Neuroprotection of the preterm infant

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Abstract

The past 30 years has seen an increase in the survival of extremely preterm infants, however, lifelong neurodisability remains a significant problem for this population. No single intervention can prevent preterm brain injury, given the complex interaction between pathological processes, developmental trajectory, genetic susceptibility and environmental influences. However, a number of interventions, both antenatal and postnatal, have been shown to improve neurodevelopmental outcome. These include the antenatal administration of steroids and magnesium sulphate, delayed cord clamping, prevention and treatment of chorioamnionitis, stabilisation of the cerebral circulation, caffeine and optimising nutrition. Applying this evidence in daily practice offers the best chance of improving outcomes in this vulnerable population.

Keywords brain injuries; infant newborn; infant, premature; neuroprotection; neonatology

Introduction

Preterm infants are at an increased risk of developing neurological sequelae as they are exposed to stresses in extra-uterine life at a time of critical brain development and maturation. In the late second and third trimester of pregnancy, white and grey matter volume increase dramatically and the cortex folds into complex gyri as neural and glial cells proliferate, differentiate and migrate. Consequently, cystic and non-cystic white matter injury is the most common form of brain injury in preterm infants and is associated with the development of cerebral palsy, epilepsy, cognitive disability, and visual impairments later on in life. In this paper we present some of the evidence of practice, which has been shown to improve neurodevelopmental outcome.

Antenatal interventions

In-utero transfers

The EPICure 2 study has shown that mortality rates for extremely preterm infants born in centres that offer higher levels of intensive care are reduced when compared to those born in less specialist centres (OR 0.73 (95% CI 0.59 to 0.9)). Transporting these infants in the first 48hrs of life increases their risk of developing severe intraventricular haemorrhage (IVH). National and local policies highlight the importance of early transfers for women presenting in preterm labour to ensure that the optimal obstetric and neonatal care is received.

Antenatal steroids

Ever since their discovery by Liggins and Howie in the 1970s, antenatal steroids have revolutionised perinatal care and improved preterm survival rates. A single course of betamethasone or dexamethasone is recommended to all women presenting in preterm labour before 35 weeks gestation. In a recent meta-analysis of 21 studies, antenatal steroids were shown to reducing the rates of IVH [relative risk (RR) 0.54; 95% confidence interval (CI) 0.43−0.69], severe IVH (RR 0.28; 95% CI 0.16−0.50) and white matter damage. They protect the preterm brain with their anti-inflammatory effect, cause vasoconstriction of cerebral vessels and provide increased cardiovascular stability by reducing respiratory morbidity.

Magnesium sulphate

A meta-analysis performed in 2017 identified five clinical trials in which women at risk of preterm birth (<37 weeks' gestation) were randomised into receiving magnesium sulphate (MgSO4) or control with subsequent neurological sequelae for the baby reported as primary outcomes. Whilst there was no significant difference in mortality rates among trials, there was a significant reduction in the rates of both moderate and severe cerebral palsy combined (event rates 2.12% $MgSO_4$, 3.36% controls; RR 0.63, 95% CI 0.44 to 0.90) and severe cerebral palsy alone (event rates 0.81% $MgSO_4$, 1.50% controls; RR 0.54, 95% CI 0.30 to 0.94). In its neuroprotective role, $MgSO_4$ reduces inflammation and the accumulation of free radicals, prevents excitotoxic injury and stabilises blood pressure and cerebral arterial perfusion. In the UK, it is currently given to women with threatened preterm labour at <30 weeks' gestation as a 4 g loading dose over 20−30 min followed by an infusion of 1g/hour until birth for a maximum of 24 hrs. Despite the evidence of benefit, the implementation has not been universal, possibly because the ideal dose and the gestational age at which therapy is beneficial remain controversial.

Reducing chorioamnionitis and early-onset infections

Chorioamnionitis and infections within the first 72 hrs of life are associated with white matter injury and adverse neurological outcomes in preterm infants. Fetal brain injury due to infection occurs as a result of the release of cytokines, free radicals and glutamate that can easily penetrate the immature blood-brain-barrier into the cerebral tissue. Changes in the vasculature of the fetal brain, including hypoperfusion and capillary thrombosis, and an increase in white blood cell and neutrophil counts, also play a role in the fetal inflammatory response syndrome (FIRS). Current guidelines for the prevention of chorioamnionitis and early-onset infection in the newborn recommend the use of intra-partum prophylactic antibiotics and consideration of immediate delivery after 34 weeks gestation in cases of preterm prelabour rupture of membranes (PPROM). Prophylactic antibiotic use following PPROM is associated with prolongation of pregnancy and a significant reduction in both IVH (RR 0.67; 95%

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CI 0.49–0.91) and abnormal cranial ultrasound scans prior to discharge (RR 0.81; 95% CI 0.68–0.98). Early delivery in cases of PPROM remains a debated topic in view of the increased morbidity and mortality associated with preterm birth.

Postnatal interventions

Delayed cord clamping

In 1988, a randomised study by Hofmeyr et al. showed that the rate of preterm brain haemorrhage was 35% in cases where the umbilical cord was clamped one minute after birth compared to 77% when it was clamped immediately; motor function at 18–22 months has also been found to be improved following delayed cord clamping (DCC). DCC is hypothesised to increase the circulating blood volume thus avoiding the risk of cerebral hypoperfusion and improving oxygen delivery to the brain. It is also believed to lead to an increase in the concentration of coagulation factors and in the number of stem and progenitor cells essential in tissue repair and immunocompetence. Current recommendations by the Resuscitation Council (UK) is to delay clamping by at least one minute from the complete delivery of all infants unless the baby is severely compromised and requires immediate resuscitation. The associated risks of delayed resuscitation, volume overload, polycythaemia and hyperbilirubinemia continue to cause hesitation for this practice amongst clinicians.

Caffeine

Caffeine, widely used in preterm infants to treat apnoea of prematurity, is a methylxanthine and a non-selective adenosine antagonist. It has been shown to enhance oligodendroglial maturation and reduce ventriculomegaly in neonatal models of diffuse white matter injury. In the Caffeine for Apnoea of Prematurity (CAP) trial, the use of caffeine was associated with reduced rates of bronchopulmonary dysplasia and patent ductus arteriosus, both of which cause cardiovascular instability and are associated with poor neurodevelopmental outcomes. Infants who received caffeine had significantly lower rates of cerebral palsy (4.4 vs. 7.3%) and cognitive delay (33.8 vs. 38.3%) than the control group at 18–21 months of age. This was sustained at the age of 5 years and with better scores in coordination and visual perception. However, there was no difference in the primary outcome of death or disability at 5 years of age between the two groups. Further studies are being undertaken to determine the optimum time to start caffeine and the ideal dose to be used in preterm infants, as current practices vary.

Cerebral vascular regulation and co-morbidities

Due to the immature cerebral vasculature, blood flow in preterm cerebral white matter is low and blood vessels have reduced vasoreactive properties when compared to other regions in the brain. Changes in cerebral perfusion pressure, oxygen, carbon dioxide and metabolites can result in extensive brain injury. Common conditions such as systemic hypotension, patent ductus arteriosus (PDA), respiratory distress syndrome, hypocarbia and sepsis can disturb cerebral autoregulation and lead to a worse neurodevelopmental outcome. Assessment of cerebral autoregulation, however, is not routinely undertaken outside of a research setting. Ventilation strategies, such as volume-targeted ventilation, minimise inadvertent hypocarbia. Clinical trials investigating the efficacy of indomethacin in management of the PDA, demonstrated a reduction in the incidence of severe IVH, however, the studies were not powered to see if this effect improved neurodevelopmental outcome. Although some centres use prophylactic indomethacin for neuroprotection, its use in the UK is limited by lack of availability of the drug.

Nutrition

Early nutrition and the optimisation of protein and energy intake in the neonatal period is well known to have a positive impact on postnatal head growth and neurodevelopmental outcomes in preterm infants. Research to determine the optimal nutritional regime and vitamin and mineral supplementation for preterm infants is ongoing, and includes evaluation of the roles of long-chain polyunsaturated fatty acids (LCPUFA), vitamin A, iron, and iodine in improving neurodevelopmental outcomes.

Conclusion

Following an increase in the survival rates of extremely preterm infants, there has been a growing interest in the discovery of novel neuroprotective strategies. Ongoing research studies on the use of melatonin, erythropoietin, oestradiol, progesterone, nutritional supplements and stem cell therapy have all shown promising results in the initial stages of development. Raising awareness of the current available strategies is key to reducing the burden of neurological impairment in this vulnerable population of infants. ◆

FURTHER READING

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