New strategies to protect the newborn brain

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Acute asphyxia at the time of birth remains a principal cause of perinatal death or long-term disability. In high-resource countries, perinatal asphyxia affects about 3-5 per 1000 term infants, while worldwide, birth asphyxia accounts for nearly one in four of all neonatal deaths. Birth asphyxia is the primary antecedent to hypoxic ischemic encephalopathy (HIE) and the consequences of HIE are significant; between 10% and 60% of babies with moderate to severe HIE will die in the neonatal period and, of surviving infants, at least one in four will have long-term adverse neurodevelopmental sequelae.

Currently, the only proven therapy for babies with HIE is to perform cooling in the immediate newborn period. Meta-analysis finds that hypothermia significantly reduces death or major disability at 18 months and in well-resourced settings hypothermia has been adopted as standard neuroprotective therapy. However hypothermia must begin with 6 h after birth to be effective and even so, almost half of asphyxiated infants treated with hypothermia still either die or suffer significant disability. There is currently a variety of compounds undergoing pre-clinical or clinical testing, either stand-alone or adjuvant to hypothermia. These compounds address multiple and overlapping aspects of the evolution of brain injury, such as cerebral excitotoxicity, oxidative stress and/or inflammation.

In recent years our group has been investigating new neuroprotective therapies that could be initiated after birth asphyxia. Caesarean-section is undertaken in pregnant sheep at ~141 days gestation and with the ewe under general anaesthetic, severe birth asphyxia is induced in lambs by occluding the umbilical cord while the lamb remains *in utero*. After birth asphyxia, lambs are delivered, resuscitated and cared-for in an intensive-care setting over a period of 72 h. In asphyxic and control lambs we continuously collect physiological data, clinical outcomes and injury biomarkers in addition to cerebral magnetic resonance imaging (MRI) and spectroscopy (MRS) at 12 and 72 h. Lambs are euthanized at 72 h and brains collected for histopathology. We have collected data for two strategies that have received much attention with respect to their neuroprotective potential. In a subset of asphyxiated lambs, we have collected umbilical cord blood at the time of birth. Cord blood stem cells are isolated and labeled with iron oxide and a fluorescent tag, and autologous cord blood stem cells are re-administered to asphyxiated lambs at 12 h after birth. To date, we find that asphyxiated lambs administered stem cells show early signs of encephalopathy and brain injury prior to stem cells, but outcomes are improved at 72 h. In a further subset of lambs, we have administered the antioxidant melatonin soon after birth asphyxia, with the first i.v. administration of melatonin 30 min after birth, then further melatonin every 2 h for 24 h. We find that melatonin is effective in reducing oxidative stress and reducing cell death within the brain following birth asphyxia.

Our data have implications for asphyxiated neonates in both high- and low-resource settings. Melatonin could be an effective and cheap antioxidant therapy for perinatal use in low-resource settings to reduce the severity and incidence of newborn encephalopathy. Whilst our cord blood stem cell data remain preliminary, they support the idea that collection and use of cord blood stem cells for re-administration after birth asphyxia may reduce the progression of brain injury.