UGT system and its clearance has a similar maturation profile.[42]

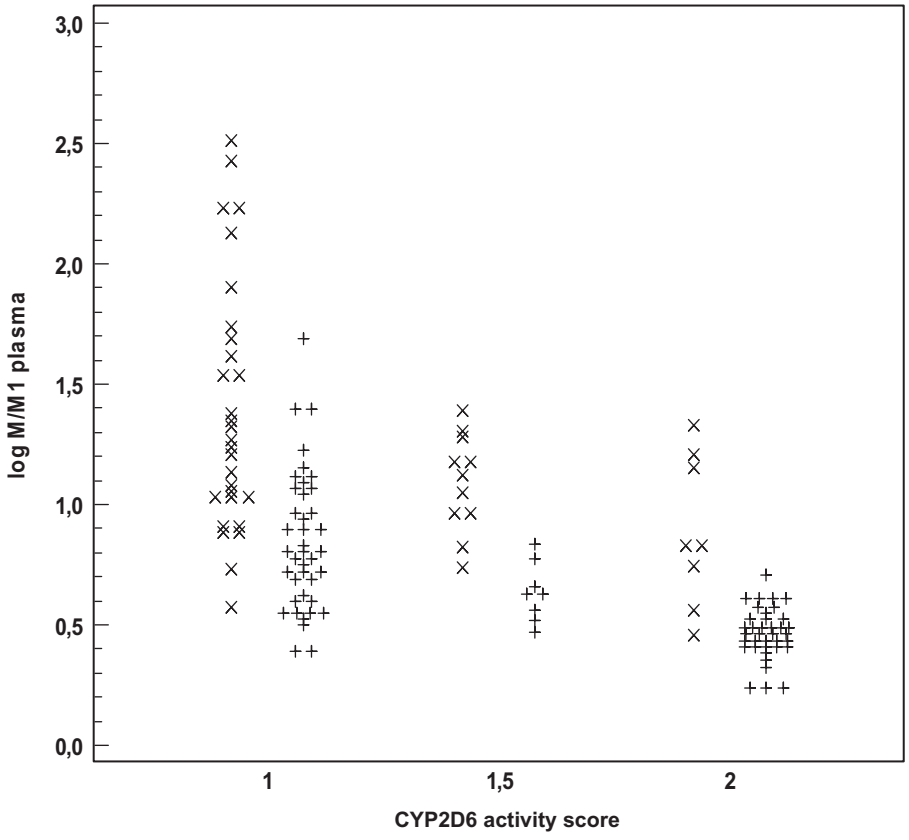

Fig. 1. The impact of both postmenstrual age (either <40, × or ≥40 weeks, +) and CYP2D6 activity score on the plasma log M/M1 values is illustrated in patients with an CYP2D6 activity score of either 1, 1.5 or 2. The lower the log M/M1 value, the higher the phenotypic CYP2D6 iso-enzyme activity. There is a PMA-dependent effect (either or not younger than 40 weeks PMA) and a polymorphism dependent effect (either CYP2D6 activity score of 1, 1.5 or 2) Adapted from Allegaert et al.[88]

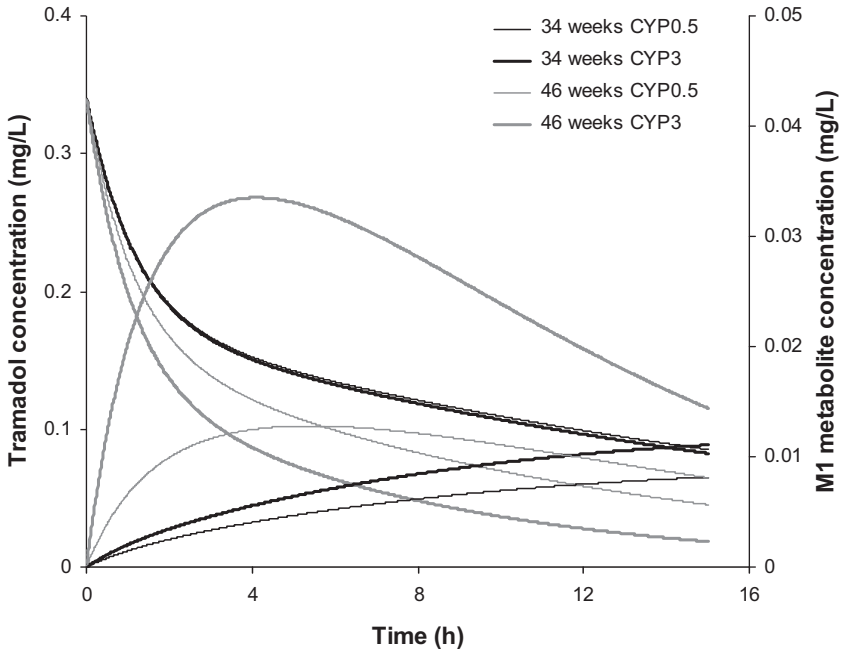

Fig. 2. Time-concentration profiles for tramadol and the M1 metabolite in neonates. CYP2D6 activity has been assigned a score of 0–3. Clearance of the parent drug is reduced in the 34-week PMA neonate compared to the 46 week PMA neonate and CYP activity has little impact on profiles. At 46 weeks both total clearance and CYP2D6 activity has increased, resulting in distinct profiles. The M1 metabolite is cleared by renal function and the rapid maturation of glomerular filtration rate around 40 weeks PMA has impact on the M1 metabolite profile, resulting in a peak concentration and subsequent decrease. Adapted from Allegaert et al.[88]

Glucuronidation is the major metabolic pathway of propofol. This pathway is immature in neonates, although multiple CYP iso-enzymes (e.g., CYP2B6, CYP2C9 and CYP2A6) also contribute to its metabolism and cause a faster maturation profile than expected from glucuronidation alone[43] (Fig. 3). Urine collections after intravenous bolus of propofol in neonates (PNA 11 days, PMA 38 weeks) support this contention. Urinary metabolites included both propofol glucuronide and 1- and 4-quinol glucuronide in a ratio of 1:2. Hydroxylation to quinol metabolites was active in these neonates[44], contributing to the rapid rise in clearance at this age that exhibited more rapid maturation than that reported for glucuronide conjugation alone (e.g., paracetamol and morphine). Maturation of propofol clearance has been expressed in terms of PMA with an additional contribution from PNA.[43]

Disease characteristics also contribute to UGT-related clearance variability. Maturation of morphine clearance occurs more quickly in infants undergoing non-cardiac surgery than those following cardiac surgery.[45] Extracorporeal membrane oxygenation[46] or positive pressure ventilation[39] also reduces clearance. Similarly, clearance of propofol was reduced after cardiac surgery in children.[47]

Extrahepatic routes of metabolic clearance

Many drugs undergo metabolic clearance at extrahepatic sites. Remifentanil and atracurium are broken down by non-specific esterase in tissue and erythrocytes. Clearance, expressed per kilogram, is increased in younger children[48–52]; this is likely attributable to size because clearance is similar when scaled to a 70-kg person using allometry.[48] Local anaesthetics are metabolised by plasma pseudocholinesterase, the activity of which is reduced in neonates. The *in vitro* plasma half-life of 2-chloroprocaine in umbilical cord blood is twice that in maternal blood[53], but there are no *in vivo* studies examining the effects of age.

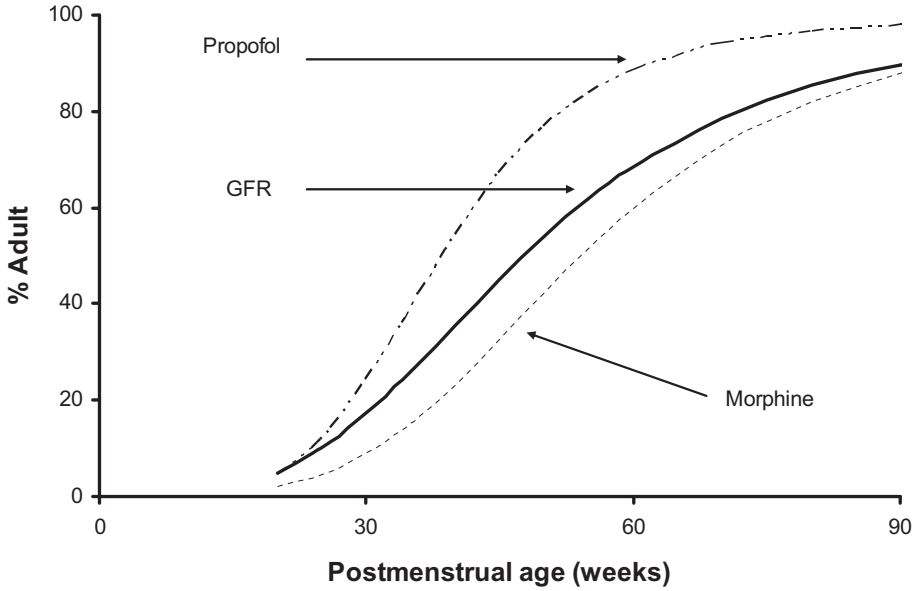

Fig. 3. Clearance maturation, expressed as a percentage of mature clearance for morphine and propofol. The morphine maturation profile (glucuronide conjugation) is similar to glomerular filtration rate (GFR). In contrast, cytochrome P450 iso-enzymes also contribute to propofol metabolism and cause a faster maturation profile than expected from glucuronide conjugation alone. Maturation parameter estimates were taken from references [39,55,89].

Pulmonary elimination

The factors determining anaesthetic absorption through the lung (alveolar ventilation, FRC, cardiac output, solubility) also contribute to elimination kinetics. We might anticipate more rapid wash-out in neonates for any given duration of anaesthesia because there is less distribution to fat and muscle content. The greater decrease in cardiac output induced by halothane in neonates might be expected to speed elimination, but brain perfusion will also be reduced and this slows recovery. Halothane, and to a far lesser extent isoflurane and sevoflurane, undergo hepatic metabolism. Halothane is reported to undergo as much as 20–25% metabolism but at typical anaesthetising concentrations, hepatic halothane removal is extremely small.[54]

Renal elimination

Renal elimination of drugs and their metabolites is by two processes: glomerular filtration and tubular secretion. Glomerular filtration rate (GFR) is only 10% that of adult GFR at 25 weeks, 35% at term and 90% at 1 year of age.[55] Aminoglycosides are almost exclusively cleared by renal elimination and maintenance dose is predicted by PMA because it predicts the time course of renal maturation.[56]

Immaturity of clearance pathways can be used to our advantage when managing apnoea after anaesthesia in the preterm neonate. N_7-methylation of theophylline in the newborn to produce caffeine is well developed whereas oxidative demethylation (CYP1A2) responsible for caffeine metabolism is still deficient. Theophylline is effective for the management of postoperative apnoea in the premature neonate, partly because it is a prodrug of caffeine, which is effective controlling apnoea, in this age group and caffeine can be only slowly cleared by the immature kidney.[57]

Milrinone, an inodilator, is used increasingly in children after congenital cardiac surgery. Renal clearance is the primary route of elimination. A clearance of $9\,l\,h^{-1}$ per 70 kg is reported in adults with congestive heart failure and we might anticipate that clearance in premature neonates is reduced to 10% of this value because of a corresponding renal function immaturity in this cohort. This has been confirmed in 26-week PMA infants who had a clearance of $0.96\,l\,h^{-1}$ per 70 kg.[58] Similarly, the

clearance of the NMBD, d-tubocurare, can be directly correlated with GFR.[59] Some drugs such as the non-steroidal anti-inflammatory agents (NSAIDs) may compromise renal elimination clearance in early life; ibuprofen reduced GFR by 20% in premature neonates, independent of gestational age.[60,61]

Neonatal PD differences

Children's responses to drugs have much in common with the responses in adults once developmental PK aspects are considered.[62] The perception that drug effects differ in children arises because these drugs have not been adequately studied in paediatric populations who have size- and age-related effects as well as different diseases. However, even after taking these covariates into account, neonates often have altered pharmacodynamics.

The minimal alveolar concentration (MAC) is commonly used to express anaesthetic vapour potency. The MAC for almost all these vapours is less in neonates than in infancy.[7] MAC of isoflurane in preterm neonates less than 32 weeks' gestation is 1.28 (SD 0.17%), and MAC in neonates 32–37 weeks' gestation is 1.41 (SD 0.18%).[63] Similarly, the MAC of halothane in neonates (0.87% SEM 0.03) is lower than that in infants (1.20% SEM), while the decrease in blood pressure and the incidence of hypotension in neonates are similar to those in infants at approximately 1 MAC of halothane.[64] The cause of these differences is uncertain.

Changes in regional blood flow may influence the amount of drug going to the brain. Gamma-aminobutyric acid ($GABA_A$) receptor numbers or developmental shifts in the regulation of chloride transporters in the brain may change with age, altering response (e.g., midazolam). Data from rodents over an age range from immediate newborn to PNA 40 days have shown developmental PD changes for sedation that mimic those seen in human childhood.[65] Such models offer potential to improve understanding of developmental pharmacology.[66]

Neonates have an increased sensitivity to the effects of NMBDs.[59] The reason for this is unknown but it is consistent with the observation that there is a threefold reduction in the release of acetylcholine from the infant rat phrenic nerve.[67,68] The increased volume of distribution means that a single NMBD dose is the same as the older child, but reduced clearance and increased sensitivity prolongs duration.

Amide local anaesthetic agents induce shorter block duration and require a larger weight-scaled dose to achieve similar dermatomal levels when given by subarachnoid block to infants. This may in part be due to myelination, spacing of nodes of Ranvier and length of nerve exposed.

There is an age-dependent expression of intestinal motilin receptors and the modulation of antral contractions in neonates. Prokinetic agents may not be useful in very preterm infants, partially useful in older preterm infants and useful in full-term infants. Similarly, bronchodilators are ineffective because of the paucity of bronchial smooth muscle that can cause bronchospasm.

Cardiac calcium stores in the endoplasmic reticulum are reduced in the neonatal heart. Thus, exogenous calcium has greater impact on contractility in this age group than in older children or adults. Catecholamine release and response to vasoactive drugs vary with age. These PD differences are based in part upon developmental changes in myocardial structure, cardiac innervation and adrenergic receptor function. For example, the immature myocardium has fewer contractile elements and therefore a decreased ability to increase contractility; it also responds poorly to standard techniques of manipulating preload.[69] Dopaminergic receptors are present in the pulmonary vasculature and are thought to cause pulmonary vasoconstriction in preterm neonates. However, systemic circulation vasoconstriction is greater than that observed in the pulmonary circulation, and this differential response contributes to the use of dopamine in neonates with known pulmonary hypertension after cardiac surgery. Neonates have underdeveloped sympathetic innervation and reduced store of noradrenaline. Signs of cardiovascular α-receptor stimulation may occur at lower doses than β-receptor stimulation because β-receptor maturation lags behind α-receptor maturation during the development of the adrenergic system.[70] Although initial higher infusion doses are required to achieve a similar pharmacologic effect observed in children or adults[69], the preterm neonate has immature metabolic and elimination pathways leading to an increased dopamine concentrations with prolonged infusion.[70–73] These maturation changes in PK and PD may contribute to dopamine's continued popularity in the neonatal nursery whereas its popularity wanes in the adult population.

Towards a tailored approach in neonates

Although the general principles of clinical pharmacology also apply in neonates, their characteristics warrant a tailored approach. History provides us with evidence on the deleterious effects of chloramphenicol (grey baby syndrome), benzyl alcohol (gasping syndrome) or dexamethasone (cerebral palsy) in neonates. Neonatal bupivacaine toxicity in those receiving long-term infusion[30] and acute fentanyl tolerance[74] are two recent anaesthesia examples.

Effective and safe pharmacotherapy is dependent upon an understanding of the clinical PK and PD properties of the drugs employed. Besides age-dependent differences in PK and PD, differences in adverse effects should also be considered. Although the available data on drug disposition and its effects in the neonate have increased considerably in the past few years, PK–PD interactions for many drugs remain poorly understood. Clinical studies in neonates encompass multiple difficulties, of which ethical issues, the perceived high vulnerability, technical difficulties, lack of self-assessment, immaturity and the need for specific formulations are examples of such complicating factors. However, in recent years, important progress has been made that has improved the feasibility and the clinical relevance of such studies in neonates. First, models have been developed to handle extensive between-individual variability in PK and PD parameter estimates and to formulate dose estimation.[75] Second, to a lesser extent, population-based modelling tools have helped quantify pharmacodynamics.[76]

Population PK and PD modelling using non-linear mixed effects models has had enormous impact on adult anaesthetic pharmacology. This methodology has particular applicability in neonates where the blood volume available for sampling is limited. Sparse data from multiple subjects can be used. Sampling times are not crucial for population methods and can be fitted around clinical procedures or outpatient appointments. Sampling time bands rather than exact times are equally effective and allow flexibility in neonates. Sampling cannulae for PK studies may block or tissue, parents may refuse repeat sampling and repeat venipuncture is frowned upon. Missing data, however, can still be used in a paediatric population analysis. Data from different studies can be pooled.[77,78]

The use of physiologically based pharmacokinetic modelling (PBPK) has proved to be useful for estimation of clearance maturation and consequent dose approximation. Clearance estimates from PBPK models use data on ontogeny of individual clearance pathways, derived from measurements of enzyme expression and activity in post-mortem livers[26,35] and from *in vivo* data from drugs that are cleared by similar pathways.[79] Continued input of information concerning genetic, physiological, organ and tissue size and composition, protein binding, demographic and clinical data into the library and algorithms for PBPK model programmes has progressively improved their prediction ability.[80–82] These models have been used to assist with first-time dosing in children. A general PBPK model for drug disposition in infants and children, covering the age range from birth to adulthood, has been successfully evaluated using theophylline and midazolam as model drugs.[17]

Pharmacodynamic measures

In general, outcome measures are more difficult to assess in neonates than in children or adults. The common effects measured in anaesthesia are neuromuscular blockade, depth of anaesthesia and sedation or pain. Electromyography response of the adductor pollicis is a consistent effect measure for investigation of neuromuscular blockade in both neonates and adults. Differences are minor, for example, neonates do not tolerate repetitive stimulations as long as older children because of limited acetylcholine reserves. Assessment of outcome variables however becomes more difficult when depth of anaesthesia, sedation or pain is considered.

A common effect measure used to assess depth of anaesthesia is the electroencephalogram (EEG) or a modification of detected EEG signals (spectral edge frequency, Bispectral index, entropy). Physiological studies in adults and children indicate that EEG-derived anaesthesia depth monitors can provide an imprecise and drug-dependent measure of arousal. They can be used as guides for anaesthesia and have improved outcomes in adults. In older children, the physiology, anatomy and clinical observations indicate the performance of the monitors may be similar to that in adults. In infants their use cannot yet be supported in theory or in practice.[83,84] Both outside and during

anaesthesia, the EEG in infants is fundamentally different from the EEG in older children; there remains a need for specific neonate-derived algorithms if EEG-derived anaesthesia depth monitors are to be used in neonates.[85,86]

The existence of an extensive number of sedation or pain scales does not mean that all assessment-related problems have been solved. Most scores are validated for the acute, procedural setting and perform less for subacute or chronic pain or stress. Scales seldom take into account the limited capacity of the more immature infants to mount a consistent behavioural and physiological response to pain. Validation is based on assessment of intra- and inter-individual variability and correlations with neuroendocrine markers of stress or pain. Future research may provide us with objective tools to quantify pain and sedation, but will have to take into account maturational aspects of the newborn. Using the combination of a validated sedation score (COMFORT) and the above-mentioned PK/PD population modelling approach, a circadian night rhythm effect was noted in an investigation of infant propofol sedation after major craniofacial surgery.[87]

In summary, neonates, although distinct as a group of newborns, are not a homogeneous population. They represent a cohort of broad maturation status, weight range and disease spectrum. These factors, along with co-administration of drugs, genetic polymorphisms and treatment effects, contribute to the extensive between-individual variability observed in both PK and PD parameters.

Size and age are major covariates that require consideration during PK maturation. Most PK processes are immature at birth and reach adult status sometime in the first year of life. These processes vary enormously. Phase 1 clearance processes (e.g., CYP3A4 and fentanyl) mature within weeks while phase 2 enzymes such as UGT2B7 (morphine) and GFR mature at 1 year of age. PMA is a useful marker of this maturation process, but PNA may also have an impact.

Although neonatal drug responses have much in common with responses in adults, there are distinct PD differences; the decreased MAC in this cohort is the classic anaesthesia example. PD assessment is hampered by the need for tailored tools. Electromyography response of the adductor pollicis is a consistent effect measure of neuromuscular blockade. By contrast, neonate-derived algorithms for EEG-derived anaesthesia depth monitors are required, whereas the extensive number of sedation or pain scores suggests that these scores only in part cover the perceived need and that the 'fit all patients' score is not available.

The introduction of population and PBPK modelling provides us with the tools that will extend our pharmacological knowledge in this population and ultimately improve anaesthetic care of this cohort.

Practice points

- Neonates are the group of children up to the age of 28 days of life. In practice, the word 'neonate' further extends to former preterm neonates. Age may range from extreme preterm birth at 22 weeks up to 50 weeks of postmenstrual age whereas weight ranges from 0.5 to 5 kg and results in a very heterogeneous group of patients.
- The larger relative skin surface area, increased cutaneous perfusion and thinner stratum corneum in neonates increase transcutaneous water losses, absorption and systemic exposure of topical drugs.
- Distribution is influenced by body composition, protein binding, regional blood flow and membrane permeability. Total body water and extracellular fluid are relatively increased and body fat relatively decreased in neonates, affecting volumes of distribution of drugs.
- The main routes of elimination are the hepatobiliary system, kidneys and lungs. Water-soluble drugs are excreted unchanged in the kidneys, which display age-dependent maturation. Iso-enzyme-specific phenotypic metabolic clearance is based on constitutional, environmental and genetic factors, but in early neonatal life, mainly reflects ontogeny, that is, age-dependent activity.
- Neonates display altered pharmacodynamics. Differences in MAC of gaseous vapours, GABA-receptor-related sedative effects, effectiveness of neuromuscular blockage and effectiveness of inotropes or bronchodilator drugs in neonates have been documented.

Research agenda

- Development of PK and PD models for clearance maturation and consequent dose approximation. Population PK/PD approaches provide us with the tools to learn more on what we want to know, that is, degree and sources of variability.
- Development of robust research and clinically applicable tools to assess the effects of drugs in neonates. In neonatal anaesthesia, specific focuses of interest should be tools to assess depth of anaesthesia, to assess sedation and to quantify pain in neonates.

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Conflicts of interest statement

None.

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The impact of the perioperative period on neurocognitive development, with a focus on pharmacological concerns

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Mounting evidence from animal studies has implicated that all commonly used anaesthetics and sedatives may induce widespread neuronal cell death and result in long-term neurological abnormalities. These findings have led to serious questions regarding the safe use of these drugs in young children. In humans, recent findings from retrospective, epidemiological studies do not exclude the possibility of an association between surgery with anaesthesia early in life and subsequent learning abnormalities. These results have sparked discussions regarding the appropriate timing of paediatric surgery and the safe management of paediatric anaesthesia. However, important questions need to be addressed before findings from laboratory studies and retrospective clinical surveys can be used to guide clinical practice. This article summarises the currently available preclinical and clinical information regarding the impact of anaesthetics, sedatives, opioids, pain and stress, inflammation, hypoxia–ischaemia, co-morbidities and genetic predisposition on brain structure and long-term neurological function. Moreover, this article outlines the putative

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NMDA
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mechanisms of anaesthetic neurotoxicity, and the phenomenon's implications for clinical practice in this rapidly emerging field.

General anaesthesia and sedation, the ability to pharmacologically render patients insensible to noxious stimulation, represents one of the greatest discoveries in medicine. Worldwide, millions of children are exposed every year to general anaesthetics, sedatives and opioids in operating rooms, radiology suites, emergency departments and intensive care units. However, these compounds have recently been implicated in interfering with normal central nervous system development when administered early in life. Unsurprisingly, the possibility of inadvertently introducing iatrogenic effects on learning and behaviour following an otherwise uneventful surgical procedure has created significant concern among paediatric practitioners. Some of these concerns are already influencing the decision for timing of surgery.[1] To provide the practitioner with an overview of this rapidly emerging field of research, this article summarises the currently available data in animal models, examines the proposed underlying cytotoxic mechanisms, outlines the evidence for anaesthetic neurotoxicity in humans and discusses the implications for clinical practice. Additionally, we review the impact of other perioperative confounders, such as pain and stress, inflammation, hypoxia–ischaemia, co-morbidities and genetic predisposition on long-term neurological function.

Historical perspective

Concerns regarding potentially deleterious effects of general anaesthetics on brain development were first raised after more than a century of their routine clinical use. Personality changes observed in young children following administration of vinyl ether, cyclopropane or ethylchloride for otolaryngological surgery were interpreted as long-term sequelae of the anaesthetic agents.[2] Approximately 20 years later, concerns were raised related to the occupational exposure to anaesthetics during pregnancy and their effects on the unborn fetus.[3–6] In these animal studies, chronic exposure to subanaesthetic doses of halothane in pregnant rats led to delayed synaptogenesis and behavioural abnormalities in their offspring. However, it took almost another two decades until initial studies more closely representing paediatric anaesthesia practice were first carried out. In their groundbreaking studies, Dr. Olney's laboratory demonstrated widespread neuronal degeneration following a prolonged exposure to ketamine in neonatal rat pups[7], likening this phenomenon to abnormalities observed in children suffering from foetal alcohol syndrome.[8,9] More recently, in addition to these immediate structural abnormalities, long-term decreases in neuronal density and impaired neurocognitive function were observed in adult rats that were exposed to a combination anaesthetic of midazolam, nitrous oxide and isoflurane as neonates.[10,11] These pioneering findings by Dr. Jevtovic-Todorovic and co-workers of widespread neuronal degeneration immediately following exposure have now been confirmed by numerous laboratories for all routinely used anaesthetics and sedatives in several immature animal models (most recently reviewed in references 12 and 13). However, the long-term effects in animals remain controversial[14,15] and the clinical implications of these laboratory findings continue to be intensely debated.[16,17] Accordingly, several retrospective human studies have been carried out within the last year to examine the effects of surgery and anaesthesia in young children on long-term behaviour and learning abilities.[18–20]

While the exact molecular mechanisms by which general anaesthetics afford their therapeutic properties are not completely understood, common pathways of all currently utilised general anesthetics and sedatives include potentiation at γ-aminobutyrate (GABA) receptors, inhibition of *N*-methyl-D-aspartate (NMDA) glutamate receptors or a combination of the two; similar activity is seen with ethanol.[21] Since GABA- and NMDA-mediated neuronal activity is essential for mammalian brain development, it seems conceivable that these compounds could interfere with early brain

development.[22,23] While opioids do not act on these receptors, the effects of narcotics on brain development are also discussed.

Experimental evidence for anaesthetic neurotoxicity

NMDA antagonists

Glutamate represents the most ubiquitous excitatory neurotransmitter in the mammalian central nervous system. Drugs routinely used in clinical anaesthesia and sedation practice thought to predominantly provide their hypnotic effects by inhibition of the NMDA-type glutamate receptor include ketamine and nitrous oxide.[24] The less frequently utilised noble gas Xenon also falls into this category.[25] Pioneering animal studies carried out by the Olney laboratory demonstrated >10 years ago that the administration of ketamine in newborn rat pups led to widespread degeneration of brain cells.[7] These findings have subsequently been replicated and expanded upon by several other laboratories (see reference 12 for review). Most of the studies involving ketamine had to administer multiple doses of up to 75 mg kg^{-1} to generate significant brain cell degeneration. Conversely, one study found that multiple doses of 25 mg kg^{-1} or a single dose of up to 75 mg kg^{-1} of ketamine did not lead to widespread cytotoxic effects.[26] However, it remains unknown whether these seemingly large ketamine doses, used due to increased anaesthetic requirements in small rodents and monkeys, can be directly compared with the relatively smaller doses used clinically in humans.

Long-term neurological function following neonatal ketamine exposure has so far only been examined in a few studies. A single ketamine exposure of 50 mg kg^{-1} in newborn mice subsequently led to abnormal behaviour and impaired learning and memory acquisition in adolescent animals[27]; however, no gross neurobehavioural abnormalities were observed 7 days after neonatal administration of up to 40 mg kg^{-1} of ketamine in newborn mice.[28] Moreover, adult rats injected with four daily doses of 5 mg kg^{-1} as neonates performed as well as their unexposed peers in learning and memory tasks.[29] More importantly, this small dose of ketamine prevented widespread neuronal degeneration caused by repetitive painful stimulation in these animals.[29] Co-administration of GABA-mimetic drugs, such as midazolam, thiopental or propofol, common practice during clinical anaesthesia and sedation, significantly exacerbates ketamine's deleterious effects.[30,31]

Less information is available regarding the effects of the NMDA antagonists nitrous oxide or xenon on brain development. Whereas nitrous oxide by itself, even under hyperbaric conditions, does not seem to increase neuronal cell death[10,32], the effects of xenon were deleterious in one study[33] and not so in another one.[32] The two compounds, however, differ in their effects when co-administered with isoflurane; nitous oxide exacerbates[10,11,32,34], whereas xenon alleviates, some of isoflurane's neurotoxic effects.[32,33]

$GABA_A$ agonists

GABA represents the main inhibitory neurotransmitter in the adult central nervous system. During early brain development, however, GABA, in fact, has excitatory properties.[35] To date, the impact of this developmental switch of GABA on anaesthesia-induced neurotoxicity remains unresolved. Regardless of these uncertainties, numerous $GABA_A$ agonists are commonly used as anaesthetics or sedatives in young children and animal studies have demonstrated the harmful impact of exposure to these compounds during early development on brain cell structure and later neurological function. Several animal studies have been carried out in immature animal species examining the effects of isoflurane, sevoflurane, halothane, enflurane, thiopental, pentobarbital, clonazepam, diazepam, midazolam, chloral hydrate and propofol (for detailed review see references 12 and 13).

Many of these studies have been carried out by the Jevtovic-Todorovic laboratory focussing on the combined administration of the $GABA_A$ agonists isoflurane and midazolam with the NMDA antagonist nitrous oxide. This combination caused a widespread, dramatic increase in the rate of brain cell degeneration in newborn animals shortly after cessation of a 6-h exposure.[10,36–38] In addition to the immediate deleterious effects on brain structure, long-term abnormalities in certain learning tasks[10] and decreased neuronal cell density were observed in adult rats exposed to the anaesthetic

combination as neonates.[11] Dr. Olney's laboratory has recently presented preliminary data extending neurostructural abnormalities immediately following isoflurane exposure to non-human primates.[39,40]

However, the long-term correlates of neonatal brain cell death on subsequent neurological function remain unresolved. Our group has recently demonstrated that isoflurane as a single agent, while causing widespread neuronal degeneration in neonatal mice immediately following the exposure, does not lead to long-term impairment in learning and memory tasks or to decreases in neuronal density in adult animals.[14] Similar results have been observed following the single administration of midazolam[15], suggesting that, under certain circumstances, the developing brain is either able to recover from the neonatal neuronal degeneration or that neonatal brain cell loss may not be causatively linked to adult learning impairment.

Other anaesthetics and sedatives

Recently, the α_2-agonist dexmedetomidine, which has gained more prominence in paediatric clinical practice, was found devoid of neurotoxic effects.[34] Moreover, dexmedetomidine prevented isoflurane's deleterious consequences on neonatal brain structure and adult learning ability.[34] Another study, however, found that dexmedetomidine can produce a similar degree of neuronal cell death to low-dose ketamine.[41]

Opioid analgesics

Opioids are another class of potent medications commonly administered to young children in conjunction with anaesthetics and sedatives.[42,43] Since opioids can reduce dose requirements for anaesthetics and sedatives, their co-administration could potentially mitigate anaesthesia-induced cytotoxicity by lowering the doses of the toxic agents. However, numerous preclinical studies have also demonstrated deleterious effects of opioid administration in developing animals. Some studies even suggested that opioid co-administration can enhance cell death of immature brain cells induced by other compounds.[44] Chronic perinatal exposure to morphine, fentanyl or methadone has been shown to induce acute neuronal degeneration in the neonatal brain[45], to alter brain opioid-receptor density[46–48] and to disrupt nerve growth factor expression as well as dopaminergic, noradrenergic, serotonergic and cholinergic activity.[49,50] Moreover, perinatal opioid administration can cause long-lasting desensitisation to opioid analgesia in adult animals[51] and has also been shown to induce long-term behavioural changes, cognitive deficits and learning impairment extending into adulthood.[52–57]

Putative mechanisms of anaesthesia-induced neurotoxicity

The exact mechanisms of neurotoxicity induced by anaesthetics, sedatives and analgesics in the developing brain remain unknown. Elucidating these mechanisms will be essential in assessing the relevance of toxicity for paediatric anaesthesia and critical care medicine and for devising mitigating therapies, if necessary. The currently prevailing hypothesis suggests that exposure to $GABA_A$-receptor agonists and/or NMDA-receptor antagonists during a vulnerable period in brain development will cause abnormal neuronal inhibition, triggering cell death in susceptible neurones, which in turn leads to adult learning impairment and decreased neuronal density.[10,11,58] However, several observations seriously question this hypothesis. Specifically, while $GABA_A$-receptor stimulation results in decreased activity in mature neurones, it causes excitation in developing neurones[35], thereby contradicting the hypothesis of abnormal neuronal inhibition being the cell death trigger in developing neurones. Moreover, while xenon and hypothermia cause neuronal inhibition and deepen the level of isoflurane anaesthesia, they do not exacerbate isoflurane-induced neuronal cell death, but rather significantly reduce it.[32,33,59] Lastly, but most importantly, preliminary studies have failed to link the anaesthetic and cell death mechanisms. Specifically, while racemic ketamine and S-ketamine both elicit their anaesthetic effects via NMDA-receptor blockade, S-ketamine induced up to 80% less cell death when compared with equipotent doses of racemic ketamine.[60] Moreover, preliminary data by Januszewski et al. suggest that isoflurane neurotoxicity is not blocked by concomitant administration of a $GABA_A$-receptor antagonist, as predicted by the neuronal inhibition hypothesis.[61] Rather, as groundbreaking work by Dr. Vutskits and co-workers

has recently demonstrated, the decrease in neuronal activity induced by anaesthetics may be less important than the disruption of the neuronal balance of excitation and inhibition in triggering structural abnormalities in the developing brain.[62] Accordingly, while simultaneous blockade of excitatory and inhibitory activity with tetrodotoxin did not lead to structural changes in synaptogenesis, as expected for a causative relationship between neuronal activity and structural changes, administration of $GABA_A$-agonistic or NMDA-antagonistic compounds did alter synaptogenesis.[62]

Regardless of the exact trigger of neuronal cell death, animal studies have clearly shown that anaesthesia-induced neurodegeneration is not caused by cellular energy failure and necrosis, such as occurring during ischaemic stroke, but rather predominantly involves a cellular suicide programme, termed apoptosis.[36] Apoptosis, or programmed cell death, represents an inherent, energy-consuming process, which is highly conserved among species and culminates in self-destruction and elimination of cells that are functionally redundant or potentially detrimental to the organism, utilising a cascade of enzymes called caspases.[63] Apoptotic cell death represents an integral part of normal development, as demonstrated by the embryonal cell death of interdigital mesenchymal tissue to separate the digits of the hands and feet as well as during ablation of tail tissue as part of tadpole metamorphosis in amphibians. In the central nervous system, cells are also produced in excess and up to 50–70% of developing neurones are eliminated during normal brain development, be it in rodents, primates or humans.[64,65] This process establishes proper central nervous system structure and function, and any disruption of the physiological apoptotic cell death mechanism will lead to brain malformation and premature, intrauterine death.[66] However, apoptosis can also be triggered by pathological insults, such as hypoxia and ischaemia.[67] It currently remains unknown whether anaesthesia-induced cell death only hastens physiological neuroapoptosis or whether it eliminates cells not destined to die, that is, pathological apoptosis. Normal adult neuronal density following isoflurane exposure in neonatal mice may suggest accelerated physiological apoptosis[14], whereas decreased neuronal density following a combination of isoflurane, nitrous oxide and midazolam in neonatal rats could represent pathological apoptosis.[11]

Anaesthetic exposure has been shown to trigger both the intrinsic and the extrinsic pathways of the apoptotic cascade[36] and to be associated with a decrease in brain-derived neurotrophic factor (BDNF)[37], a protein integral to neuronal survival, growth and differentiation. Recently, exciting work by Dr. Patel's group has highlighted the impact of reductions in synaptic tissue plasminogen activator (tPA) release and increases in proBDNF/$p75^{NTR}$-mediated apoptosis in isoflurane neurotoxicity observed in mice.[68] However, it is not entirely clear at this point whether cytotoxicity is a direct effect of the anaesthetic exposure or whether it occurs due to significant metabolic and respiratory derangements, such as hypercarbia and acidosis, observed during anaesthetic exposure in small rodents.[14,69,70] A significant study, recently published by Dr. Stratmann and co-workers, casts doubt on whether neuronal cell death is entirely caused by the anaesthetic effects of isoflurane, or whether cell death is also affected by other events potentially related to anaesthesia, such as hypercarbia.[70] Hypercarbia caused neuronal cell death in unanaesthetised neonatal rats, which was, in several brain areas, quantitatively indistinguishable from neurodegeneration observed in isoflurane-treated littermates. However, adult neurocognitive abnormalities where only observed in the isoflurane-exposed animals.[70] Other studies by Dr. Jevtovic-Todorovic's and Dr. Vutskits' groups demonstrated prolonged effects of anaesthetic exposure beyond cell death, albeit some of their findings were somewhat conflicting. Jevtovic-Todorovic et al. observed a decrease in synaptic density following anaesthetic exposure in immature animals, whereas Dr. Vutskits' group found an increased formation of functional dendritic spines.[62] While both studies demonstrated alterations in synaptic plasticity in neonatal animals following anaesthetic exposure, their seemingly dissimilar results might be explained by differences in species, anaesthetic regimen or developmental age at exposure between the two studies.

Interspecies comparison

While abundant experimental evidence is available in animals implicating anaesthetics and sedatives as causing cytotoxic effects in the developing brain, such as immediate structural damage and long-term neurocognitive impairment, the implications of these findings for clinical practice remain entirely unclear. Unlike animal studies, administration of anaesthetics and analgesics in clinical paediatric medicine almost always coincide with significant noxious stimulation, such as during

Table 1
Interspecies comparison of anesthetic doses.

	Mouse	Rat	Monkey	Human
Toxic ketamine dose	20–40 or 50 mg/kg[27,30]	14–17 mg/kg/h for 11 h[7,26,73]	20–50 mg/kg/h for 24 h in 5 day-old[74,75]	
Estimated equivalent human dose	1.6–3.3 or 4.1 mg/kg	2.3–2.7 mg/kg/h for 11 h	6.5–16 mg/kg/h for 24 h	
Safe ketamine dose	10 mg/kg[30]	75 mg/kg or 17 mg/kg/h for 6 h[26]	20–50 mg/kg/h for 24 h in 35 day-old[74]	
Estimated equivalent human dose	0.8 mg/kg	12.2 mg/kg or 2.7 mg/kg/h for 6 h	6.5–16 mg/kg/h for 24 h	
				0.5–2 mg/kg or 0.1–1.2 mg/kg/h
Toxic propofol dose	60 mg/kg[31]	25 mg/kg[76]		
Estimated equivalent human dose	4.9 mg/kg	4 mg/kg		
Safe propofol dose	10 mg/kg[31]	n.a.		
Estimated equivalent human dose	0.8 mg/kg			
				2–3 mg/kg
Toxic diazepam dose	n.a.	10–30 mg/kg[8,77]		
Estimated equivalent human dose		1.6–4.9 mg/kg		
Safe diazepam dose	5 mg/kg[27]	5 mg/kg[77]		
Estimated equivalent human dose	0.4 mg/kg	0.8 mg/kg		
				0.1 mg/kg
Toxic midazolam dose	9 mg/kg[30]	n.a.		
Estimated equivalent human dose	0.7 mg/kg			
Safe midazolam dose	n.a.	9 mg/kg[10]		
Estimated equivalent human dose		1.5 mg/kg		
				0.1 mg/kg

Comparison of doses for commonly used anesthetics and sedatives found to be neurotoxic (toxic) or without neurotoxic effects (safe) in animal studies, the equivalent human doses (calculated according to reference #72), and the respective clinically used doses in humans (right column).

painful procedures and surgical operations. In this setting, animal models have actually demonstrated therapeutic effects of analgesics or sedatives, without evidence for neurodegeneration.[29,57] Moreover, several studies have demonstrated significant discrepancies between the metabolic and respiratory effects of anaesthetic exposure in small rodent species and those in humans, such as extensive hypercarbia, metabolic acidosis and hypoglycaemia in some animals.[14,69,70] Importantly, unlike during paediatric anaesthesia, exposure to clinical doses of anaesthetics for only 2–4 h can be lethal in ~20% of small rodents.[14,70] These findings seriously limit the direct applicability of findings obtained in small rodents to clinical paediatric anaesthesia. Moreover, doses needed for injectable anaesthetics to cause neuronal degeneration in animals are much higher than those used in clinical practice. Animal studies have shown that toxic doses for ketamine are 10 times higher and doses for propofol are up to 20–30 times higher than clinically used doses, on a weight-based comparison. Some of these discrepancies might be due to differences in body size and whole-body metabolic rates among species, resulting in higher dose requirements for smaller animals on a milligram-per-kilogram basis, compared with larger animals.[71] However, even when allometric scaling is performed to account for differences in body size[72], toxic doses in animal studies still remain higher than clinically used doses for many of these compounds (Table 1). These simple scaling methods of drug doses, however, do not correct for other important species differences, such as variability in protein binding, physicochemical drug properties or physiological time.[71] For instance, even after using allometric scaling methods to adjust ketamine doses for rodents and monkeys, plasma levels measured in several studies were still 3–10 times higher than those observed during clinical human practice.[73,74]

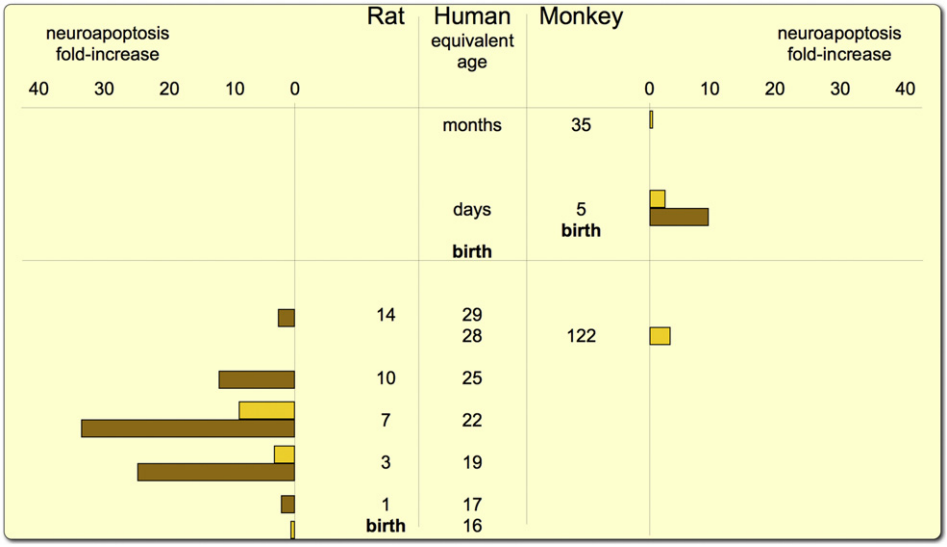

Fig. 1. Quantification and developmental timing of anesthesia-induced neuroapoptosis. Brown bars signify relative increase in neuroapotosis compared with physiological apoptosis (fold-increase) following an isoflurane-based anesthetic, yellow bars signify ketamine exposure. Ages indicate postnatal days for rats (left), embryological and postnatal days for rhesus monkeys (right) and estimated, equivalent gestational weeks in humans. Data derived from references #7, 37, 40, and 74. Human developmental equivalency estimated using reference #78.

Another critical finding from several animal studies is the narrow age window of neurotoxic susceptibility. According to these studies, exposure to ketamine or ethanol only inflicts damage in the developing brain prior to 14 days of age in rats, or 35 days in monkeys, but not in older animals.[7,8,74] Similarly, the cytotoxic effects of isoflurane do not seem to affect 1-day-old rats, peak in 7-day-old animals and dramatically subside after 10 days of age.[36] Anaesthetic exposure outside of this period, such as in prenatal rats, for example, may actually decrease physiological apoptosis and improve subsequent memory retention.[78]

Given these findings, it is important to identify the corresponding developmental state of the human brain, in order to predict the age range for possible susceptibility in humans (Fig. 1). Previously, simple estimations of brain cell numbers and degree of myelination defined this period as spanning from the last trimester of pregnancy all the way to the third year of life.[58,79,80] However, using a more contemporary neuroinformatics approach, this period has been approximated closer to the 20th week of gestation until early postnatally (calculator available at http://www.translatingtime.net).[81] If these calculations prove correct, susceptibility to anaesthesia-induced, neuroapoptotic cell death may seem more plausible in premature neonates and less likely during routine paediatric anaesthesia.

Implications for paediatric medicine

Obvious ethical concerns preclude randomisation of young children to undergo painful procedures with or without anaesthesia and analgesia. Evidence for the effects of anaesthetics and sedatives in young children, therefore, have been gathered from non-randomised studies, case reports, retrospective analyses or studies into long-term neurological outcome in children suffering from disorders requiring the administration of anaesthetics and sedatives at a very young age.[12,13] The great majority of studies into neurological effects following anaesthetic exposure either examines postoperative behavioural changes or assesses long-term neurological performance in children suffering from specific paediatric illnesses. While the former set of studies exactly specified the anaesthetic drugs used and usually involved healthy patient cohorts, their neurological assessment frequently only consisted of short-term, parent-reported behavioural questionnaires or observations. Moreover,

behavioural abnormalities were generally attributed to a psychological, and not a cytotoxic, aetiology. On the other hand, whereas the latter set of studies utilised validated neurological assessment tools, reports consistently failed to specify the exact anaesthetic agents used and often involved several potent confounders, such as severe prematurity, prolonged ventilator support, considerable pain and distress, significant co-morbidities, latent episodes of hypoxia or hypoxia–ischaemia and frequently involved invasive surgical procedures with potentially significant inflammatory response.

Confounders

The presence of significant co-morbidities and serious confounders in children undergoing surgery and anaesthesia early in life and the lack thereof in animal studies represents a serious limitation of directly applying findings of preclinical studies to humans.

Pain and stress

Given the overwhelming evidence for pharmacological interference with normal development of the central nervous system and the lack of anaesthetics devoid of cytotoxic effects, one could be tempted to withhold all suspect medications during medical interventions early in life.

Animal models testing the effects of repetitive maternal separation and exposure to recurrent painful stimulation on neurological outcome have demonstrated widespread neuronal cell death due to this practice.[29] Moreover, early adverse emotional experiences can induce long-lasting age-, brain region- and neuronal subgroup-specific imbalances of the inhibitory nervous system[82], disturb development of the nociceptive system and cause long-term behavioural changes[83], as well as lead to persistent learning impairment.[57] Repetitive painful stimulation in neonatal animals leads to decreased pain thresholds and increased anxiety later in life.[84–86] In addition to alterations of the central nervous system, repetitive painful skin lacerations have also locally been found to lead to long-term sensory hyperinnervation.[87]

In this context, pre-emptive administration of analgesics and sedatives, such as morphine or ketamine, have been found to ameliorate the deleterious effects of neonatal pain.[29,86] Importantly, painful stimulation in turn obviated adult behavioural impairment due to neonatally administered morphine.[57]

Similar to these animal studies, clinical reports have demonstrated that neonates and infants can mount a metabolic and endocrine response to perioperative stress and painful stimulation[88,89], which include increases in catecholamines, cortisol, beta-endorphins, insulin, glucagon and growth hormone.[88,90,91] Some of these markers, such as cortisol, can remain elevated for more than a year, potentially due to cumulative stress related to multiple painful procedures early in life.[92] Administration of potent anaesthetics, opioid analgesics and regional anaesthesia have been shown to inhibit intra-operative stress and to improve postoperative outcome[90,93,94] by reducing the incidence sepsis, disseminated intravascular coagulation and mortality.[95] Even less invasive procedures, such as circumcisions, when performed without analgesia, exaggerate pain responses later in life.[96] In contrast, topical or regional anaesthesia blunt the immediate humoral stress response[97] and long-term hyperalgesia.[96]

Recently, an association between increased painful stimulation in premature neonates and diminished cognition and motor function later in life has been observed.[98] Children born at <32 weeks gestational age that had no significant neonatal brain injury or major sensorineural impairment were followed from birth and compared with full-term controls at >1 year of age with respect to cognitive and motor development. Cumulative painful stimulations, such as number of skin-breaking procedures performed (including attempts at heel sticks, intramuscular injections, chest tube placements and central line insertions) were quantified and neurocognition was assessed using the Bayley Scales of Infant Development-II. Results demonstrated that the number of skin-breaking procedures from birth to term predicted lower subsequent cognitive and motor development. Importantly, after controlling for severity of illness and days on intravenous morphine or dexamethasone, gestational age at birth was not significantly associated with cognitive or motor outcome. These findings could suggest that repetitive pain-related stressful experiences, and not prematurity *per se,* were responsible for poor

outcome.[98] Another retrospective study suggested that painful stimulation during reduction of herniated bowel without anaesthesia in infants suffering from gastroschisis tended to more frequently lead to serious adverse events, such as bowel ischaemia, need for total parenteral nutrition and unplanned re-operation than in infants undergoing the same procedure with general anaesthesia.[99]

Taken together, the data from animal and human studies suggest that pain-related stress experienced early in life is deleterious to the developing nervous system, that sedatives and analgesics can alleviate many of the degenerative effects and that pain in children still remains undertreated.

Inflammatory response

Neurological impairment of infants following physical trauma or surgery may also be related to long-term effects of infection and inflammatory response.

In animal studies, local neonatal inflammation leads to excessive hyperalgesia in adulthood.[100] Chronic persistent inflammation experienced early during development is capable of altering behaviour and sensitivity to pain later in life, especially in response to recurrent inflammatory events.[101] Systemic infection, as demonstrated in a mouse model of neonatal injection of live bacteria, leads to sustained increases in microglial activation in the brain.[102] In these animals, cytokine levels are exaggerated following an immune-challenge in adulthood, which can also lead to memory impairment.[102] Injection of lipopolysaccharides during a critical postnatal period can affect adult sensation and pain responses[103] and may also cause long-lasting increases in seizure susceptibility.[104]

Importantly, in an adult mouse endotoxaemia model, isoflurane anaesthesia immediately following the injection of a lethal dose of *Escherichia coli* lipopolysaccharide dramatically improved survival by 300% compared with unanaesthetised animals. In these animals, the administration of isoflurane, pentobarbital, or ketamine/xylazine attenuated serum levels of the inflammatory markers tumour necrosis factor-alpha, interleukin-10 and interleukin-6.[105] These findings suggest that anaesthetic administration during endotoxaemia may not only improve survival, but also lead to attenuation of the inflammatory process.

In children, abdominal surgery can lead to significant increases in blood levels of the cytokines C-reactive protein and interleukin-6[106,107], which have been linked to increased complication rates in adult patients.[108] Moreover, invasive surgery in children has also shown to depress the patients' immune system.[106,109] Neuromotor abnormalities 6 months after open heart surgery have been correlated with plasma levels of interleukin-6 that were measured immediately postoperatively.[110] While the effects of surgery and anaesthetics cannot be differentiated in this study, the results nevertheless justify further studies into the long-term effects of anaesthetics on cytokine levels and outcome.

Hypoxia and hypoxia–ischaemia

Due to the brain's limited ischaemia tolerance, episodes of inadequate supply of oxygen or nutrients can lead to long-term neurological impairment in critically ill children. Several patient populations at higher risk for episodes of hypoxia or brain hypoxia–ischaemia, such as infants with congenital heart disease and premature neonates undergoing surgical procedures have been studied regarding their long-term neurodevelopmental outcome. Many of these studies demonstrate neurobehavioural abnormalities, motor deficiencies and decreased intelligence in many of these patients.[111–115] However, none of these studies describe the anaesthetic and sedative regimens utilised or discuss their impact on subsequent neurological outcome. Conversely, neonatal animal models have repeatedly confirmed the neuroprotective properties of anaesthetics when administered during episodes of hypoxia–ischaemia.[116–121] These findings in immature animals suggest that critically ill human neonates might also benefit from these protective properties during clinical scenarios of inadequate blood flow to the brain.

Environmental factors

Environmental factors and exposures outside anaesthesia can interfere with normal brain development in humans. *In utero*, environmental compounds that may negatively influence subsequent neurocognition include such diverse substances as pesticides[122], methyl mercury, manganese, lead and

polychlorinated biphenyls.[123] Foetal exposure to prescription medications have also been found to lead to subsequent neurological sequelae, such as drugs for the treatment of acne[124], antihypertensives[125] and anticoagulants.[126] Prenatal exposure to alcohol and cocaine can impair children's speech, language, hearing and cognitive development.[127] Recently, intrauterine exposure to antiepileptic drugs, which share many pharmacodynamic properties with anaesthetics, have been linked to brain structural abnormalities in young adults.[128]

Other 'environmental' factors known to affect learning and behaviour in children are not as easily measured by subjective standards. Socioeconomic aspects related to family dynamics, neighbourhoods and school environments all contribute to development and learning in children. In this context, factors negatively influencing neurodevelopment include economic deprivation, minority and/or immigrant status, exposure to violence and chronic poverty.[129] Even when providing a strong community and positive family support, differences in school quality, and negative encounters with teachers and/or peers, can dramatically affect development and learning outcomes.[129] Moreover, negative influences on neurocognition have also been suggested by prolonged television viewing in early childhood.[130]

Due to this myriad of confounders, studies into the potential detrimental effects of anaesthetic exposures need to take these socioeconomic and environmental influences into account. However, common knowledge of the negative effects of environmental factors and certain drugs on later neurodevelopmental outcome may provide plausibility for parents for a potential association of anaesthetic exposure early in life and long-term neurological impairment.

Genetic predisposition

Even more than environmental confounders, genetic composition can also affect neurodevelopment. Close relationships have been demonstrated between genetic factors and cognitive abilities, including reading and mathematics skills, and intelligence.[131] Moreover, genetic predisposition can influence the effects of environmental stressors and vice versa.[132]

Investigating the effects of anaesthetic exposure on learning abilities in children with an emphasis on genetic predisposition, a recent twin study found no causal relationship between anaesthetic exposure and cognitive impairment.[133] A review of data for >1000 monozygotic twin pairs in the Netherlands Twin Registry demonstrated that children exposed to anaesthesia before age 3 in fact scored significantly lower on educational achievement tests and experienced more cognitive problems than children not exposed to anaesthesia. Importantly, however, cognitive performance of the unexposed co-twin did not differ from that of the exposed twin. Thus, no evidence for a causal relationship between anaesthesia administration and later learning-related outcomes was found, but rather, the data supported the notion that anaesthetic exposure prior to 3 years of age only represented a marker for subsequent learning problems, regardless of exposure to anaesthetics.

Recent human epidemiological studies

Several other research groups have also utilised retrospective reviews of large-scale epidemiological data sets to investigate neurodevelopmental outcome following surgery and anaesthesia.

One of these studies used billing codes to identify a birth cohort of children in the New York State Medicaid database who underwent inguinal hernia repair during the first 3 years of life and compared these patients with a sample of more than 5000 age-matched children without the same billing code.[134] After controlling for gender- and birth-related complications, such as low birth weight, children who underwent hernia repair were more than twice as likely as their age-matched peers to be diagnosed with a developmental or behavioural disorder, as defined by the presence of a diagnostic code. Interestingly, highlighting the importance of co-morbidities in retrospective data sets, surgical patients were more likely to carry secondary diagnoses, including congenital anomalies of the central nervous system (10% of patients), birth weight <2500 g (32%) or perinatal hypoxia (17%). They were also more likely to be male and African American.

Two other recently published epidemiological studies in more heterogeneous patient populations investigated the effects of anaesthetic exposure either during caesarean delivery or for paediatric surgery prior to age 4 on subsequent learning abilities.[20,135]

After adjusting for gestational age, sex, birth weight and American Society of Anesthesiologist Physical Status, children who underwent multiple surgical procedures with general anaesthesia prior to age 4 were found to be at increased risk for learning disabilities, while children who only underwent one operation with anaesthesia or none at all were not.[20] While listing the anaesthetic regimen as predominantly including halothane, nitrous oxide and ketamine, the study did not specifically break down learning disabilities by anaesthetic drug. The important confounding influence of co-morbidities in this patient cohort was highlighted by the fact that almost half the previously anaesthetised patients diagnosed with developmental disability had suffered from serous otitis media prior to age 4, a potential predictor of neurocognitive disabilities, whereas only one-third of children without learning disabilities had experienced chronic ear infections[20]; thus providing weak evidence for an association between chronic ear infections and subsequent learning disabilities ($P = 0.074$). However, a more definitive analysis including the unanaesthetised children is needed to assess this potential association.

In a second retrospective review, the same research group collected school and health data from almost 5000 children born via vaginal delivery and compared them to almost 200 neonates delivered via caesarean section with either general anaesthesia, consisting predominantly of sodium thiopental, halothane and nitrous oxide, or with about 300 children delivered via caesarean delivery with regional anaesthesia.[135] The overall rate of potential learning disability was found to be 26% in their study population and did not differ between those children delivered with or without anaesthesia. This finding could not have been easily predicted, because neonates in the general anaesthesia group experienced lower birth weights, lower gestational age and lower Apgar scores. In addition, their delivery was more commonly complicated by haemorrhage and eclampsia/preeclampsia, and was more frequently performed due to an emergency indication. Importantly, other risk factors independent from anaesthetic exposure, such as male gender and mother's educational status, were strongly correlated with subsequent learning impairment. Children born to mothers with only some high school education were 3 times more likely to acquire learning disabilities than children from mothers with college education, suggesting genetic and/or socioeconomic confounders. Interestingly, babies born with regional anaesthesia were less likely to be diagnosed with a later learning disability than those born vaginally without anaesthesia, more likely than not, because their parents also tended to be better educated.

Kalkman et al. tried to control for the fact that there might exist a causal relationship between the requirement for surgery and subsequent behavioural and learning impairment independent of anaesthetic exposure.[19] They examined behavioural outcome following similar urological procedures, performed either before or after age 2. In this small retrospective pilot study involving $<$300 patients, children in the younger group were more likely to develop behavioural disturbances than the older patients, although results were not statistically significant. Parental evaluations of children's competencies and behavioural/emotional issues were based on a combination of the child's activities, social relationships and performance in school. There was only very weak evidence for a relationship between timing of surgery and the risk for developing deviant behaviour, even after adjusting for confounders such as the education of the parents, number of total anaesthetic exposures, gestational age and birth weight. However, the authors correctly point out in their discussion that the indication for the surgery or the timing of the procedure may not be entirely independent of factors that may also influence neurobehavioural development, such as co-morbidities. In other words, the decision to operate on a child prior to age 2 could depend on the severity of symptoms resulting from the anatomical anomaly, which in turn may influence neurobehavioural development independent of anaesthetic exposure.

Arguably, the most vulnerable group of patients potentially susceptible to the effects of prolonged exposure to anaesthetics and sedatives during an immature brain developmental state would not be healthy paediatric patients undergoing brief, elective surgical procedures, but rather premature neonates in intensive care units.[136] In this vulnerable patient population, Rozé and co-workers employed a prospective population-based study approach to evaluate the effects of prolonged sedation and analgesia of very preterm infants on their long-term neurological outcome.[18] A birth cohort of preterm infants born prior to 33 weeks gestational age, who were subjected to mechanical ventilation and/or surgery were tested at 5 years of age with the Kaufman Assessment Battery for Children. While

74% of those treated with sedatives and/or analgesics for <7 days or not at all showed no disabilities, only 58% of those treated for >7 days were deemed without disability. However, after adjustment for gestational age and for propensity score, which included significant confounders, such as birth weight, malformations, complications of pregnancy, characteristics of the delivering hospital, neonatal complications, need for surgery and postnatal corticotherapy, this association was no longer statistically significant. While the study did not have the power to detect differences in disability of <10%, the long exposure times suggest that effect sizes during comparably brief surgical anaesthesia will be even smaller.

Ongoing and future research

The potentially immense impact of neurotoxicity induced by anaesthetics and sedatives on child health necessitates significant research efforts into this phenomenon. These efforts must include both preclinical studies investigating the exact structural changes, underlying molecular mechanisms, and the susceptible target cells, and carefully designed clinical studies have to delineate human susceptibility, taking into full account the above-mentioned perioperative confounding variables. Some of the clinical research studies already enrolling patients include the GAS and Pediatric Anesthesia NeuroDevelopmental Assessment (PANDA) studies.

GAS study

This international, multi-site, randomised-controlled trial which compares the effects of regional versus general anaesthesia on neurodevelopmental outcome and apnoea in infants (GAS study) has so far enrolled almost one-third of the goal of 660 patients (A. Davidson, personal communication, September 2009). The patients' intelligence quotient will be compared at 2 years following a neonatal inguinal hernia repair performed either with general anaesthesia or with caudal or spinal anaesthesia.[137]

PANDA study

A different approach of retrospective identification and prospective study of subjects has been taken in the PANDA study.[138] The PANDA study aims to assess the effects of anaesthetic exposure for inguinal hernia repair within the first 3 years of life in a retrospectively identified cohort on prospectively measured neurodevelopmental performance, compared with that of an unexposed sibling.

Danish registry

In an epidemiological approach, Hansen and co-workers are using a database of all 45 000 children who underwent surgical operations in Denmark from 1977–1990 prior to 1 year of age, comparing their academic achievement with that of the general Danish population.[139]

Conclusion

In conclusion, neonatal exposure to numerous anaesthetics causes widespread neurodegeneration in a dose- and duration-dependent fashion and can lead to long-term neurological impairment following administration of anaesthetic combinations in newborn animals. However, the relevance of these findings to paediatric anaesthesia is unknown. The phenomenon's exact underlying mechanism has not yet been determined, but does not seem to be entirely explained by anaesthetic-induced neuronal inhibition. While animal studies reveal susceptibility to be limited to a very brief stage during brain development, the corresponding human maturational state has not been clearly defined; several lines of evidence point towards the prenatal or early postnatal period. Whereas anaesthetic administration in animals differs significantly from paediatric anaesthesia practice and numerous confounders exist in humans that do not occur in animal populations, emerging human epidemiological studies do not exclude anaesthetics as a factor for impaired learning and neurodevelopment

observed following surgical procedures. However, unlike the consistent neurodegeneration and neurological impairment demonstrated in anaesthetised animals, neurological sequelae observed in retrospective epidemiological studies seem sporadic and do not affect all exposed individuals to the same degree, suggesting a potential genetic or other influence on this association. Since existing epidemiological studies are unable to establish causality and cannot distinguish between the differential effects of surgery and anaesthesia on neurological outcome, further well-designed preclinical and clinical studies are needed to examine the phenomenon's mechanisms and its clinical relevance. Given the serious consequences of unopposed pain for the developing brain, current anaesthetic practices should only be changed once results from these future studies become available.

Practice points

- All currently used anaesthetics and sedatives have been found to be neurotoxic in neonatal animal studies.
- The phenomenon's clinical relevance is unknown.
- Animal and preliminary human studies suggest the maximum potential for susceptibility in humans to occur early in life, potentially prenatally
- Pain and stress in unanaesthetised, immature animals and humans has also been found to cause neuronal cell death and neurocognitive impairment.
- More studies into this phenomenon are needed before recommending changes to current anaesthetic and sedation practices.

Research agenda

- Given the rapid progression of brain maturity in animals, a serious consideration for all preclinical studies is the maturational equivalency to the human brain.
- Human and animal brains are sufficiently dissimilar in size, complexity and developmental duration that similar insults do not necessarily translate to a similar degree of impairment.
- Animal studies cannot replicate the significant genetic, co-morbid, socioeconomic, educational and environmental confounders that impact human brain development.
- Given the phenomenon's potential serious effects on paediatric health, further research efforts are urgently required to delineate the cytotoxic mechanism, selectivity, its clinical relevance, and to develop alleviating strategies, if required.

Conflict of interest statement

None.

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Use of pharmaceuticals 'Off-Label' in the neonate

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Neonates are frequently not studied in the development of a novel pharmacological agent. With lack of data to support safe and effective use of a new agent in this population, sponsors will not receive approval for labelling the agent for use in this age group from the United States Food and Drug Administration (US FDA). This causes a significant conundrum for the clinician. Neonates are often precluded the benefits of new pharmaceuticals until investigators begin to report their clinical experience with novel agents. This article provides the clinician with an introductory understanding of the approval process of pharmaceuticals in the United States by USFDA. Models of clinical trial design are noted. Examples of anaesthetic and non-anaesthetic agents and their development and use are discussed as either 'labelled' or 'off-label' indications.

Neonates and children are often not included in the study and development of a new pharmaceutical. Approximately 80% of all approved pharmaceuticals in the United States do not include labelling for infants and children. Sponsors (manufacturers) fear the possible liability of a child being injured during drug development. However, the reluctance to study infants and children precludes labelling the drug for intended use in these vulnerable populations. Clinical experience is often gained by individual clinicians willing to use new agents in children without guidance from the label. This 'off-label' use is extraordinarily common and essential to developing appropriate recommendations for neonatal and paediatric pharmacotherapy.

As children are often excluded from initial drug-development trials, neonates and premature newborns are an even more excluded group in early studies. Sponsors are understandably concerned about exposing a neonate to a new chemical moiety. Even in adult populations, the heterogeneity of effectiveness and side-effect profiles of a new agent can be quite extensive. This may be either genetic

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or environmental in nature. Add to this the developmental differences in metabolic pathways and immature development of hepatic and renal function,[1] and the study of new compounds in neonates may be very complicated. In order for a new compound to be approved by the United States Food and Drug Administration (FDA), the sponsor must demonstrate effectiveness of the product. Most newborns that require some type of pharmacotherapy are ill, possibly with multiple co-morbidities, which makes the study of a new compound and demonstration of effectiveness very difficult.

Off-label prescribing of a pharmaceutical agent is defined as "the unauthorised use of a drug for a purpose other than that approved by the United States Food and Drug Administration".[2] These unapproved uses may include using the agent for an unapproved indication (disease state or physiological condition), dose, route of administration or in an age group or population not authorised from the approval process. The FDA is responsible for the drug evaluation and research of the effectiveness of new agents, and for protecting the public health. The FDA requires that "labeling shall be informative and accurate without being promotional, false or misleading".[2] The FDA requires a sponsor to provide highly detailed data establishing the effectiveness of the drug for a specific condition (e.g., pain) or disease process. The supportive data permit the agency to evaluate the extent to which the sponsor will be allowed to market the new pharmaceutical. Broadening the indications for use of a drug following the initial approval may also be considered with new supportive information.

For example, if a sponsor has developed and tested a novel antibiotic in the adult population for a traditional type of infection (sinusitis or pneumonia), these data are forwarded to the FDA for evaluation of safety and efficacy in the clinical trial. If approved, the sponsor will be permitted to advertise to physicians and direct to consumers (DTC), in most circumstances, that a new agent is available for treatment of the studied condition in the appropriate populations.

'Off-label' experience would occur when a clinician decides to use this newly approved agent for a different disease or different population. In neonatal and paediatric anaesthesia, clinicians routinely use pharmaceuticals in an 'off-label' manner. This is necessitated by the lack of sponsor-provided data for the FDA to evaluate. Some of these agents include propofol, ondansetron and hydromorphone. In addition to systemic agents, local anaesthetics via the neuraxial route have not received FDA approval in newborns (with the exception of lidocaine), even though they are widely used.

Off-label pharmaceutical use is ubiquitous, legal and ethical. With millions of surgical and diagnostic procedures performed on infants and children every year, safety continues to improve with the educated and experienced clinician, and a widening array of pharmaceuticals to provide for the care of the neonate. Our challenges are to develop best practices, continue to support expanded labelling of agents and encourage/participate with sponsors to perform neonatal trials. Investigator-initiated trials are an alternative to traditional sponsor-initiated trials. Even small trials to examine the early effectiveness of novel agents may provide guidance for the design of a larger trial which may be able to support expanded labelling.

The approval process

When a new chemical moiety is discovered or synthesised, a sponsor may claim legal rights as intellectual property for either 'composition of matter' or intended 'use' of a discovery. These patent protections are time limited and sponsors will engage with drug development as quickly as possible. Preclinical trials may include use of cell or tissue culture, or whole-animal studies. For example, effectiveness of new antibiotics are first screened *in vitro*, and then in cultures before being systemically administered to an animal model. Multiple animal models exist and are well described in different pharmacological fields. These studies are critical to determine early potential consequences from systemic administration. Early trials may only include short-term results without examination of potential repetitive dosing, or long-term side effects.

Following preclinical trials, a sponsor may make an application to the FDA to conduct human trials. An Investigational New Drug (IND) application is tendered and, if not challenged, allows the sponsor to move forward. Phase 1 trials are conducted and the tolerability of the drug is examined. These studies limit the human exposure as much as possible while attempting to obtain key evidence of major side-effect profiles that might be undesirable. In addition, very early pharmacokinetic data to examine

volume of distribution and clearance may be performed. These trials often involve only a few dozen study subjects.

Phase 2 trials are then conducted to establish more rigorous data regarding pharmacokinetics and pharmacodynamics of an agent. Biochemical and metabolic side-effect profiles are established. The larger group of patients studied may permit less common side effects to be discovered. These side effects may be innocuous or potentially quite dangerous, even if not in high frequency. Phase 2 trials may include 30 to a few hundred patients. Phase 3 trials extend the patient population to be studied to a significantly larger group size. Further, in Phase 2 and 3 studies, disease states may be studied to determine the potential effectiveness of a novel compound. Although healthy subjects are frequently recruited (e.g., for antibiotic or vaccine trials), specific toxic new compounds (e.g., antineoplastics) might be used directly in patients with existing significant disease states such as neoplastic diseases. Healthy patients would not be exposed to known toxic compounds. Another type of trial would possibly involve a novel antihypertensive for use in adults with primary hypertension. In this case there would be less risk to these patients if the trial did not demonstrate effectiveness of the medication as uncontrolled hypertension for a few months is less dangerous than letting a neoplastic process go untreated. Results from the Phase 2 and 3 studies would provide the effectiveness data requested by the FDA (Fig. 1).

In evaluating the effectiveness of a new compound, it is compared to the current standard(s) of care. If a disease state is currently cured in a high percentage of patients with current therapy, it may take quite a large study (thousands of patients) to determine whether the new treatment is equally, less or more effective. In studies this size, even rare side-effect profiles may be noted. Nonetheless, following successful completion of Phase 3 trials, it is well established that complete side-effect profiles have not been discovered. In total, maybe a few thousand patients have been studied in the process before the data are submitted to the FDA. Anaphylaxis, as a side effect occurring in 1:200 000 patients, would likely not be known with the existing data at the time of the FDA review.

Following completion of Phase 3 trials, the sponsor may approach the FDA for an evaluation of data compiled and request a New Drug Approval (NDA). If an NDA is forthcoming, the sponsor works with the FDA for appropriate labelling of the drug and how it will be packaged. Once the NDA is evaluated, the FDA will decide on whether to approve the drug, require further information, or not approve the drug. Once approved, the drug may be distributed and used by appropriate professionals. The FDA does not guarantee safety in this process. The FDA approval does not protect healthcare professionals from liability for prescribing the new drug. The FDA's responsibility is to evaluate the provided data and see if the sponsor has provided sufficient data to consider approval of the drug for the general population. If circumstances warrant, the FDA can require Phase 4, or post-marketing, trials to be performed so that it

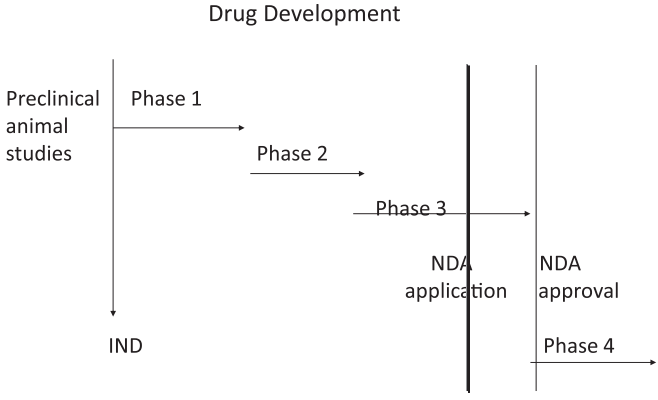

Fig. 1. Drug development occurs in phases over many years. Preclinical trials are followed by three Phases of clinical trials. Data from the three phases of trials are considered by the FDA and a New Drug Application(NDA) is filed. The FDA considers the data and then may approve the drug for marketing and release. Phase 4 trials follow release of the drug and may include pediatric trials to broaden the scope of the drug label.

may continue to assess new data. These trials may be specifically aimed at the neonatal or paediatric populations.

The drug-development and approval process is often unknown to clinicians. This is a very expensive process and many failures of promising new agents occur at any of the levels involved. As will be presented later, some drugs complete the approval process and are later withdrawn as side-effect profiles become better established. Recently, the FDA has been under pressure to streamline the approval process, but their primary concern is for the safety of public health. This goal is imperative to protect vulnerable populations such as newborns.

Neonatal-specific approvals and 'off-label' uses

In the entire process above, the newborn is not considered, unless, the new compound is specifically being developed for a specific condition of the neonate or infant. Most pharmaceuticals are only tested on the healthy general population study volunteers, or in groups with a specific disease state. For example, a new compound might be evaluated for adult patients with chronic obstructive pulmonary disease, but not tested in infants with chronic respiratory insufficiency secondary to prematurity, or an antibiotic for pneumonia may become approved after testing in adults and the elderly, but not infants and children. The commercial market for a new agent is larger in the adult population than for children or infants. Sponsors wish to have a commercial return on their investment as soon as possible, so there is an economic motive to develop and test agents in the adult population rather than in children. Clinicians usually only begin using a new agent in children after a few, or in some cases, many years of experience are reported.

Volatile anaesthetics are ubiquitously used in neonatal and infant anesthesia. Sevoflurane and isoflurane have been studied in children and in infants younger than 1 month of age, and minimum alveolar concentrations have been determined and reported.[3–5]However, isoflurane still does not have paediatric labelling approval for use in children younger than age 2, even after decades of experience with this agent. Now available in generic form, it is not likely that the sponsor/manufacturer would ever perform controlled trials to expand its labelling. Sevoflurane does have FDA approval and labelling for paediatric and adult patients without restriction. Desflurane is not recommended for induction of anaesthesia in infants or children due to its respiratory adverse effects. However, desflurane has been studied for maintenance of anaesthesia from 6 to 12 months of age.[6,7]There are no data supporting the use of desflurane in newborns. There is a wealth of experience with volatile anaesthetics in newborns, despite some lack of approval and labelling. The neurodevelopmental issues associated with the use of general anaesthesia in newborns is being presented elsewhere in this issue.

Benzodiazepines are commonly used sedatives in neonatal intensive care units. Although not primarily developed for paediatric patients, this class of agents has been useful for short- and long-term sedation, particularly with children receiving assisted ventilation. Lorazepam is a long-acting, water-soluble agent that is prescribed intravenously in the hospital, but is also available in an oral formulation for treatment of anxiety and insomnia in children older than 12 years of age. It has no labelling in the newborn age group, but it is given as intravenous bolus or infusion formats in the USA. Lorazepam is not frequently used in paediatric anaesthesia, but the infant may come under our care from a neonatal intensive care use where frequent or continuous dosing of lorazepam has been initiated.

Midazolam is labelled without age restriction by intravenous administration for procedural sedation, sedation of mechanically ventilated patients and for amnesia and preoperative sedation. Oral midazolam is labelled for use in children older than 6 months of age. In 2008, Koch et al. reported paradoxical effects of midazolam in neonatal rats.[8]By clinical observation, there does appear to be a developmental difference in the response to midazolam. Higher dose ranges are often required to achieve the desired clinical effects and tolerance appears to occur at a faster rate than in adults.[9]In addition to the concerns currently being raised about anaesthesia in newborns, we have not yet been able to determine whether there is a contribution of benzodiazepine use in this young age.[10]

Opioid medications are routinely given to newborns, infants and children when there is an expectation of moderate-to-severe pain. Commonly used opioid analgesics used in the newborn include fentanyl, morphine and hydromorphone. Of these, only morphine is FDA labelled without age

restriction for analgesia in children receiving mechanical ventilation. Fentanyl is often used off-label for its stable haemodynamic profile compared with morphine. Hydromorphone is used less commonly than either of the above agents, and fewer clinicians have experience in using hydromorphone in young infants. Hydromorphone is more potent and efficacious than morphine, and has a long half-life. Paediatric pain specialists use hydromorphone for infants with significant tolerance to fentanyl to improve pain therapy and initiate plans for weaning.

Non-anaesthetic medications

Some pharmaceuticals are specifically aimed at indications for use in the neonate. These have become important therapeutic agents in this age group (Table 1). Premature infants often suffer from acute respiratory distress which is significantly improved by intra-tracheal administration of surfactant (s). [11]Since prematurity is associated with insufficient surfactant present, this has been a natural development of surfactants for this age group and disease state. Beractant (Survanta) and calfactant (Infasurf) have both been studied and approved for use in respiratory distress syndrome (RDS) of the newborn as well as a prophylaxis of RDS of the newborn. Trials and uses of surfactant in adults for adult respiratory distress syndrome (ARDS) have not consistently found favourable results. Therefore, if surfactant development had only been aimed at adults with ARDS, surfactant quite possibly would not have been successfully approved by the FDA for lack of evidence of therapeutic effectiveness. At present, multiple surfactant products are approved and available to clinicians.

Infants born with complex cyanotic congenital heart disease often are the beneficiaries of use of intravenous prostaglandin E_1 (Alprostadil) to palliate their conditions by keeping the ductus arteriosus patent until a more definitive procedure can be performed. Prostaglandin E_1 has been used in this way for many decades. By keeping the ductus arteriosus patent, this allows some exchange of blood between the systemic and pulmonary circulatory trees. In the infant that suffers from right-sided lesions (e.g., Ebstein's anomaly, tricuspid atresia, pulmonary stenosis or atresia), a lack of pulmonary blood flow will result in profound hypoxaemia. With prostaglandin E_1, the infant may continue to provide blood to the pulmonary circuit from the systemic circuit and temporarily keep the child from a cardiopulmonary crisis and death until a more suitable circulation can be prepared by surgery or therapeutic cardiac catheterisation. With left-sided obstructive lesions, maintaining a patent ductus arteriosus will ensure at least some systemic blood flow diverted from the pulmonary artery. Although this is not fully saturated blood (mixed venous oxygen saturation) from the pulmonary artery, this blood will provide some oxygen and carry away carbon dioxide from major organs. Other non-FDA-labelled indications for prostaglandin E_1 have included neonatal respiratory failure, perinatal hypoxia and pulmonary hypertension. These are considered off-label uses, but prostaglandin E_1 certainly is widely used by neonatologists for complex cardiopulmonary disease states.

In the 1990s, many clinicians became interested in the potential favourable effects of inhaled nitric oxide (NO). Decades of work eventually revealed that NO was an endogenous neurotransmitter, endothelial-derived relaxing factor and the active compound from the administration of nitroglycerine and sodium nitroprusside. By further understanding of its mechanism of action, to stimulate guanylate cyclase, NO was heralded as an important discovery in both cardiovascular sciences and neurosciences.[12]

No commercial sponsor felt that NO, a known industrial waste product (and potential health hazard), would benefit from support to develop a medical grade product. Clinicians and investigators

Table 1
Pharmaceuticals specifically useful and approved* for use in neonates.

Prostaglandin E1 (alprostadil)	Maintain ductus arteriosus patency
Inhaled Nitric Oxide (iNO)	Hypoxic respiratory failure
Surfactants	Prematurity – acute respiratory distress
Indomethacin	Closure of the ductus arteriosus
Sildenafil*	Pulmonary hypertension

*Sildenafil is approved for pulmonary hypertension in adults, but not pediatrics although growing evidence supports its use.

felt that administration of NO via inhalation might be of value in treatment of pulmonary hypertension and improvement in ventilation/perfusion matching in the pulmonary system in multiple disease states such as pneumonia and ARDS. Investigators developed delivery systems and monitoring systems for using inhaled NO. Anecdotal and some early controlled data suggested the merits of inhaled NO (iNO) for neonatal and paediatric disease states. Eventually, commercial sponsor interest developed a medical device for the delivery and monitoring of NO and a patent was awarded. Although the pharmaceutical agent NO was not awarded an independent patent, the delivery device was awarded patent protection.

NO is sometimes referred to in the medical literature as a 'selective pulmonary vasodilator'. This is not true. NO is a systemic and pulmonary vasodilator. The delivery of NO as a therapeutic gas to the pulmonary system is really better termed 'selectively delivered to the pulmonary system'. As the NO may reach the bloodstream, it is quickly scavenged by haemoglobin to inactivate it prior to it reaching the systemic circulation. Therefore, its activity stays restricted to the pulmonary system. Since NO only reaches alveoli where ventilation is actively occurring, only the arteriolar–capillary complex of those alveoli will relax and enhance blood flow to this area. With this selective delivery, the ratio of ventilation to perfusion (V/Q) improves and arterial oxygen saturation improves, and there is a reduction in pulmonary vascular resistance.

The FDA-labelled indication for NO is neonatal respiratory failure.[13]However, its use has been reported for ARDS, pulmonary hypertension secondary to cardiac surgery (and exposure to cardiopulmonary bypass), diagnostic testing of responsiveness of pulmonary hypertension, RDS of the newborn and paediatric respiratory failure. Similar to the development of surfactants, had newborn and paediatric disease states and age groups not been considered, the entire commercial development of iNO may not have been successful.

In adult populations, iNO does not appear to be as useful therapeutically in treating ARDS or other pulmonary conditions. Nitrate pharmaceuticals are not first-line therapy for adult pulmonary hypertension. They are one of many classes that are used following initiation of calcium channel blockers and/or oxygen. Calcium channel blockers are rarely used in newborns with the known associated risk of bradycardic dysrhythmias.

Sildenafil (Revatio, Viagra) was developed, tested and highly marketed as an agent for the treatment of erectile dysfunction. Sildenafil is a phosphodiesterase inhibitor which keeps levels of cyclic guanine monophosphate (GMP) elevated resulting in vasodilatation. Not only are these effects systemic, but also this occurs in the pulmonary circulation. As noted in Table 1, sildenafil is FDA approved for adult pulmonary hypertension, but not for paediatric or neonatal pulmonary hypertension. With the availability of 'off-label' use of an approved drug, multiple investigators and clinicians have authored their experiences with sildenafil in children,[14,15]and the current strength of the recommendation for its use in newborns is Class IIb: The treatment may be useful, and is indicated in some, but not most, cases.

Recently approved agents with potential for use in newborns

Fenoldopam (Corlopam) is an agent developed as a selective D1-dopamine receptor agonist. It is approved in adults for hypertension. Fenoldopam was originally studied and approved for treatment of severe hypertension requiring intravenous therapy. No paediatric approval is under consideration. Although the sponsor did pursue neonatal and paediatric clinical trials, there has not been sufficient support to pursue labelling for the drug. The request for a change or addition to labelling by the FDA can only come from the sponsor.

Paediatric anaesthesiologists are interested in fenoldopam due to its antihypertensive action and its ability to be intravenously titrated with a short half-life. Traditionally, anaesthesiologists interested in inducing controlled hypotension or normotension, would use nitroglycerine or sodium nitroprusside.[16,17]Sodium nitroprusside is more dependable; however, use at high doses or for long intervals may be associated with the development of cyanide toxicity, metabolic acidosis and death. In surgical cases where nitroprusside is considered, there might also be other factors causing metabolic acidosis for which clinicians would still worry about the contribution of nitroprusside.

The approval of fenoldopam brought another dependable, titratable pharmaceutical to the practice of controlling blood pressure. Off-label indications for this type of drug include control of blood

pressure following coarctation repair in the newborn. Recently published data are consistent with earlier reports that the pharmacokinetics and pharmacodynamics of fenoldopam in the infant and paediatric population are different than the adult population.[17–19]Infants and children have a higher dose requirement to achieve desired endpoints. These data demonstrate the need for neonatal and paediatric studies to provide better labelling for use of drugs in infants and children.

As a systemic vasodilating agent, fenoldopam might be useful in infants following open heart surgery with the use of cardiopulmonary bypass. By reducing systemic resistance, fenoldopam may improve ventricular function and counteract the inflammatory vasoconstricitve cascade induced by cardiopulmonary bypass. FenoIdopam appears to be natriuretic, kaliuretic and diuretic which would all be useful.

In 1999, the US FDA approved a novel agent, dexmedetomidine. This short-acting alpha$_2$ -adrenergic agonist was approved for sedation of intubated/mechanically ventilated adult patients in the ICU and non-intubated patients (e.g. procedure requiring short interval of sedation). The US FDA recognised the usefulness of the agent and its side effects, including adrenal suppression. Multiple paediatric investigators felt this was an agent of potential great benefit to children. Although the sponsor was supportive of possible paediatric indications, when they approached the FDA, they were informed that longer trials of dexmedetomidine (up to 7 days) in adults would be required prior to approval for paediatric studies intended to support approved paediatric labelling.

At present, >10 years later, dexmedetomidine has been studied and reported in multiple paediatric circumstances and is in common use[20,21]in paediatric intensive care units in the USA. However, without some commercial interest in paediatric labelling, investigations have been slowed to study the potential usefulness of dexmedetomidine in neonates. Dexmedetomidine may be very useful in this population as there is growing concern regarding agents that enhance gamma aminobutyric acid (GABA) activity or are glutamate antagonists. Although the agent may never prove generally useful in neonates, a report of use in a very preterm infant has been published.[22]In general, newborns have been denied the opportunity for possible benefit of the drug by appropriate studies being designed and implemented.

Off-label route of administration

Two common procedures performed in infants without intravenous access include myringotomy tube placement and circumcision. For myringotomy tube placement, infants are usually anaesthetised with inhalational anaesthetics, and awaken quickly following the procedure. Infants for circumcision may have the procedure performed with or without local anaesthesia or regional block, and sometimes with an oral sugar-containing-solution coating on a pacifier.

Without intravenous access, practitioners have limited themselves to administration of oral or rectal acetaminophen. Most clinicians avoid intramuscular injection of more potent analgesics, attempting to avoid the pain experienced by injection.

Off-label use of fentanyl by intranasal administration was described in 2000. During administration of anaesthesia for myringotomy tube placements, infants received 2 $\mu g\,kg^{-1}$ of intranasal fentanyl. Infants receiving this dose were found to have lower pain and agitation scores and no increase in time to discharge.[23]In our experience following this report, we noted some delayed awakening from anaesthesia using this dosing. We have empirically reduced our administration of intranasal fentanyl to 1–1.5 $\mu g\,kg^{-1}$ divided half into each nostril. We have been pleased with this clinical practice.

As fentantyl is generic, and very inexpensive, there would be little interest by a sponsor to approach the FDA to enhance labelling for fentanyl or even to request a new route of administration. Clinicians have the privilege of continuing to use this agent in this manner for the benefit of their patients. Intranasal fentanyl is not reported to have the burning sensation noted with nasal administration of midazolam. Whether intranasal or per oral/transbuccal, absorption of doses of fentanyl along these lines might be a useful adjunct in providing analgesia for circumcision. As circumcision is often performed prior to the newborn being discharged from the hospital, cardiorespiratory monitoring availability has been a limitation to providing opioid analgesia for this common neonatal surgical procedure.

Why all these concerns?

As discussed elsewhere in the issue, neonates may have very different pharmacokinetics and pharmacodynamics compared to adults. Studies in adults do not always translate to similar experiences with infants and children. We profess to 'first, do no harm'. In neonatal medicine and anaesthesia, the experience from adult studies may be sufficient to recommend dosing an agent on a 'per kilogram' basis. However, despite that common teaching, we know that we are underdosing or possibly overdosing infants and newborns. The side-effect profile may also differ. Rapacuronium provides an important example of differing safety profiles between adults and children. In anaesthesiology, neonates and young children demonstrated a greater frequency of side effect to the drug rapacuronium shortly after it was approved. Rapacuronium (Raplon) was approved for use in adults and children 1 month to 12 years of age by the FDA in 1999. It had not been studied in newborns. Following its availability, anaesthesia providers were very pleased to have an alternative fast-acting neuromuscular relaxant to succinylcholine. It was noted and marketed with the known side effect of bronchospasm with an ~8% frequency. By 2001, an increasing number of post-marketing surveillance reports of fatal or near-fatal bronchospasm were made.[24,25]Some of the early and striking events occurred in infants where an alternative to succinylcholine would have been quite useful. Rapacuronium was voluntarily withdrawn from the market by its sponsor.

Propofol-infusion syndrome was first reported in children prior to later reports in young adults.[26–28]Propofol is approved for use from 2 months of age to adults, but not in neonates. Although commonly used in neonatal anaesthesia, propofol for long-term sedation in neonates has not been reported and should be considered only cautiously. Metabolic pathways for its degradation in newborns are not well described. Accumulation of propofol may occur and its effects on synaptogenesis suggest an inhibitory pattern.

Clinical trials practice

Clinical trials are becoming increasingly regulated and expensive. Neonates as subjects in clinical trials cannot provide independent informed consent. In randomised controlled trials, the current state of the art treatment is considered appropriate for the control arm of the trial. When current therapies are effective, the ability to demonstrate equivalency or improved efficacy requires enrolment of hundreds to thousands of patients.

Understandably, parents are hesitant to permit their infant or child's participation in a randomised controlled trial. Therefore, trial designs often centre on pharmacokinetic and pharmacodynamic data as primary endpoints. Although useful, these are usually only pharmacologic/surrogate endpoints, and do not generate the outcomes data which the FDA would find more robust.

Neonates are a challenging group to study with the significant co-morbidities they have from prematurity and hospitalisation. Limitations may be placed on the maximum quantity of blood sampled for pharmacokinetic/pharmacodynamic studies so as not to contribute to the requirement for transfusions. Since hospitalised newborns are at risk for major morbidities, they remain a subgroup from which investigators often are reluctant to study. As improved modalities of sampling blood and less invasive monitors become available, the newborn may become a more attractive candidate for clinical trials and thereby benefit from the results obtained more quickly.

Conclusion

Off-label use of pharmacotherapeutic agents in newborns is ubiquitous! With most drugs never studied in the newborn population, the US FDA cannot provide evidence-based guidelines for practitioners. Off-label use is not illegal. Off-label use is not immoral or unethical. Off-label use is so common that it is not usually a major issue with plaintiff's attorneys when a poor outcome has occurred. Clinicians are required to exercise their best judgement in dealing with patients, particularly in an emergency. Not all information or variables about pharmacological agents may be known at the time an ill neonate presents for anaesthetic care and surgery.

As I educate our younger colleagues, I often suggest that they become more familiar with the drug-approval process and understand that they have a duty to report clinical observations to the FDA through the MEDWATCH program (www.fda.gov/Safety/MedWatch/default.htm). Insightful clinicians often discover and report the first new experience of a side effect or unanticipated effect of a drug. Through a central reporting mechanism, more reports can be collated for evaluation.

When questioned about whether I support the use of a drug in a newborn, I reflect upon what is known, but more importantly on what is not known about use of the drug in this vulnerable population. Clinical experience reports and case reports are quite helpful to busy clinicians to alert them to potential issues. Without a willingness to consider use of modern agents in newborns, they will be 'pharmacotherapeutic orphans' for decades to come. Medicine has advanced greatly in the past many decades. We must continue our support and advancement of care of newborns for their best outcomes in the future.

Practice points

- Most pharmaceuticals used in newborns are used in an 'off-label' manner
- Some recently developed agents are targeted specifically at diseases of the newborn and have been tested and FDA labelled for use in newborns
- Clinical trials in newborns are increasingly difficult to perform
- Clinicians often rely on case reports and experiential reports to make progress in providing guidelines for drug use in neonates

Research agenda

- Further research is warranted for the most commonly used agents in the newborn to determine whether current guidelines provide for effective treatments in this age group
- The US FDA requires data sufficient to evaluate pharmaceuticals for labelling in newborns, and this will require further trials to be performed in this age group

Disclosure

Dr. Tobin was a member of the United States Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Anesthesia Life Support Advisory Committee from 1998 to2002, and he has been a consultant to the CDER following his Committee membership.

Conflict of interest statement

None declared.

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Neonatal resuscitation

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Neonatal resuscitation techniques are evolving. More sophisticated methods of monitoring have emerged and current practices have been challenged. It is recognised that most newborns will require only gentle assistance to facilitate the transition from intrauterine life. The routine use of suction and oxygen supplementation is no longer recommended and the effectiveness of current methods of delivering ventilatory support has been questioned. The importance of effective use of masks and optimising tidal ventilation rather than pressure generation is emphasised. Newer oximetry technologies and the routine use of capnography may facilitate clinical assessment even during active resuscitation. Methods of warming infants have become increasingly effective and the use of servo-control is emphasised to prevent overheating. Evidence to support therapeutic hypothermia for the birth-asphyxiated baby is solid and cooling should be considered a standard of care. The next revision of the International Liason Committee on Resuscitation (ILCOR) Guidelines is eagerly awaited in 2010.

The anaesthetist is unlikely to be called upon to resuscitate the newborn. This is a pity as they may have skills in airway and ventilatory management germane to gently supporting the transition.

The 2005 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) of the Pediatric and Neonatal Patients: Neonatal Resuscitation Guidelines were published in *Circulation* in November 2005[1] and *Pediatrics*[2] in May 2006.

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They were intended for practitioners responsible for resuscitating neonates undergoing the transition from intrauterine life and were applicable to those neonates requiring resuscitation in the first weeks to months following birth.

At the time of writing (December 2009), worksheets for the 2010 Consort Statement of the International Liason Committee on Resuscitation (ILCOR) from which the next generation of Guidelines will be derived are yet to be completed – but many can be accessed via the AHA Website.[3]

Morley[4] has described 'true' neonatal resuscitation (as adult practitioners imagine resuscitation) as very uncommon. He likens the practitioner's role more to one of "gentle assistance to make the transition from placental to pulmonary gas exchange" and this emphasis (on stabilisation rather than resuscitation) has been extended by reviewers into the preterm infants at birth.[5]

Indeed, estimates vary between 1 in 2000–5000 for those defined by the need for extended ventilation or cardiac compressions and cardioactive medications.[6,7] Identification of those infants requiring resuscitation requires rapid assessment of four characteristics – an estimate of gestation, presence of meconium in the amniotic fluid, breathing and muscle tone.

The initial steps in response to this assessment include the following sequence-

A. Initial steps in stabilisation (i.e., provide warmth, position, clear airway, dry and stimulate)
B. Ventilation
C. Chest compressions
D. Administration of epinephrine and/or volume expansion

Brief reviews of some of the components of this 'bundle' of care follow with emphasis on some of the areas of controversy and future trends.

Pulse oximetry

The current ILCOR Guidelines recommend the decision to initiate resuscitative measures be based on clinical assessment of colour and heart rate[1,2] despite evidence that clinicians vary markedly in the capacity to identify normal and abnormal saturations[8] and even heart rate.[9]

Pulse oximetry has thus become increasingly used during neonatal resuscitation[10,11] to identify the adequacy of resuscitative efforts and increasingly to titrate those efforts – particularly oxygen therapy.[12]

In utero saturations are ~60% and, during labour and delivery, can fall to 30%.[4] Multiple studies now report the normal changes in oxygen saturation (SpO_2) in term and near-term infants not requiring resuscitation in the first minutes after birth.[13,14] Data are also available for preterm infants.[13]

Recent studies using pulse oximeters with algorithms to deal with low perfusion and artefact have even enabled monitoring during resuscitation.[15] Some investigators have suggested that the oximeter probe be placed on the infant before connecting to the monitor[15] to minimise delays from data acquisition and averaging. It should ideally be placed in a pre-ductal position[16] as a significant gradient between pre- and post-ductal values is known to persist for the first 15 min of life.

Concerns about oxygen toxicity (even in term newborns) must be balanced by caution that correlation between oxygen saturation monitored and displayed by various oximeters (SpO_2) and measured blood gases (saturation of oxygen in haemoglobin (SaO_2)) has been relatively poor outside the range 92–97%.[17] Continuing improvements in pulse oximetry technology have improved its capacity as a heart-rate monitor[18] whilst it remains slower than an electrocardiogram (ECG).[19]

Pulse oximetry, a standard monitor in the Neonatal Intensive Care Unit and for anaesthetists, appears to be establishing itself as an aid to resuscitation and assisting the transition in the delivery suite. Its application, however, should not distract single operators from the principal task of resuscitating the infant if necessary.

Oxygen

The most recent ILCOR statement concluded that there was insufficient evidence to specify the concentration of oxygen to be used for the initiation of resuscitation.[2] However, the recent revision to

recommendations for Canada suggested "positive pressure ventilation should be initiated with 21% oxygen" while in Australia "100% oxygen is inappropriate as the initial gas".[4,20]

Studies in human neonates have shown the use of high concentrations of oxygen (fractional inspired oxygen (FIO_2) approximating 1.0) during resuscitation create oxidative stress and may damage the heart and kidney, affect the lungs and brain – with potential for a negative impact on survival. Thus, the presumed dominance of an FIO_2 of 1.0 is questioned and readers are referred to excellent reviews on the topic.[21,22]

Once considered a standard for delivery-room resuscitation, there is an increasing trend to the use of air for the initial resuscitation of term infants and of lower FIO_2 (0.3–0.4) for preterms.[20]

A metanalysis of four human studies has shown a reduction in mortality rate and no evidence of harm in infants resuscitated in air.[23] Studies have demonstrated decreases in minute volume with as little as a single breath of 100% O_2 and decreases in cerebral blood flow when exposed to 80% O_2.[24,25] Evidence of oxidative stress may last well beyond the immediate resuscitative exposure.[26]

Rabi recently reported a prospective observational trial in healthy term newborns titrating air or supplemental O_2. By 2 min, the groups were equivalent (a mean SpO_2 of 78%) and by 10 min the SpO_2 was lower in the oxygen-enriched group; this effect was nullified if the oxygen was provided by positive pressure ventilation.[27]

Whilst there is evidence that very preterm infants exposed to FIO_2 of 1.0 will become hyperoxic, it would also appear that many preterm infants resuscitated with air will require supplemental oxygen; although this may be related to high SpO_2 targets.[4] The Canadian recommendations suggested the use of pulse oximetry, especially in those babies <32 weeks' gestation, and to avoid saturations >95% when supplemental oxygen is used.[20]

There have been two recent randomised trials in the preterm group. The first, by Escrig, demonstrating that 30% was as effective as 90% in reaching a target SpO_2 of 85% by 5–7 min for infants <28 weeks of age.[28] The second, by Wang, showed air was not as effective as 30–40% O_2 in infants <32 weeks of age to produce an SpO2 of >70% by 3 min.[29] Recently, Escrig's group have also provided tantalising evidence that resuscitation with air may provide longer-term benefits with respect to minimisation of chronic lung disease.[30]

It would appear a reasonable compromise in full-term infants to commence resuscitation in air and titrate FIO_2 according to clinical (and/or SpO_2) response. In preterm babies, beginning with 30–40% O_2, using a pulse oximeter and titrate to a target SpO_2 of 85–95%.

Suction

Most anaesthetists would not embark on an airway manoeuvre without available and working suction and the possibility of airway contamination at birth is high, but somewhat surprisingly, well-conducted randomised controlled trials of suction in newborns weigh heavily against it routine use.

Historically, oronasopharyngeal suction has been used to remove secretions, blood and, occasionally, meconium with the expectation of facilitating airflow, establishing a functional residual capacity (FRC) and improving saturations to promote successful transition.[4,31] However, routine suctioning at birth in the absence of meconium staining has been shown to have significant adverse affects: promoting bradycardia (with and without apnoea),[32] lowering saturations[33,34] and delaying their return to normal.[35] This effect was similar for vaginal[35] and caesarean[36] deliveries.

Infants born through meconium-stained amniotic fluid (MSAF) can be suctioned intra-partum (with delivery of the head but before the first breath) and subsequently intubated and suctioned below the cords – the aim being to reduce aspiration of meconium and thus meconium aspiration syndrome (MAS). In the only large randomised controlled trial reporting on intra-partum suctioning, Vain[37] demonstrated no difference in outcome and failure to prevent MAS. Another observational study[38] has added support to this finding and raised the possibility of an increased rate of pneumothorax.

What of suctioning below the cords? If the infant is vigorous tracheal suctioning offers no benefit[39–41] and may cause harm.[39] In the depressed neonate born through MSAF, there is no evidence of benefit.[32]

It may be that MAS is a syndrome that begins *in utero*,[42] may be unrelated to meconium[43] and thus tracheal suction will not prevent it. Indeed, observations of secondary surfactant deficiency have raised the tantalising possibility of a role for surfactant lavage. Its role has been suggested with caution[44] and the use of large aliquots of dilute surfactant solution has been demonstrated to be feasible.[45]

Readers are referred to a recent review[46] and the results of a multicentre trial (LessMAS trial currently in press) are awaited with interest.[47]

Airway and ventilation

How best should practitioners provide the necessary substrate for transition to functional residual capacity?

Providing a patent airway and use of a recruitment manoeuvre using a flow-inflating anaesthetic bag would be considered a basic skill-set for the practitioner providing anaesthesia for neonates. However, in the newborn, covered in slippery vernix, providing an optimal seal with a facemask can be problematic,[4] as can inflating lungs that are bilaterally collapsed and noncompliant, without inflating the stomach.

Indeed, the optimal device, pressure, inflation time and flow rate required to establish FRC are unknown[2,48]; neither is the role (and level) of continuous positive airway pressure (CPAP) or positive end expiratory pressure (PEEP) in preterm infants.

It is well accepted that the immediate response of the infant heart rate to respiratory manoeuvres (i.e., increased and maintained $>$100 beats per minute) is the best guide to how well the practitioner is performing. Unfortunately, clinical palpation of a pulse has been shown to be difficult and inaccurate.[9] There is no evidence supporting improved accuracy with cord palpation or auscultation of the praecordium; however, both are commonly practiced.

What is becoming more obvious is that we need better ways to monitor the effectiveness of our respiratory interventions and limit their potential harm.[19]

Strategies for managing the depressed term[49] and preterm[50,51] neonate have been recently well reviewed.

Neonates appear to acquire FRC not only by adequate inspiratory effort but also by a 'Valsalva' manoeuvre during expiration generating high positive pressures.[52] This 'grunt' has been simulated as a prolonged positive pressure hold or sustained inflation (without demonstrable benefit) and more commonly as PEEP and CPAP.

Masks

To achieve adequate positive pressure ventilation requires an adequate facemask seal. This is often difficult. Leaks are common and mitigate the effectiveness of obtained pressure even with high gas flows.[53,54] Soft, rounded facemasks appear easier to use[55] and are preferred, although this does not necessarily correlate with effectiveness.[56] Possibly, the introduction of flow meters (but not manometers) can optimise effectiveness.[53–56]

Cuffed endotracheal tubes

The European Resuscitation Council Guidelines for Paediatric Life Support comment that cuffed endotracheal tubes may be useful in certain circumstances.[57] They go on to identify poor lung compliance, high airway resistance or a large glottic leak as situations where a cuffed endotracheal tube might be of benefit in the paediatric population. Interest in the use of cuffed endotracheal tubes for resuscitation has been driven by increasing experience in paediatric intensive care[58,59] and anaesthesia.[60,61]

The guidelines point out that "the correctly sized cuffed tracheal tube is as safe as an uncuffed tube for infants and children" with the caveat "provided attention is paid to its placement, size and cuff inflation pressure." Excessive cuff pressure can lead to ischaemic necrosis of the surrounding laryngeal tissue and stenosis and the guidelines recommend the cuff-inflation pressure be kept $<$20 cmH_2O and it is checked regularly.

Newer understanding of cricoid anatomy[62,63] and design features[64,65] suggest the role of cuffed endotracheal tubes should be reconsidered, at least in the term infant. Whilst lively debate continues amongst anaesthetists[66] trials in newborn resuscitation are awaited.

Laryngeal mask airways

Laryngeal masks are well known to the anaesthetist. They form the basis of much day-case anaesthesia and as a rescue device for the 'cannot intubate, cannot ventilate' scenario. These 'supraglottic' devices have been reviewed both in the context of paediatric and neonatal anaesthesia[67] and neonatal resuscitation.[68]

Potential advantages of the laryngeal mask airway (LMA) are high rates of successful placement with minimal training and practice. Disadvantages include increased rates of obstruction and laryngospasm (in the anaesthetic setting), with inadequate alveolar ventilation and potential for gastric distension. Evidence for their role in neonatal resuscitation is limited to observational studies with high rates of successful insertion, ventilation and heart rate response. This included infants as small as 1000 g.[69–71]

The only small randomised controlled trial compared the LMA with endotracheal intubation for infants born via caesarean section with persistent heart rates <100 beats per minute after 1 min of bag–mask ventilation.[72] Similar rates of failure and airway injury were documented with 'remarkably short' insertion times. The operators were anaesthetists and 'the generalisability to paediatricians' was questioned; however, the study did suggest that the devices may be equivalent for trained operators when ventilation with a facemask had failed.

Numerous case reports demonstrate the utility of the device to salvage an airway and provide an option for ongoing positive pressure ventilation. It would serve the neonatologist well to become familiar with the device.[68]

Devices for ventilation

The T-piece resuscitator has been recommended to Canadian neonatal resuscitation instructors as an acceptable method that they should "be familiar with" despite potential delays when modifying pressures.[20] In manikin studies, the flow-driven pressure limiting the T-piece resuscitator would appear to be no more effective than a self-inflating bag. Leaks at the level of the mask seem most important and difficult to detect, even with a manometer *in situ*.[53]

Ventilation can be performed effectively with a flow-inflating anaesthetic bag, self-inflating bag or a pressure-limited T-piece.[1,2,49] Inflation pressure is recommended to start at 20 cmH_2O but >40 cmH_2O may be required[2]; but how often is it measured? Pressure levels are more easily and consistently achieved with a T-piece; however, this may be achieved without tidal ventilation.[53] Potentially, we need monitors of tidal ventilation when using a resuscitator and a mask.[56]

Methods for delivery of tidal volume should be monitored, a 'rising chest' may no longer be considered adequate, nor should manometric pressure and either are more likely to be achieved with a T-piece.[49] In the absence of a flowmeter, excessive tidal volumes can be given and may cause lung injury, especially in preterms. Bjorkund[73] has demonstrated that as few as six large inflations can injure the lungs of newborn lambs and lung function at 4 h was inversely related to inflations at birth.[74]

The adequacy of ventilation has been consistently associated with a rising heart rate (despite the recognised limitations of its assessment). Over-ventilation will not be identified in the absence of flow monitoring and/or capnography. Hypocarbia has been shown to adversely affect neurodevelopment[75] and be common within minutes of resuscitation of preterm babies.[76]

End tidal CO_2 monitoring (capnography)

Calorimetric carbon dioxide (CO_2) detectors are effective in quickly confirming tracheal intubation and the return of cardiac output,[48,77] whilst continuous monitors of end tidal CO_2 ($ETCO_2$) serve as a trend monitor for the adequacy of ventilation and assist in identification of disconnection during transport.[78] They have been recommended for all high-risk resuscitations in the delivery room[4,48] and have also been used as a guide to the return and perhaps adequacy of cardiac output (pulmonary blood flow) during chest compressions.[79] They have demonstrated utility even in premature infants[80] and their role in neonatal resuscitation has been recently reviewed.[81]

Continuous positive airway pressure (CPAP) and positive end expiratory pressure (PEEP)

The role of CPAP and or PEEP in neonatal resuscitation has been extensively reviewed.[82,83] It would appear to be used extensively despite "insufficient data to support or refute the routine use" of CPAP during or immediately after resuscitation in the delivery room.[2,49]

PEEP (CPAP) may have additional benefits acting to create and stabilise established FRC in intubated infants and prevent some preterm infants being ventilated, but the device chosen must be able to do it effectively. Anaesthetic bags are variable,[84] self-inflating bags more so (even with an adjustable PEEP valve), therefore, a flow-driven T-piece system with a manometer would appear the most appropriate.

More recently the CPAP Or Intubation at Birth (COIN) trial,[85] randomised preterm infants (25–28 weeks of gestational age) who breathed at birth to either nasal CPAP or intubation with positive pressure ventilation. There were no differences in mortality, requirement for oxygen therapy or complications of prematurity at 36 weeks of gestation. The CPAP group did have a significantly increased risk of pneumothorax (9% vs. 3%) but fewer days of mechanical ventilation. The authors concluded that not all preterm infants require intubation, and those that fail an initial trial of nasal CPAP do no worse.

Chest compressions

Cardiac compressions are infrequent in term[86] and only slightly more frequent in preterm deliveries.[87] When needed, effective compressions have been shown to optimise cardiac output and cerebral blood flow[88] and ameliorate the decline in outcomes due to delays in defibrillation for adults.[89,90] ILCOR has recommended chest compressions should be commenced if the heart rate remains $<$60 beats per minute, despite adequate ventilation with supplementary oxygen for 30 s.[1]

Optimal positions, ratios, methods and depth of compressions are all largely based on extrapolations from manikin studies, adult and animal data.[91] The primacy of protecting cardiac compressions in adults (often at the expense or even in the absence of adequate respiration) must be tempered in neonates in the knowledge that most neonatal resuscitation has its origins in asphyxia.

The 'lower part' of the sternum is ideally displaced one-third of the antero-posterior diameter using the 'two thumb technique' (compression with two thumbs with fingers encircling the chest and supporting the back). An alternative is the 'two finger technique' involving compression with two fingers and a second hand supporting the back. The second method probably requires more force (hence energy) to achieve an adequate systolic blood pressure[92] and will lead to quicker rescuer fatigue.[93,94]

A shorter compression than relaxation phase theoretically improves blood flow, when delivered as a ratio of compression to ventilation of 3:1 that provides 90 compressions and 30 breaths each minute. Simultaneous compression and inspiration are not recommended in neonates and compressions should generate a palpable pulse.

Medications route and dosage

A recent review by Wyllie[95] stated "the only drugs that can be used in resuscitation at birth are adrenaline (epinephrine) and more controversially sodium bicarbonate, glucose and volume expansion" but admitted that there is limited quality evidence regarding the use of any medications during neonatal resuscitation.

Adrenaline is recommended at a dose of 10 $\mu g\,kg^{-1}$ intravenously or intra-osseously and 30 $\mu g\,kg^{-1}$ endotracheally. Higher doses (up to 100 $\mu g\,kg^{-1}$) have been shown to be unhelpful in adults[96] and children[97] and potentially harmful in preterm animals.[98,99] The endotracheal route provides a second-rate option. Delivery is erratic, requires larger doses and diluted volumes[100–102] and much of the dose may remain in the bag or the tube! Evidence for its continued use is sparse at any specific dose[95] and should be considered a last resort.

Intra-osseous delivery can successfully deliver fluids and medications during resuscitation of neonates when equipment or personnel skilled in intravenous access are not available, or if intravenous access cannot be established within minutes[103] it might be quicker and easier to learn than

umbilical venous access,[104] and more useful in neonates outside the immediate newborn period.[105] There are, however no randomised controlled trials evaluating its use.

Most non-responsive resuscitations are due to failures of ventilatory management rather than a need for adrenaline. There would appear to be no current evidence to support the routine use of vasopressin, bicarbonate, glucose or volume.[95]

Volume expansion

ILCOR made the recommendation that volume expansion be considered for suspected blood loss or shock (with signs such as pallor, poor perfusion and weak pulses) not responding to other measures.[1] Volume resuscitation for the newborn has been reviewed.[95,106] Isotonic crystalloid rather than albumin is considered first choice at a dose of 10 ml kg^{-1}. This was based on a small number of randomised controlled trials.[107–109] No trials of volume expansion versus withholding volume have been published but it has been identified that rapid infusions of large volumes have been associated with intraventricular haemorrhage in preterms.

The use of foetal blood transfusion via delayed cord clamping has been assessed in recent trials of preterm[110] and term[111] infants. Whilst higher haemoglobin (and haematocrit)[112] and iron stores[113] with less anaemia and rates of blood transfusion (in preterms)[114] have been documented, an increase in the risk of polycythaemia (self-limited) does occur. To date, these small trials have not been powered to examine for resuscitative or long-term neurodevelopmental outcomes.[95]

Defibrillation

The asphyxiated newborn is likely to have an agonal bradycardia or asystole as the initial rhythm and ventricular tachycardia or fibrillation is expected to be uncommon. If it occurs it will likely be secondary with a poorer prognosis,[90] or potentially in theatre in neonates accidentally exposed to intravenous local anaesthetic toxicity.

Recent evaluation[115] would suggest recommended doses of $\sim$2 J $kg^{-12}$for the initial shock may be too low. A recent observational study from our institution would appear to confirm that an initial shock of 4 J kg^{-1} with a biphasic defibrillator appears appropriate. Of interest, the subsequent dosing recommended at 4 J kg^{-1} may also be inadequate for optimal return of circulation and 5 or even 6 J kg^{-1} may be needed.[116]

Self-adhesive pads are superior to paddles (accepting the size limitations in infants $<$2 kg where small paddles may be the only alternative) and placement should be antero-posterior.[116,117]

Energy dosages for supraventricular tachydysrythmias have likewise been questioned and may well need to be increased from the currently recommended 0.5 J kg^{-1} (with subsequent doses of 1 J kg^{-1}) to 1 J kg^{-1} (with subsequent doses of 2 J kg^{-1}).

Post-resuscitation care

Post-resuscitation management has long focussed on prevention of secondary injury; limiting the effects of systemic organ dysfunction and methods to prevent ongoing brain injury.[118] Optimisation of ventilatory management to prevent hypoxia and episodes of hyper- or hypocapnoea has long been recommended, as has the protection of cerebral perfusion by maintaining adequate blood pressure. Metabolic homeostasis of glucose and electrolytes aims to prevent intracellular stress and osmotic shifts. These strategies are largely to avoid secondary insults to the damaged organism; particularly the brain.

Recent neuroprotective strategies have included a host of agents including antioxidants such as allopurinol, blockade of the excitatory aminoacids with magnesium and induction of neuroprotection with erythropoietin and hypothermia.[120] Despite the importance of preventing hypothermia in non-asphyxiated term and preterm newborns, to date, the intervention with the strongest evidence base would appear to be the early induction of modest hypothermia.

Glucose

Adverse neurological outcome has been associated with low blood glucose in the setting of asphyxia and resuscitation. This is based on some neonatal animal models with hypoglycaemia at the time of the insult and one human study looking restrospectively at the association of hypoglycaemia and poorer outcome.[1,119]

In adults (and children) the association with hyperglycaemia and worse outcome for intensive care has led to prospective randomised controlled trials of tight glucose control.[120,121] Initial studies suggested a benefit to maintaining blood sugar in a narrow therapeutic range but the subsequent The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study in adults failed to confirm this.[122] The dangers of hypoglycaemia in newborn babies make tight glucose control an unlikely effective therapeutic endeavour.[123] Glucose management during and after resucitation of the newborn has been reviewed.[124]

Temperature

The accepted standard for preterm infants and non-asphyxiated term infants is an environment that provides for minimal heat loss and thus metabolic oxygen consumption.[48] The exact range of core body temperature that is physiologically appropriate for a newborn has not been rigorously defined[125] but a core body temperature of 37 °C with a range of ±0.5 °C is accepted as normothermia. Aural and axillary temperature (properly performed) correlate with deep rectal (core) temperature measurements.[126]

Heat loss to the environment is composed of evaporative, convective, conductive and radiant heat loss and measures should be undertaken immediately after birth to mitigate these losses. Warming the delivery room to 25–26 °C has been recommended[20] despite an anecdotal evidence base[48] and the recognition that the ability to regulate room temperature is often not at the discretion of providers for the newborn; particularly with gowned operating surgeons![125]

Drying the newborn followed by swaddling or using an overhead heat source will limit the fall in rectal temperature,[127] as will heated mattresses[128] and carefully planned skin-to-skin contact with the mother. This is true for both term[129] and low-birth-weight babies.[130] Head coverings have been shown to be useful but appear somewhat constrained by the choice of material, that is, gamgee-lined wool.[131]

Newborns requiring resuscitation will benefit from occlusive wraps – food-grade polyethylene plastic bags below the neck – especially if <28 weeks gestational age.[20,126,132] So effective is this intervention combined with radiant warming that care must be taken to avoid overheating.[20,126,133]

Recommendations have been made for resuscitation teams to attach temperature sensors early and allow for servo-control to prevent under- and overheating.[20,48] The importance of avoiding the deleterious effects of overheating have been emphasised in both the term and preterm infants and particularly in those with birth asphyxia.[134]

Induced hypothermia

In 2005, ILCOR concluded that there was insufficient data to recommend the routine use of modest systemic or selective cerebral hypothermia after resuscitation of infants with suspected asphyxia. The prevention of hyperthermia in post-asphyxial infants was felt, however, to be "particularly important"[1] and has been recently reviewed.[118]

Hypothermia has been used for post-asphyxial and post-traumatic neuroprotection in children and adults with mixed results.[135–138] The timing, temperature and duration of therapy all appear important.[139]

Modest hypothermia, cooling the brain by 2–4 °C reduces the extent of tissue injury in experimental animals and in humans. Mechanisms may well be varied and include reduction of metabolism, inhibition of excitatory amino acid (particularly glutamate) release and protein kinase activation, preservation of endogenous antioxidants and the blood–brain barrier and inhibition of apoptosis.[140]

To optimise this protective effect, it needs to occur early (within 6 h), achieve a temperature of 32–34 °C and be prolonged for 72 h. This would appear to be obtained in neonates with isolated head or whole-body methods. For the infant at risk of birth asphyxia, the inclination to warm should be resisted as hyperthermia will exacerbate injury in this context.

Hypothermia may be associated with bradycardia and hypertension; usually not requiring treatment. At core temperature <33 °C, dysrythmias, bleeding, thrombosis and sepsis have been reported; however, these have not been observed in those trials limited to modest hypothermia (33–35 °C).

Two major studies in neonates informed the ILCOR statement of 2005. The first reported selective head cooling in 234 infants with moderate-to-severe encephalopathy.[141] A significant improvement was observed in the group with the least severe encephalopathy but a *post hoc* analysis suggested a protective effect for the entire cohort.

In the second study of whole-body hypothermia, Shankaran randomised 102 infants with predetermined severe hypoxic ischaemic encephalopathy to a rectal temperature of 33.5 °C. Death or moderate disability was reduced in the hypothermic group with a number needed to treat of six.[142]

At the time of writing, the Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY) study group has published in the New England Journal of Medicine.[143] This trial randomised 325 infants <6 h of age (and >36 weeks gestational age) with perinatal asphyxial encephalopathy to normothermia or cooling of the body to 33 °C for 72 h. Infants cooled had an increased rate of survival without neurological abnormality, with reduced rates of cerebral palsy and improved Mental Development Index and Psychomotor Developmental Index of the Bayley Scales of Infant Development II and the Gross Motor Function Classification System assessed at 18 months of age. Adverse effects were described as minor and not associated with cooling. The authors concluded that the induction of moderate hypothermia for 72 h in infants who had perinatal asphyxia did *not* (my emphasis) significantly reduce the combined rate of death or severe disability but *did* result in improved neurological outcomes in survivors.

Conclusion

Neonatal resuscitation continues to evolve and current practice is being evaluated. It appears we could do better.[144] The future of neonatal resuscitation is likely to involve increased expectations – in training[145] and performance.[146] Sophisticated analysis of each component of care in these complex situations continue to be published and the new ILCOR Guidelines are eagerly awaited in 2010.

Practice points

- Routine nasopharyngeal suction is unnecessary and may be harmful
- Pulse oximetry is helpful and should be applied early
- Resuscitation should begin in air for term babies and 30–40% for preterm babies and titrated to pulse oximetry
- Optimisation of mask seal and use of a flow-driven T-piece device is recommended
- CPAP/PEEP is particularly important to maintain functional residual capacity
- The use of flow sensors to measure expired tidal volume may be very useful
- End tidal CO_2 monitoring (capnography) should be used to confirm endotracheal intubation
- Infants with perinatal asphyxia should be cooled to 33 °C for 72 h

Research agenda

- Current studies of the use of oximetry, capnography and advanced modes of ventilatory monitoring are limited to observational data
- Studies of oximetry, capnography and different ventilatory strategies using survival and neurodevelopmental outcome as primary outcomes are needed
- Studies of the benefits of training and simulation in neonatal resuscitation are awaited
- Further analysis of roles and behaviour in complex resuscitative environments would also be of interest

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Evidence for the need for anaesthesia in the neonate

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Neonates are both capable of experiencing pain and memory formation, albeit implicit memory. During surgical procedures, insufficient ablation of the stress response and possible implicit memory formation of intra-operative events might result in adverse early and long-term outcomes. Neonates deserve the same respect as adult patients. It is thus the responsibility of the anaesthetist to provide sufficient anaesthesia for neonates undergoing surgery. A critical approach in weighing the risks and benefits of exposing a neonate to anaesthesia is prudent, and truly elective surgery should be delayed.

Today most anaesthetists regard anaesthesia as mandatory for surgery in neonates. Thirty years ago this was not the case, then health-care professionals believed that, due to the immaturity of the central nervous system, neonates were not able to experience pain. As a consequence of this, many anaesthetists were firmly convinced that newborns did not require analgesics or anaesthetics for surgical procedures such as ligation of the patent ductus arteriosus.[1]

In 1987, Anand et al.[2] were the first to show the negative effects of insufficient analgesia and the benefits of an anaesthesia technique using high-dose fentanyl for preterm neonates. This milestone publication encouraged anaesthetists all over the world to develop various techniques to provide what we today call adequate anaesthetic care for the neonate.

In 1999, Ikononomidou et al.[3] reported in *Science* that in infant rats several *N*-methyl-D-aspartate (NMDA) antagonists, among them ketamine, produced evidence of neurotoxicity. These findings were subsequently confirmed by the same group and others, who demonstrated that many anaesthetics, both NMDA antagonists and drugs with γ-aminobutyric acid type A ($GABA_A$)-mimetic properties, such as ketamine, nitrous oxide, midazolame, propofol and isoflurane, induced apoptosis in the brains of infant rodents.[4–6] The work of Ikonomidou et al. and others has sparked a worldwide debate about the

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safety of neonatal anaesthesia. This topic will be addressed extensively by Dr. Andreas Loepke in another review in this issue of *Best Practice and Research in Clinical Anaesthesiology*.

As opposed to a rather large number of publications which have mainly focussed on the treatment of neonatal pain, the list of papers dealing with all aspects of neonatal anaesthesia, such as the recent review in *Peditatric Anesthesia* by A. Davidson,[7] is very short.

In this review, the rationale for the need for anaesthesia in the neonate is discussed together with the specific aims and risks of anaesthesia in this particular patient population.

What are the aims of anaesthesia?

Before we can start to discuss the need for anaesthesia in the newborn, we first have to point out that there is no clear definition for what we call anaesthesia.

Regardless of which technique we apply, be it general or regional anaesthesia, a combination of both, or procedural sedation, all these approaches aim to reduce the humoral stress response, pain and emotional distress. General anaesthesia, as opposed to regional techniques, aims to produce unconsciousness, the total absence of perception of any experience and amnesia.

In adults and at least in older children, the aims of general anaesthesia are well defined. During surgery a patient must not suffer from pain and/or any form of emotional distress. Opioids or locoregional techniques provide sufficient suppression of the stress response. Furthermore, the patient wants to be sure that he will be unconscious and that he would not remember anything that happened during surgery. Intra-operative awareness, explicit memory of intra-operative consciousness is being regarded as a major adverse event, which may lead to significant long-term psychological problems such as post-traumatic stress disorder.[8] However, intra-operative awareness *per se* is not the problem, what makes it such a dramatic event is that intra-operative consciousness was not expected. The so-called intra-operative wake-up test is a common procedure during scoliosis surgery. Patients, usually teenagers, are instructed preoperatively that they will be conscious for a short while during surgery in order to follow some instructions and asserted that they feel no pain. In these patients, intra-operative wakefulness is an expected event, which is usually well tolerated and without any negative consequences even when remembered postoperatively.[9,10]

In young children, and especially in neonates, very little is known about the significance of unconsciousness as a facet of general anaesthesia. We are even unsure to what extent consciousness exists in neonates.

Consciousness

There is no clear definition for what we call consciousness, despite this being a subject much discussed by philosophers and theologians for centuries. A very simple definition of consciousness is sensory awareness of the body, the self and the world.[11] Philosopher of mind JR Searle[12] defines consciousness as "inner, qualitative, subjective states and processes of sentience or awareness," including "one's autobiography and mental time" as well as the ability and capacity to introspect and report about the aforementioned mental states both verbally and non-verbally. Another way to define consciousness is to describe it as a list of components and signs, such as wakefulness, somatosensory awareness, awareness of smell, hearing and seeing, self-awareness, conjure background emotions, purposeful behaviour, internal perspective, memory and language.[13]

Recently, neuroscientists have begun to address the phenomenon of consciousness. Crick and Koch[14] suggest a link of consciousness with synchronous neural activity at 40 Hz, whereas Tononi and Edelman[15] advocate thalamocortical re-entry circuits. Dehaene et al.[16] developed a model of a "global neuronal workspace (GNW)." The GNW consists of five relatively autonomous processors involved in perception, motor activity, attention, evaluation and long-term memory formation. These five processors are connected throughout the brain by long-axon neurons in order to form the GNW circuits.

According to Lagercrantz and Changeux[11] consciousness is a "progressive, stepwise, structural and functional evolution of its multiple intricate components."

Consciousness versus wakefulness

Consciousness requires cortical processing. To make consciousness possible, all the information from the internal and external environment must be simultaneously available at all parts of the cortex.[17]

As opposed to the above, natural sleep is an arousable state of unconsciousness.[18] Wakefulness can be best described as a state of brainstem and thalamic activity, a state of non-sleep arousal. It is thus possible to be awake but unconscious, whereas it is impossible to be asleep and conscious.[17]

The development of human consciousness

Neuroscientists try to approach the emergence and development of consciousness via the development of the neural circuits of consciousness as a part of the GNW.

Term neonates have a brain which can best be described to be in a transitional stage of development with almost the same amount of neurons as an adult, but immature connections between the neurons, thus immature GNW circuits. A process of an overproduction of synapses and simultaneous elimination and stabilisation lasts until adolescence. Myelinisation of the frontal cortex, the area where the highest executive and conscious thoughts take place, begins prenatally, but lasts until the end of the third decade. At around 24 weeks of gestation, an ingrowth of thalamocortical axons in the somatosensory, auditory visual and frontal cortex begins.[19] There is significant evidence that preterm infants born before 24 weeks of gestation do not seem to have a state of consciousness at a cortical level. Pathways mediating pain perception become functional at about 29–30 weeks of gestation, resulting in the processing of noxious stimuli in the somatosensory cortex.[20,21] However, according to Lagercrantz,[22] the possibility of "some kind of consciousness at a subordinal level" cannot be excluded.

The neurochemistry of the developing brain is also important for a good understanding of the emergence of consciousness and the effects of anaesthetics on the neonatal brain. During foetal life, γ-aminobutyric acid (GABA) is the dominant excitatory neurotransmitter.[23] Around birth, GABA becomes the main inhibitory neurotransmitter, whereas glutamate and aspartate become the most important excitatory amino acids.[24]

Als et al.[25] scored the behaviour of very preterm infants in response to individualised developmental care and found it to be beneficial in terms of neurodevelopmental and medical outcome. As a consequence of these findings, Lagercrantz[13] concludes that even very preterm infants should be regarded as conscious persons and that they thus require the same respect as adult patients.

Today there is some degree of evidence that even *in utero* various sensory modalities are processed in the developing brain, at least to some extent, among them pain, olfactation, vision, hearing, memory and language.[11]

Consciousness in the human foetus and the very preterm neonate

Irrespective of the gestational age the human foetus is almost continuously asleep. Endogenous neuroinhibitors produced within the foeto-placental unit, such as adenosine, prostaglandin D2 and neuroactive steroids such as allopregnalolone and pregnalolone, together with a physiologic low oxygen tension and warmth, play a significant role in the suppression of foetal awareness. The foetus lives in a state of "endogenous anaesthesia," which is maintained during stress situations by significant increases of the aforementioned CNS suppressor effects.[26]

Sleep is the dominant state of the foetus for at least 95% of the time, and there is, especially in late-gestation foetuses, no evidence of wakefulness during the remaining 5% of time when they are in neither REM nor NREM sleep.[26]

The stress of being born, together with the discontinuation of delivery of endogenous neuroinhibitors via the placenta, brings an end to the state of "foetal endogenous anaesthesia."

Consciousness and memory formation in neonates

Development of memory is a process that already begins *in utero*, albeit implicit memory formation.[27] Implicit memory formation has also been found in neonates.[28,29] Unfortunately, till date, the

complete significance of implicit memory in neonates and infant remains unclear. There is furthermore some evidence that long-term explicit memory emerges near the end of the first year of life, slowly leading to the offset of what neuropsychologists call infantile amnesia[30] at approximately 3 years of age.[7] There is furthermore at least some evidence of a significant degree of cognition from early infancy, both in terms of evidence of thought[31,32] and a cognitive sense for self.[33]

According to Rochat,[34] neonates are already capable of demonstrating a sense of their body as a differentiated entity, which is indicative of some degree of self-awareness.

Do neonates experience pain?

Firstly one needs to define pain. Pain is fundamentally a psychological construct, a subjective sensory and emotional experience, which as such requires the presence of consciousness to permit recognition of a stimulus as unpleasant.[19] In contrast to the psychological nature of pain, nociception only involves physical activation of nociceptive pathways, not necessarily resulting in the emotional experience of pain. The experience of pain requires the presence of functional thalamocortical circuitry for conscious perception. These thalamocortical pathways are not functional before approximately week 29 of gestation. In the foetus, from week 19 of gestation,[35] as well as in very young preterm neonates, nociceptive reactions can best be described as reflex movement as a response to a noxious stimulus without cortical involvement.[19] The responses of preterm infants to noxious stimulation could thus be entirely mediated at spinal or brainstem level. Interestingly, Slater et al.[20] recently reported significant changes in cerebral oxygenation over the somatosensory cortex measured in response to noxious stimuli in infants as young as 25 weeks using real-time near-infrared spectroscopy (NIRS). The investigators interpreted these findings to be indicative of the potential for cortical pain processing and pain-induced plasticity in the human brain at very young age. Care must be taken to avoid misinterpretation of this conclusion, which was only that there is a potential for cortical pain processing.

In addition to the aforementioned approach to nociception, which is totally based on 'facts' such as neuroanatomy, cytochemistry and the development of neurophysiology, there is also the possibility to evaluate the phenomenon of neonatal pain by assessing clinical parameters, such as behavioural, haemodynamic and stress responses to stimuli.[36]

So did Haourari et al.,[37] who found that in term neonates oral sucrose significantly reduced, in a dose-related fashion, the overall crying and heart rate as a reaction to heel-prick blood sampling. The authors of that study claimed that their findings suggested an analgesic effect of oral sucrose. In 2001, the International Evidence-Based Group for Neonatal Pain listed oral sucrose as an analgesic.[38] In a recent review, Wolf[36] recommended the use of oral sucrose and other non-pharmacological techniques such as tactile stimulation. However, given that it has been shown that oral pacifiers alter visible reactions to painful stimuli but have no effect on the cardiovascular and stress responses,[37,39] Wolf[36] recommended to regard these techniques as comforting procedures, not as analgesics. This is in accordance with a recent Cochrane review,[40] which categorises sucrose as a "non-pharmacologic intervention for relief of procedural pain in neonates."

There is significant evidence for an increased sensitivity to pain in neonates than in older children, which is even further accentuated in preterm neonates. Unfortunately, preterm infants do not mount vigorous reactions to noxious stimuli although their pain sensitivity is even more accentuated than in term neonates. Due to the greater hormonal, metabolic and cardiovascular response to painful stimuli, neonates furthermore require relatively higher doses of anaesthetics and analgesics than older children.[38]

Furthermore, in critically ill neonates behavioural responses to painful stimuli may be difficult to detect, which makes particular detailed assessment crucial.

At present, we are still lacking a reliable tool to objectively assess pain in the neonate. Clinical pain scores, even those which have been validated in neonates, are, by their nature, only indicative for specific moments. In an attempt to continuously measure the level of stress, especially in preterm infants, the technique of skin-conductance was introduced. After an enthusiastic initial report about the applicability of this technique to measure the stress or pain in neonates,[41] recent papers were not able to reproduce these findings.[42,43] However, further research on skin-conductance as a measure of stress in the neonate appears to be meaningful.

There is a growing body of evidence that neonates may be particularly sensitive to pain stimuli.[44] Anand et al. postulated that effective suppression of the humoral stress response is indispensable during neonatal surgery.[2,45,46]

Gruber et al.[47] compared a high-dose fentanyl technique to a combination of fentanyl with midazolam in neonates undergoing cardiac surgery. With respect to early adverse outcomes, they found no differences between the techniques, notwithstanding that stress hormone levels were significantly higher than in the adverse outcome groups in the studies by Anand et al.[2,45,46] There is thus at least some evidence that suppression of the stress response is not the only factor that is linked to outcome after neonatal anaesthesia.

Long-term effects of neonatal nociceptive input

Evidence is accumulating that even single painful events in neonates may lead to long-term effects on the developing organism including pain systems.

To start with the very beginning of extra-uterine life, Taylor et al.[29] demonstrated that the stress response, crying and saliva cortisol level to inoculation at 8 weeks' postnatal age was highest in infants born by assisted delivery and lowest in infants delivered by elective caesarean section.

Bergqvist et al.[48] also found that in term neonates the mode of delivery modulates physiological and behavioural responses to painful stimulation during the first hours of life. Neonates who were delivered vaginally showed dampened behavioural and physiologic response to pain and cold stimuli directly after birth ($> 30 < 90$ min.) than those born by caesarean section. This phenomenon decreased progressively during the first hours after birth. In neonates delivered via caesarean section this pattern was not evident. The authors drew the conclusion that vaginal delivery itself triggers the activation of an analgesic mechanism, probably due to the mobilisation of noradrenaline in both the periphery and the brain. Another contributing factor could be that vaginal delivery leads to much higher plasma levels of β-endorphine than caesarean section. Ultimately, Bergqvist et al. recommended injecting vitamin K or blood sampling within the first 90 min of life to prevent neonatal pain and possible long-term changes in pain behaviour.

Taddio et al.[49] published a study on the effects of neonatal circumcision on pain responses during subsequent vaccination. Infants who had been circumcised with Eutectic Mixture of Local Anaesthetics (EMLA) had significantly lower visual analogue scale pain scores than those who had not received analgesia for circumcision. The authors concluded that neonatal tissue injury might lead to persisting effects on central neural function and behavioural responses to noxious stimuli even months later. As a consequence, they recommend pre-treatment and postoperative management of neonatal circumcision pain.

Peters et al.[50] studied the effects of major surgery with pre-emptive analgesia in infants younger than 4 months on behavioural pain responses to immunisation at 14 or 45 months of life. When compared to an age-matched control group, there were no intergroup differences in outcome measures of facial reaction, heart rate and cortisol saliva concentration. From their findings the authors draw the conclusion that major surgery with adequate pre-emptive analgesia within the first 3 months of life has no effects on the pain response to subsequent noxious stimulation in childhood.

The stress response and clinical outcome in neonates

The stress response to noxious stimuli or tissue damage is, to a certain degree, a protective mechanism. According to Anand,[51] we have to distinguish a physiologic stress response from a pathologic form. One of the factors associated with a pathologic stress response is patient vulnerability. As mentioned earlier, neonates are extremely sensitive to painful stimuli, which make them a highly vulnerable patient group. In preterm neonates, this phenomenon is even more accentuated. Not surprisingly, in surgical neonates, decreased stress responses have been associated with improved clinical outcome in terms of postoperative morbidity and mortality.[2,45] However, as recently mentioned by Wolf,[36] over-aggressive treatment of pain, intra- and postoperatively has its own morbidity. The short-term adverse effects of opioids, such as bradycardia, hypotension[44] can usually be managed clinically in the operating theatre setting. Potential respiratory depression is of concern for the postoperative period but, if anticipated, usually not a real problem.

The aims of general anaesthesia in a neonate

Sufficient reduction of humoral and behavioural signs of distress during surgery is indispensable in neonates. Furthermore, when general anaesthesia is given to neonates, care should be given to prevent the child from being conscious with the subsequent possibility of implicit memory formation. The overdosing of anaesthetics, which might compromise cardiovascular stability, should be avoided, although it is a big challenge to define the right dose of the anaesthetic. All in all, the aims of general anaesthesia in neonates are almost the same as in adults.

Spinal anaesthesia versus general anaesthesia

The effectiveness of spinal anaesthesia for sub-umbilical surgery in high-risk infants has been supported by multiple case series.[52] Besides sub-umbilical surgery, there are a growing number of different procedures such as ligation of the patent ductus arteriosus,[53] repair of meningomyelocele[54] or cardiac catheterisation,[55] where case series demonstrated both the efficacy and safety of infant spinal anaesthesia.

Combined spinal–epidural anaesthesia was recently suggested to be an effective technique for elective major upper abdominal surgery in awake or sedated neonates and infants.[56]

However, it remains speculative whether spinal anaesthesia is safer than general anaesthesia. There is at least a theoretical chance that sub-arachnoidal application of local anaesthetics might directly harm the developing central nervous system.

At present, there are no data available on long-term outcome after spinal anaesthesia in neonates. The conclusion of a Cochrane review[57] was that it was unclear whether or not spinal anaesthesia improves outcomes for babies having surgery for inguinal hernia.

A multi-site randomised controlled trial comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants, the so-called GAS Study,[58] has recently been started. The estimated completion date of this study is December 2016. This time frame gives us an impression how long it takes until results can be expected, even with the most sophisticated study design.

The risks of anaesthesia in neonates

According to the Pediatric Perioperative Cardiac Arrest Registry,[59] infants younger than 1 year accounted for 55% of anaesthesia-related cardiac arrests. Medication-related problems could be identified as the most frequent cause of cardiac arrest. The authors concluded that there is an urgent need for protective strategies. Protective strategies for neonatal anaesthesia may cover aspects of airway management, general versus regional anaesthesia and the choice and dose of medication.

There is emerging evidence, at least from preclinical data, that dexmedetomidine,[60] erythropoietin,[61] L-carnitine,[62] melatonin[63] and lithium [64] may protect the developing brain from anaesthesia-induced apoptotic neurodegeneration.

To date, little is known about pharmacokinetics and pharmacodynamics of anaesthetics and analgesics in neonates. Our knowledge of both desired and adverse effects of drug combinations, as well as interactions with non-pharmacological interventions, is very limited.[65] As recently mentioned by Davidson,[7] due this lack of knowledge “in many circumstances, we have no idea, if we are giving too little or too much.”

Besides pharmacological approaches, there are other ways to develop protective strategies. There is an urgent need for enhanced monitoring systems of anaesthesia effects in newborns and infants, such as depth of anaesthesia monitors with algorithms based on infant electroencephalography (EEG) data.

Cerebral monitoring with NIRS, almost a standard of care during neonatal cardiac surgery,[66,67] could probably add safety to our daily practice of neonatal anaesthesia for non-cardiac surgery as well.

Furthermore, we should also focus on the pre- and postoperative periods. Meticulous attention must be paid when preparing a newborn for surgery. For elective surgery it should be a prerequisite for accepting a patient that vital as well as metabolic parameters are within normal limits, or at least as normal as possible in children with specific diseases. In the early postoperative period, particularly in

those infants who had to be admitted to the paediatric intensive care unit (PICU) after major surgery, good control of perfusion, blood glucose levels, metabolic status and temperature are of paramount importance.[67]

McGowan and Davis[68] recently suggested that not potential neurotoxicity, but hypoxaemia and cardiovascular collapse, as known and understood causes of brain injury and fatal outcome in children during anaesthesia are the real enemies.

Neurodevelopmental outcome after neonatal surgery – impact of anaesthesia

Several longitudinal studies, conducted by paediatricians, psychologists and paediatric surgeons, showed an association between neonatal surgery and sensorineural or neurdevelopmental impairment in young children[69,70] and educational attainments in teenagers.[71] The possible impact of anaesthesia on the developing brain was not specifically addressed. Numerous confounding factors, among them prematurity, severity of disease, days on ventilator in the PICU, APGAR scores and social class might influence neurodevelopmental outcome after neonatal surgery.

Sprung et al.[72] assessed children who were exposed to either general anaesthesia ($n = 193$) or regional anaesthesia ($n = 304$) during caesarean delivery (CD) or delivered vaginally ($n = 4923$) for learning disabilities at age 5 years. The authors of this retrospective study found the incidence of learning disabilities in children who were delivered vaginally was not different from those exposed to general anaesthesia for CD, suggesting that a brief exposure to anaesthesia during CD does not adversely affect long-term neurodevelopmental outcomes. Surprisingly, the incidence of learning disabilities in children who were delivered by CD under regional anaesthesia was lower than in those who were vaginally delivered. The authors suggested being cautious when interpreting this unexpected finding, due to the possibilities of unidentified confounding factors. Nonetheless, they proposed the hypothesis that regional anaesthesia for CD may attenuate the neonatal stress response to vaginal delivery, the latter having significant effects on later neural development.

Great care has to be taken not to equate an association of exposure to anaesthetics at early age and later learning disabilities with causality.

Neonatal surgery – decision finding, timing and communication with the parents

A critical approach in weighing the risks and benefits of exposing a young child to general anaesthesia appears to be prudent.[73] Any kind of surgery that could be technically performed in a neonate should only be performed after significant consideration. In opposition to the actual common practice that the surgeon's opinion about the timing of an operation is decisive, we should establish multidisciplinary rounds, consisting of neonatologists, surgeons and anaesthetists, for all neonates that probably might have to undergo surgery. Procedures that can be delayed without additional risks should be delayed. However, neonatal surgery is almost always at least to some degree emergency surgery that cannot be delayed for months or years. If a neonate needs to undergo surgery, anaesthesia should be given according to the current best practice at each particular institution.

The neurotoxicity discussion has just begun. It is our responsibility as professionals to provide adequate information to parents about the risks of anaesthesia, and it is a question of empathy whether or not to address the issue of potential or putative anaesthetic neurotoxicity.

Conclusions

There is considerable clinical evidence that insufficient anaesthesia is associated with poor outcome, whereas modulation of the stress response by anaesthetics is suggested to improve outcome.[2] For the surgical neonate, there is thus no alternative to a 'good' anaesthetic.

However, it must be kept in mind that the risks of neonatal anaesthesia are significantly higher than in older children. Fortunately, there are a number of quite simple and established measures that can be implemented in our daily practice of neonatal anaesthesia, which can, no doubt, add some safety without posing any potential to harm the patient. Optimal preoperative preparation of the patient is indispensable. Intra-operative NIRS monitoring is certainly expensive, but proven to be effective during

neonatal cardiac surgery, perhaps it should be used for major non-cardiac surgery as well. Last but not least, a good control of the patient's overall condition, pre- and intra-operatively, as well as in the early postoperative period, especially after PICU admission is essential.

Practice points

- Neonates are capable of experiencing pain.
- Any surgical intervention in a human neonate requires sufficient anaesthesia.
- Besides adequate suppression of the stress response, the aims of general anaesthesia in the neonate include ablation of consciousness and memory formation.

Research agenda

- There is an urgent need for clinical trials investigating the pharmacokinetics and pharmacodynamics of anaesthetics and analgesics in both term and preterm neonates.
- Special algorithms for depth of anaesthesia monitors, based on infant EEG data, need to be developed to make this technique applicable to neonates.
- NIRS monitoring might significantly contribute to future neuroprotective strategies and should therefore also be studied in non-cardiac cases.
- Further research on skin-conduction as a possible measure of stress during neonatal surgery is desirable.

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None to declare.

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