Modifiable risk factors for preterm brain injury

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Abstract

In the last decade preterm birth rates have continued to rise hand in hand with improving neonatal care. Unfortunately rates of severe disability have remained static. National benchmarking of key outcomes shows significant variations in adaptation of best practices across United Kingdom (UK). While emerging technologies give us a glimpse of fascinating possibilities, widespread adoption of evidence-based interventions should remain a priority. In this article we have attempted to outline mechanisms of preterm brain injury and identify the most promising strategies currently available to minimize it. Quality improvement strategies (QI) that can help perinatal teams adopt best practices and promising new therapies are discussed.

Keywords cerebral palsy; magnesium sulphate; necrotising enterocolitis; premature birth; sepsis; volume targeted ventilation

Introduction

Great strides have been made in improving neonatal care across the world in the last few decades. In the United Kingdom between 1995 and 2006 survival of neonates born between 22 and 25 weeks gestation improved by 13%. Survival without disability also improved by 11%. But rates of severe disability at 3 years of age stayed constant at around 19%.

Outcomes tend to be better for babies born in tertiary neonatal units. It is also influenced by several factors like maternal health and demography. This is reflected in significant and persistent geographical variation in outcomes. A recent observational study of babies born during 2007–2014 across 10 national neonatal networks demonstrated marked variability. At 24 weeks gestation survival to discharge ranged from 35 to 84% with the highest rates reported from Japan. Survival rates increased and differences between networks diminished with increasing gestational age (range 92%–98% at 29 weeks' gestation).

Improving survival at lower gestational age has prompted discussions regarding resuscitation practices at the borders of viability in several nations. As limits of viability are pushed back, protecting the neonatal brain from injury and preventing disability is evolving as one of the greatest challenges facing perinatal care.

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Mechanisms of preterm brain injury

Intraventricular haemorrhage (IVH)

The subependymal germinal matrix lies over the head of the caudate nucleus. It is highly vascular between 24 and 34 weeks gestation but this vascularity regresses by term. The highest risk of IVH is in the first 3 days of life. The venous drainage from the deep white matter converges on the terminal vein, which runs through the germinal matrix (GM). Therefore a large haemorrhage can cause venous obstruction leading to infarction of the parenchymal tissue.

It is recommended that in babies <32 weeks gestation cranial ultrasound scans (CUSS) are undertaken on days 0, 3, 7 and 28 of life to detect and monitor IVH. Papille grade 1 (limited to GM) & grade 2 (extending to lateral ventricles without filling it) haemorrages usually remain uncomplicated. Grade 3 (enlarged ventricles) and Grade 4 (venous infarction) can lead to obstructive hydrocephalus. Neurodevelopmental impairment rises to 50% if there is ventricular dilatation and rises to 80% if a shunt is required. Haemorrahgic parenchymal infarction (Grade 4) can lead to development of porencephalic cysts with or without communication to lateral ventricles. This could lead to seizures and motor or cognitive impairment.

Grey and white matter injury

With increasing quality of neonatal care the incidence of destructive lesions in the brain are reducing in frequency. Nonetheless, even with normal CUSS scans extreme prematurity can lead to neurodisability. There is increasing awareness that this is due to a *primary cerebral dysmaturation disorder*. In the preterm infant cerebral hypoxia/ischemia and systemic infection/inflammation can lead to injury to pre myelinating oligodendrocytes (pre-OL). Microglial activation, oxygen free radical damage and glutamate mediated excitotoxicity can also cause similar damage. This can lead to focal or diffuse white matter injury. Focal coagulation necrosis leads to development of cystic periventricular leukomalacia (PVL). This is associated with diplegic cerebral palsy and other cognitive defects.

Diffuse disease is due to hypomyelination associated with pre-OL injury. There is also a widespread inhibition of neuronal maturation at a critical time when neural networks are being developed. This can be seen as diffuse abnormalities in signal intensity in MRI scan and is linked to long-term cognitive impairment.

Greater awareness of these mechanisms is driving research towards development of targeted therapies aimed at preventing this inhibition of neural maturation. Stem cell therapies aimed at rebuilding the neural network are also being developed.

Evidence based interventions to minimize preterm brain injury

Antenatal interventions

Antenatal steroids (AS): cochrane systematic reviews show that in preterm birth AS significantly reduce the risk of IVH [RR 0.55 95% CI (0.4–0.76)]. However, there is no clear benefit for improved neurodevelopmental outcomes in childhood [RR 0.64 95% CI (0.14–2.98)]. There is minimal risk to the mother with no evidence of increased chorioamnionitis, endometritis or maternal death. The benefits are thought to be due to anti-

Please cite this article in press as: Ramachandran A, Nair M, Modifiable risk factors for preterm brain injury, Paediatrics and Child Health (2018), https://doi.org/10.1016/j.paed.2018.07.001

Effective interventions to target for improvement:

1. Antenatal magnesium sulphate in preterm birth <34 weeks gestation
2. Delivery of babies <33 weeks gestation in high output NICU
3. Prevention of preterm birth
4. Early detection and prevention of preterm IUGR
5. Delayed cord clamping and prevention of hypothermia
6. Reduction of early and late onset sepsis
7. Antibiotic governance
8. Early feeding with colostrum and exclusive use of breast milk in babies born <33 weeks gestation
9. Volume targeted ventilation
10. Reduction of necrotising enterocolitis (NEC)

Table 1

inflammatory effect of AS, increased cardiorespiratory stability after birth and vasoconstriction of cerebral blood vessels. NICE guidelines recommend use of AS in preterm rupture of membranes, suspected or established preterm labour <34 weeks gestation. The protection lasts for around 7 days after administration of AS.

Whilst repeated courses are not normally recommended a second course can be given if the first course was administered prior to 26 weeks gestation. As most babies born 23–24 weeks gestation are now resuscitated at birth there is little benefit in withholding AS to these mothers. NICE recommends that at this gestational age AS should be given after discussion with parents. Insufficient evidence is available on superiority of betamethasone over dexamethasone and variation of dosages required in specific situations like multiple birth. The National Neonatal Audit Project (NNAP) estimates that only 86% eligible mothers are receiving AS nationally in the United Kingdom (UK) in 2016.

Antenatal magnesium sulphate for neuroprotection of the fetus: a systematic review in 2009 showed that antenatal magnesium sulphate therapy given to women at risk of preterm birth will substantially reduce the risk of cerebral palsy (CP) in their child [RR 0.68; 95% CI 0.54 to 0.87]. It will also reduce risk of gross motor dysfunction [RR 0.61; 95% CI 0.44 to 0.85]. There is an accompanying reduction in the incidence of IVH.

$MgSO_4$ acts as a non-competitive inhibitor at N-methyl-D-aspartate channels which blocks excess release of glutamate, reduces excitotoxicity and prevents pre-OL cell death. It also limits release of inflammatory cytokines and stabilizes cerebral perfusion.

Whilst important, the overall effects are small. The number needed to treat (NNT) to prevent one case of CP is reported to be 63. NICE guidelines recommend use of $MgSO_4$ for preterm labour <30 weeks and for it to be considered <34 weeks. A 4 g intravenous bolus of $MgSO_4$ over 15 minutes, followed by an intravenous infusion of 1 g per hour until the birth or for 24 hours is recommended.

Unfortunately uptake of this practice is patchy in spite of excellent evidence supporting it. The NNAP estimates an uptake of 43% across UK. A quality improvement (QI) project 'Preventing cerebral palsy in preterm labour' (PReCePT) carried out in West of England raised uptake from 21% to 88% over 2 years. Establishing clinical champions and increasing awareness via training of staff within a QI framework will be an effective strategy to improve use of antenatal $MgSO_4$ in eligible pregnancies.

Perinatal networks ensuring delivery at specialist centres: in babies born <33 weeks gestation outcomes are better if they are delivered in hospitals with high output tertiary neonatal intensive care units (NICU). In a study undertaken in UK reductions were noted in neonatal mortality OR 0.70, 95% CI (0.53–0.92) and any in-hospital mortality OR 0.68, 95% CI (0.54–0.85). The effect of volume on any in-hospital mortality was most acute among infants born at <27 weeks gestation OR 0.51, 95% CI (0.33–0.79). IVH is the main morbidity that is reduced when need for early postnatal transfers are reduced. Outcomes also improve when structured quality improvement (QI) methods are employed in the NICU as long as a critical level of activity to maintain skills exists.

The British Association Of Perinatal Medicine (BAPM) recommends that if booked at a smaller centre it might be best to consider antenatal transfer of women with symptoms of preterm labour and one or more of the following: cervical length <15 mm, positive fetal fibronectin, history of preterm delivery or preterm prolonged rupture of membranes. Therefore access to a 24-hour perinatal transfer service is beneficial.

Prevention of chorioamnionitis and early onset sepsis (EOS): chorioamnionitis and EOS occurring within 72 hours of delivery are linked to adverse neurodevelopmental outcomes. Recent observational studies confirm that EOS is associated with a significant increased risk of cerebral palsy [OR 1.7 95% CI (0.84–3.45)].

Chorioamnionitis refers to inflammation of placental tissue either of choriodecidual space (maternal) or chorioamniotic space (mainly fetal) and is a major cause of preterm birth. Clinically the diagnosis is made based on symptoms and signs e.g. maternal pyrexia (>37.5 °C), maternal tachycardia, fetal tachycardia (>160 bpm), uterine tenderness, abnormal vaginal discharge, with supporting investigations e.g. raised WBC count (14,000 cells/mm^3), increased CRP.

Histopathologic confirmation is based on the Redline and colleagues criteria and involves varying stages of umbilical vasculitis. This is believed to be injurious to the fetal brain as it results in reduced blood flow to the brain and microbial toxins and inflammatory cytokines can pass through an immature blood brain barrier. Effective treatment is important to reduce risk of both neonatal and maternal mortality and morbidity. For confirmed cases chorioamnionitis immediate delivery is recommended.

Preterm premature rupture of membranes (PPROM): once a diagnosis of preterm premature rupture of membranes (PPROM) is made women are offered oral erythromycin for a maximum of 10 days to reduce the risk of developing chorioamnionitis. Delivery should be considered for PPROM after 34 weeks gestation.

However, caution must be exercised. In cases of preterm labour without rupture of membranes, increased levels of functional impairment have been seen in children of mothers who received antibiotics. Confirmed Group B streptococcus (GBS) colonization in mother is an exception to this and they require intrapartum antibiotic prophylaxis. Routine GBS screening is currently not undertaken in the UK. A GBS vaccine is in development.

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