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REVIEW ARTICLE

Anesthesia and long-term outcomes after neonatal intensive care

Neil Marlow

Department of Neonatal Medicine, UCL EGA Institute for Women's Health, London, UK

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Correspondence
Neil Marlow, Department of Neonatal Medicine, UCL EGA Institute for Women's Health, 74 Huntley Street, London WC1E 6AU, UK
Email: n.marlow@ucl.ac.uk

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Summary

As survival is now increasing, care of the extremely preterm infant is now directed at strategies to minimize long-term morbidity. In this study, I review the current state-of-the-art outcomes for babies born at extremely low gestations and identify strategies that may be aimed at optimizing outcomes. With respect to anesthetic practice, I then go on to discuss important issues of pain management in these babies and how this may affect long-term outcomes.

Introduction

Care of babies born at very low gestations or with important but potentially correctable malformations has always provoked challenging ethical and moral dilemmas as survivors have high prevalence of serious and lifelong sequelae. Particularly at extremely low gestations, we have seen major improvements in survival, which render decision-making more difficult and throw the adverse long-term outcomes into greater focus. Neonatologists have been effective at describing the sequelae associated with very preterm birth, and outcome evaluation programs run in many countries, both in terms of national and regional outcomes and as either primary or safety outcomes for important multicenter clinical trials.

Increasingly, neonatal practice is oriented to minimizing adverse late sequelae. Management strategies have developed to protect the developing brain, lung, and gut in particular, to minimize the effects of our care on these outcomes. Such strategies form an important part of the current philosophy of neonatal care, and in this paper I will address the issue of important long-term outcomes and how we might modify or study anesthetic and perioperative care to understand better the effect that our intervention has on the developing child. Analgesic and anesthetic agents are not necessarily safe in the developing child; perioperative management may provide high exposure to multiple risk factors, and thus, it is critical that we take steps to optimize practice to produce minimal risk of sequelae.

I will begin by describing current outcomes for the highest risk groups and then evaluate the long-term effects of different management strategies on key organ systems in the very preterm baby, emphasizing perioperative and intraoperative care issues. Separating out the effects of premorbid conditions, for example congenital anomalies, known areas of risk (such as very preterm birth or perinatal hypoxia-ischemia), surgical procedures, and anesthetic strategies, is challenging, and a consistent approach to outcome-directed care is important for each.

Outcome in very preterm infants

There is now a large literature on outcomes for babies born before 32 weeks (very preterm) and 28 weeks (extremely preterm; EP) (1). Survival has improved over the past 15 years for the most immature, rising by 15% between 1995 and 2006, despite a 44% increase in the

numbers of admissions for babies 22–25 weeks (2); survival is now the norm for babies of 27 weeks and more, rising from 60% at 24 weeks (3).

Neurocognitive morbidity

Of more concern are the relatively frequent findings of a range of neurological and behavioral problems among survivors. All adverse outcomes are inversely related to gestational age at birth and seem to be particularly problematic at gestations below 30 weeks. Data from the most recent EPICure 2 study describe outcomes for births in 2006, shown in Figure 1 alongside contemporary data from Sweden (4). Key findings at 22–25 weeks of gestation, compared with outcomes in the original EPICure study of births in 1995, are as follows:

- An improvement in developmental scores by eight points.
- Reduction in cerebral palsy and impairment rates in babies born between 24 and 25 weeks (Figure 1).
- Continuing low rates of severe cerebral palsy (Figure 2).
- Increasing numbers of survivors without impairment born between 24 and 25 weeks.

Although the risk of severe and moderate impairments appears to be declining and drives decision-making in the neonatal period, there remains a high prevalence of less severe impairments of cognitive, learning, and behavior, which are equally a cause for concern. These result in high rates of special educational needs at school (5,6) and a high prevalence of behavior problems (7). These may persist through adult life although most ex-very low birthweight children are well adjusted as young adults (8).

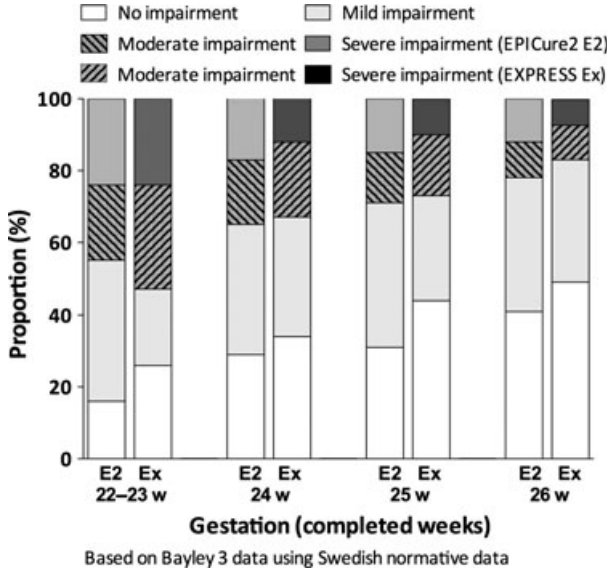

Figure 1 Outcome at extremely low gestational age at 3 years in two national cohorts from England (EPICure2; E2) (4) and Sweden (EXPRESS; Ex) (59).

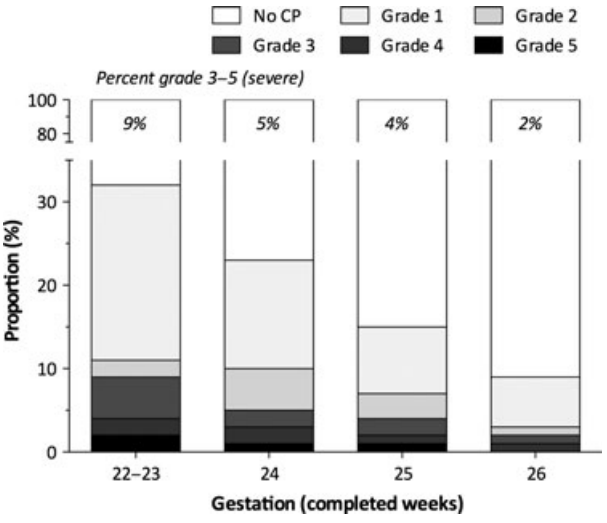

Figure 2 Prevalence and severity of cerebral palsy in a national cohort study classified using Gross Motor Function Classification System (0: no Cerebral palsy; 1 mild impairment; 2: moderate impairment; 3–4 severe impairment) (4).

Respiratory morbidity

There are many fewer studies of morbidity in other organ systems. In particular, the late sequelae of bronchopulmonary dysplasia (BPD) pose potential issues for the growing child/young adult. High rates of readmission during infancy are reported, particularly following RSV infection, and infants with neonatal BPD may require further episodes of intensive care for respiratory conditions. The high rate of readmission drops off, but in our studies, symptoms are common, as are ongoing medications over childhood. Furthermore, in early adolescence, children with and without BPD have significant impairment of lung function (9,10). Table 1 shows differences between controls and EP children at 11 years. EP children were smaller compared with classmate controls and had significantly more symptoms and poorer respiratory function. Children with neonatal BPD were similar to those without BPD in terms of symptoms and medication use but had significantly worse measured respiratory function. Current studies are directed at determining how lung function changes over adolescence into young adult life, as it seems likely that ex-preterm children will enter adulthood with less optimal maximal respiratory function and therefore be at risk of earlier onset of chronic respiratory symptoms,

Table 1 Respiratory morbidity and function following extremely preterm (EP) birth at 11 years (9)

Parameter	Differences between EP vs. controls	EP children with BPD	EP children without BPD	Differences between BPD vs. No BPD
Growth				
Height (*Z* score)	−0.58 (95% CI: −0.8; −0.4)***	−0.47 (SD: 0.99)	−0.48 (SD: 0.98)	−0.00 (−0.3; 0.3)
Weight (*Z* score)	−0.57 (95% CI: −0.8; −0.3)***	−0.37 (SD: 1.31)	−0.49 (SD: 1.25)	0.13 (−0.3; 0.5)
BMI (*Z* score)	−0.39 (95% CI: −0.7; −0.1)**	−0.22 (SD: 1.4)	−0.39 (SD: 1.4)	0.17 (−0.28, 0.62)
Respiratory symptoms				
Current asthma	12% (95% CI: 4; 21%)**	32 (28%)	10 (19%)	9% (−5; 22%)
Asthma medication	14% (95% CI: 6; 22%)**	31 (27%)	10 (19%)	8% (−6; 21%)
Seen by respiratory specialist	6% (95% CI: 1; 11%)*	7 (6%)	7 (14%)	−8% (−20; 3%)
Wheeze	7% (95% CI: −2; 15%)	29 (25%)	6 (12%)	13% (2; 25%)*
Spirometry				
FEV_1 (*Z* score)	−1.5 (95% CI: −1.7; −1.2)***	−1.7 (SD: 1.1)	−0.8 (SD: 1.3)	−0.9 (−1.2; −0.5)***
$FEF_{25-75\%}$ (*Z* score)	−1.5 (95% CI: −1.8; −1.2)***	−2.2 (SD: 1.2)	−1.5 (SD: 1.4)	−0.7 (−1.1; −0.3)***
%Δ postbronchodilator	5.3% (95% CI: 3.5; 7.0)***	10.7% (SD: 10.0)	5.5% (SD: 7.3)	5.2% (2.0; 8.5)**
ΔFEV_1 >12%	19% (95% CI: 11; 27)***	32%	16%	16% (3; 30)*

BPD, bronchopulmonary dysplasia.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

particularly if they have ongoing inflammation or they smoke (11).

Management and preterm outcomes

It is important to maintain a perspective on long-term outcomes during neonatal management as key areas of practice have unexpectedly led to therapeutic misadventure – classically in the unrestricted use of oxygen leading to retinopathy of prematurity (12), but more recently in the association between cerebral palsy and antepartum antibiotics (13). In these terms, neonatologists have developed strategies to minimize risks, primarily around brain and lung injury (Table 2), and many neonatal, and indeed perinatal studies, now include, as a minimum, 2-year evaluation as a coprimary or safety outcome.

There is a general consensus that long-term outcomes should be measured after 18 m-2 years because neurological and developmental tests are more likely to have some predictive value at those ages. There is agreement over the description of impairment in preterm populations at around 2 years (14). However well the prediction performs in populations, for individuals, it is much less accurate (15), and longer-term studies are needed if more subtle outcomes are expected or formal respiratory function testing undertaken. Longer-term evaluations run the risk of study dropout and dilution of the therapeutic effect with social and environmental influences. For example, in a recent large trial of caffeine to prevent apnea, advantages seen over the first 2 years were not detectable at 5 years (16). This does not mean that one can ignore the early findings in view of the loss to follow-up and external influences, but rather gives confidence that harm is unlikely and the short-term gains need to be weighed up against potential neonatal side effects.

The extent to which individual changes in management alter long-term outcomes outside of a randomized trial is somewhat debatable, but a range of altered management strategies as a result of neonatal research, encompassing many aspects of neonatal care, accompanied the changes in outcome between 1995 and 2006 described above. There is evidence that changes in long-term outcomes may lag behind changes in mortality (17), which is only logical, but survival is improving dramatically in developed countries (3,18) and within expert centers (19,20). Thus, it seems logical that we should modify our practice to optimize long-term outcomes.

Anesthesia and preterm outcomes

Anesthetic practice interacts with small preterm babies, not simply during perioperative care but also where stand-alone surgical units undertake neonatal surgery, which is not a recommended service configuration (21). Outside the perioperative period, there is no reason why intensive care should not be continued to the same standard as during neonatal care, and it seems logical for such units to contribute to neonatal data collection and national/regional audit as do medical intensive care services. Standards for surgical services in the UK have been published which support this position (21). This is very important as it allows continuance of research protocols during periods of neonatal surgical intensive care,

Table 2 Examples of outcome-directed treatments for the very preterm newborn

Organ/target	Intervention	Putative mechanism	References
Brain			
Germinal matrix hemorrhage	Antenatal Steroid	Improved early condition, induces antioxidants	(43)
	Indomethacin (prophylaxis)	Unknown (reduces large GMH)	(44)
Cerebral palsy	Magnesium sulfate in labor	Cellular neuroprotection (NMDA blocker)	(45)
CP/Developmental scores	Caffeine	Unknown (reduction in PDA and diuretic effect via respiratory improvement)	(46)
Developmental scores	Avoid long line infection	Reduced inflammatory white matter injury	(47)
Eye			
Retinopathy of prematurity	Targeted oxygen saturation (90–94%)	Avoid oxygen fluctuation/extremes	(22,48)
Lung			
Respiratory distress syndrome	Antenatal Steroid	Induces surfactant and antioxidants, reduces lung water	(43)
	Surfactant	Easier lung inflation	(49)
Bronchopulmonary dysplasia	Caffeine	Diuretic and avoidance of patent duct	(46)
	Early extubation	Reduce barotrauma	(50)
	Minimize ventilator pressure/Ti	Reduce volutrauma	(51)
	Early moderate PEEP	Reduce atelactotrauma	(52)
	Optimal nutrition	Encourage lung repair	(53)
	Vitamin A	Encourage lung repair	(54)
Perfusion			
Circulatory filling	Placental transfusion	Reduces large GMH	(55)
Gut			
Adaptation	Early colostrum	Earlier feeding	(56)
Necrotizing enterocolitis	Probiotics	Avoids enteropathic organisms	(57)
	Early colostrum	Encourages gut coordination/adaptation	(56)
	Early TPN	Avoids need for aggressive feeding	(58)

PDA, patent ductus arteriosus.

for example in the recent BOOST-II UK trial of oxygen saturation targeting (22).

Separating out influences of perioperative care in the complex clinical journey of a sick very preterm infant is challenging, and ascribing outcomes to care over these periods is difficult. Nonetheless, similar key strategies as set out in Table 2 should be continued during this period. Perioperative care has several key areas where these principles should be continued wherever possible, examples being:

- Targetting oxygen saturations (minimizing risk of retinopathy).
- Avoiding fluctuations in blood pressure (minimize risk of brain injury).
- Use of caffeine and careful fluid balance (minimize risk of exacerbating lung injury).
- Gentle ventilation and avoidance of over-distension (minimize barotrauma).
- Ensuring high quality nutritional input pre- and postoperatively.

Conditions presenting to surgical services bring their own challenges in this patient group, the largest groups being those with necrotizing enterocolitis (NEC) and patent ductus arteriosus (PDA).

Necrotizing enterocolitis is a devastating condition associated with widespread inflammatory activation and circulatory collapse. Maintaining outcome-focused care during the period of critical illness is challenging (23), and the neurological, nutritional and respiratory outcomes for babies with surgically treated NEC may be particularly compromised, simply due to the underlying pathological process.

Patent ductus arteriosus is a common condition with frequent referral for surgical ligation. Such babies have often been difficult to wean from ventilation and may pose considerable ventilation and fluid management challenges, with important knock on effects for chronic lung disease. The use of ligation shows much variation between different services and practice needs to be rationalized to minimize the additional risk posed by the transfer and surgery (24).

One study has attempted to dissect the influences of surgery for NEC on term-equivalent brain magnetic resonance imaging (MRI), using the latter as a biomarker for later neurodevelopment. Filan *et al.* (25) used a convenience cohort of 227 babies of <30 weeks gestation who had MRI scans at term. Thirty of these had been exposed to surgery and anesthesia, most herniotomy (n = 15) but eight had surgery for bowel problems and

10 ligation of PDA. Babies exposed to surgery had more evidence of white mater injury and smaller brain volumes, particularly in the deep gray matter. Developmental scores after appropriate adjustment were not different between the groups, but the power of this opportunistic study was small, and in the absence of randomized methodology, it is impossible to separate out premorbid, surgical, and anesthetic influences. Evidence based approaches to anesthetic management in surgery for the preterm infant are urgently required.

Management of pain

The seminal study in perioperative care, which highlighted the clear physiological and metabolic response to surgery, was carried out by Anand *et al*. (26) in 1987. Preterm babies receiving PDA ligation were randomly allocated to anesthesia with oxygen/nitrous oxide (as conventional) or to additional fentanyl analgesia. The clear outcomes in favor of fentanyl spawned a continuing interest and activity in neonatal pain and stress. More recently, we have demonstrated altered sensory perception at 11 years following EP birth that was most extreme among babies exposed to surgical procedures (27). Minimizing the perception and metabolic consequences of neonatal pain may therefore have short-term and lifelong benefit.

Important studies of long-term effects of neonatal nociception are ongoing. The group in Vancouver have identified the number of skin breaks during neonatal intensive care as a marker of allostatic load. Although this may be a poor surrogate for nociception, after controlling for other intensive care confounders, the number of skin breaks has been correlated with changes in white matter and subcortical gray matter spectroscopy on MRI, suggesting a differential effect of timing on both structures (28). Summative measures of illness and the number of skin breaks were also associated with slower development of white matter fractional anisotropy (29). Skin breaks also were associated with later changes on magnetoencephalography (MEG) (30), poorer postnatal growth (31), and behavioral measures (32). Although referred to as a measure of neonatal 'pain', it is unclear how the number of skin breaks relates to other measures of stress and to what extent it is simply a more proximal measure of neonatal sickness. Nonetheless, these studies do raise important questions and hypotheses as to the effects of neonatal pain and the benefit of their amelioration (33). Changes in term-age equivalent MRI scans may translate into later neurocognitive morbidity.

Other areas of neonatal pain research have confirmed that even the very preterm newborn can develop appropriate stress and metabolic responses to nociceptive stimuli, even if it may be difficult to observe them clinically (34). Much pain research has concentrated on procedural pain from heel prick or circumcision as controllable events, hence outcomes tend to be short-term and analgesic strategies probably insufficient to be considered for major surgical procedures requiring anesthetics.

Several groups have attempted to study the effect of analgesia in clinical intensive care practice. Levene and colleagues (35) studies the effect of morphine compared with diamorphine in a group of preterm newborns undergoing mechanical ventilation. There were minor differences between the two drugs, and morphine was associated with a fall in blood pressure over the course of the infusion, but there was equivalence in the responses as measured, and both reduced plasma epinephrine levels. In an earlier study, they had studied morphine against placebo (36) and observed at 5 years of age that there was no evidence of significant long-term benefit or harm; they noted that the morphine group tended to have better neurocognitive scores compared with controls. In the largest study of preemptive morphine in 898 preterm babies receiving mechanical ventilation (37), Anand *et al*. reported that morphine decreased the clinical signs of pain (as measured though the preterm infant pain profile and clinical variables) but had little effect on neonatal morbidities. In secondary analyses, worse outcomes (including an excess of germinal matrix hemorrhages) were evident in morphine treated babies of <26 weeks of gestation. No long-term follow-up has been reported to date.

Several small studies have evaluated morphine, synthetic opioids, and other anesthetic agents (such as propofol) for intubation procedures with varying results. All use short-term outcomes.

Thus, in summary, we have little evidence that analgesia *per se* benefits the ventilated preterm baby in the long term, and only one randomized trial during surgery, demonstrating clear superiority of opioid analgesia over the then conventional oxygen/nitrous oxide method, but with only short-term outcomes. Perioperative opioid analgesia has been recommended for ligation of PDA (24), and this is supported in the original trial. Pain itself in the preterm baby produces short-term clinical, metabolic, and endocrinological stress and would seem to be associated with neurological abnormalities on MRI and impaired long-term sensitivity, thus systemic analgesia seems appropriate but there remains a dearth of evidence as to the most appropriate drug and strategy, and little evidence that long-term outcomes are affected.

Direct toxic effects of anesthetic agents

Working from first principles that analgesia is good is fine as long as there is confidence in the safety of the agents used. Morphine (35), alfentanyl (38), and other opioid agents have been associated with cardiovascular adverse events and should be used with care and monitoring. Of more concern is the preclinical work that indicated the association of apoptosis with the administration of NMDA blockers, such as ketamine (39). Subsequently, nitrous oxide, midazolam, propofol, and isofluorane have all been found to produce similar effects in infant rodent models, associated with NMDA blockade and $GABA_A$ agonists (40). Indeed, only dexmedetomidine seems not to be associated with the generation of apoptosis. Further studies have demonstrated long-term cognitive effects in these rodent models from ketamine, phenobarbitone, and inhalational anesthetics (40). There is equally a large body of evidence that morphine may also induce similar changes even allowing for a different mode of action.

Evaluating putative effects of anesthetic agents in human studies is considerably more difficult, particularly as there are unlikely to be randomized trials against placebo, and many other influences conspire to put the very preterm baby at risk of later neuromorbidity. In a large group of studies largely not structured to assess specific effects of individual agents, the need for surgery is associated with adverse outcomes (41). Furthermore, to demonstrate differences in neurological outcomes requires large trial sizes, and disentangling the effect of sedation/anesthesia from the reasons for the therapy is nigh on impossible, although putative designs have been proposed (42).

Selection of babies for anesthetic/surgical procedures demands a careful risk benefit assessment. Whereas it is unclear as to the extent of direct toxic effect from agents used, there is a clear need to provide adequate analgesia/anesthesia during procedures. For relatively frequent conditions, such as PDA ligation, preterm laparotomy, or herniotomy, there should be sufficient patient numbers in large surgical services to facilitate comparison of different techniques and harnessing neonatal follow-up services to provide long-term outcomes is entirely possible. Local and regional anesthesia and minimally invasive techniques may help to minimize exposure to systemic drugs and minimize long-term risk; they may be relatively easily subjected to randomized trials and with appropriate stratification, for example, by gestational age, may help to answer some of the conundrums posed above.

Conclusions

Increasingly anesthetic practice interfaces with the EP baby for periods of perioperative or intensive care. Over the past 10 years, our understanding of the pathophysiology and potential for iatrogenic harm has grown, alongside the need to provide care with a view to optimizing longer-term outcomes. Sick immature babies remain one of the major challenges in pediatric anesthesia as in neonatology.

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Conflict of interest

No conflict of interest declared.

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