Cooling the Preterm Brain

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There is now strong clinical and experimental evidence that prolonged, moderate cerebral hypothermia initiated within a few hours after severe hypoxia-ischaemia and continued until resolution of the acute phase of delayed cell death can reduce subsequent neuronal loss and improve behavioral recovery (1-8). However, these studies have focused on neuroprotection for term infants and in adults. Preterm infants have a very high burden of neurological injury and subsequent neurodevelopmental handicap including overt cerebral palsy and cognitive and learning deficits. Although the etiology of brain injury in premature infants is complex and multifactorial, there is considerable evidence linking injury with exposure to hypoxia and cerebral ischemia, particularly at birth and in the first few days of life. Indeed, larger premature infants, from 31 to 36 gestation, with metabolic acidosis on umbilical cord blood samples have a high rate of clinical encephalopathy and subsequent basal ganglia damage, and thus, may be candidates for experimental neuroprotective treatments (9).

Nevertheless, direct translation of therapeutic to the preterm infant is problematic because of their greater potential susceptibility to the adverse effects of hypothermia. Historical data suggests that mild hypothermia was associated with increased mortality in preterm newborns (<1500g) (10-12). It is unknown whether this would be the case with modern intensive care, however, there are theoretical concerns that hypothermia might for example promote hypotension, increase oxygen consumption, decrease surfactant production, increase pulmonary vascular resistance, promote free fatty acid release and so increase the risk of jaundice, or reduce resistance to infection. Moreover, the characteristic pattern of injury differs in preterm infants compared with term, with a much higher rate of selective damage to the periventricular white matter (periventricular leucomalacia, PVL), with loss of immature, premelaninating oligodendrocytes.

Recent preclinical studies have confirmed that severe hypoxic-ischemic injury in preterm fetal sheep induced by umbilical cord occlusion is associated with progressive, delayed loss of mitochondrial function (13), and is associated with characteristic pattern of damage to subcortical regions and periventricular white matter. In this paradigm, moderate (extradural temperature 30 to 34°C) cerebral hypothermia started 90 minutes after umbilical cord occlusion, and continued for three days, is associated with markedly reduced loss of neurons and immature oligodendrocytes (14). Despite this improvement, the number of proliferating cells in the periventricular region remained suppressed in both occlusion groups; further studies are in progress to evaluate whether proliferation recovers in the long-term. Functionally, carotid blood flow was significantly greater in the hypothermia-occlusion group than in the normothermia-occlusion group, and EEG frequency, although not amplitude, was significantly improved to sham control levels. Further, head cooling was associated with selective protection of particular phenotypic striatal projection neurons including a significant reduction in loss of calbindin-28 kd- and neuronal nitric oxide synthase-, but not glutamic acid decarboxylase-, immunopositive neurons (15). No adverse effects were seen for arterial blood pressure, cardiac stability or endocrine responses after asphyxia (14, 16, 17).
These studies suggest that hypothermia has potential to reduce risk of cerebral palsy, provided that safety issues can be resolved. An important aspect of this will be to develop strategies to target treatment only to children who are likely to benefit. The increasing data that refinements in continuous EEG monitoring may allow such targeted treatment will be highlighted (18).

References:


