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Mini Review

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# Essential expectations-avoiding hypocapnia and hyperoxemia in neonatal encephalopathy

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## Mini review

Therapeutic hypothermia (TH) is the accepted treatment modality for newborns with moderate to severe neonatal encephalopathy likely originating from a hypoxic-ischemic event. Numerous randomized, controlled trials and meta-analyses have shown that TH reduces that the risk of death or major neurodevelopmental disability by 25-35% among treated infants.[1,2] Lung injury, with or without effective respiratory control, is present in as many as 80% of infants with moderate-to-severe neonatal encephalopathy who meet the inclusion criteria for TH.[3] Although these encephalopathic newborns often require oxygen supplementation or ventilatory support to provide adequate gas exchange, their rapidly changing pulmonary mechanics and respiratory drive makes achieving and maintaining eucapnia and normoxemia clinically challenging. Accumulating evidence from clinical trials illustrates the importance of controlling the partial pressures of carbon dioxide (PCO2) and oxygen (PO2) in order to maximize neurodevelopmental outcomes and ameliorate secondary brain injury resulting from over ventilation and oxygenation. Carbon dioxide regulates cerebrovascular tone by inducing vasodilation and augmenting perfusion at high levels (hypercapnic) and vasoconstriction and diminishing perfusion during low levels (hypocapnic). Knowing that hypocapnia-mediated vasoconstriction is maintained in hypoxic-ischemic encephalopathy raises concerns that low PCO2 may accentuate secondary brain injury, not only by reducing cerebral perfusion, but by reducing O2 delivery, increasing neuronal energy demands and DNA fragmentation, and depleting neuronal energy stores.[4–7] Indeed newborn animal models demonstrate that hypocapnia reduces cerebral blood flow following asphyxia and is associated with greater brain injury than observed in either eucapnic or hypercapnic animals.[8,9] More severe brain injury, detected on MRI, has also been identified in infants with suboptimal cerebral vasoreactivity determined by near-infrared spectroscopy.[10] Several clinical series reveal that hypocapnia is correlated with adverse neuro developmental outcomes in infants with hypoxic-ischemic encephalopathy (HIE). In a retrospective cohort study of infants with HIE prior to the use of TH, Klinger et al found that severe hypocapnia (PCO2<20 mmHg) was associated with increased risk of death or severe neurologic impairment (relative risk 2.3).[11] Analysis of data from the NICHD Research Network whole body cooling trial found both minimum and cumulative PCO2<35 mmHg were associated with poor neurodevelopment outcome.[12] More recently, post hoc analysis of the CoolCap Study data estimated the probability of poor outcome based upon PCO2, finding an inverse correlation between the lowest PCO2 and the severity of neurologic outcome after controlling for pH, aEEG pattern, birth weight, cooling status, and Sarnat score.[13]

Although hypocapnia in neonatal encephalopathy may be a surrogate marker for brain injury severity, PCO2 represents a readily modifiable factor capable of maximizing neurologic recovery. As many infants undergoing TH are intubated for apnea, frequent blood gas monitoring and/or transcutaneous or end-tidal CO2 monitoring are essential. As respiratory drive returns, many infants become tachypneic and hypocapnic. At a minimum, clinicians should minimize ventilator settings and foster rapid extubation in an attempt to not inadvertently lower PCO2. For persistent hypocapnia, both sedation and the introduction of dead space into the ventilator circuitry may restore PCO2 to "normal" levels. To date, however, neither strategy has been studied, rendering the safety and effectiveness for improving neurologic outcomes speculative.

In contrast to CO2, high partial pressures of oxygen are injurious yet frequently life-sustaining. Even a brief period of hyperoxia/hyperoxemia following a hypoxic insult promotes lipid peroxidation, enhances expression of inflammatory genes, and stimulates apoptosis in the CNS of newborn animals.[14–16] In the pre-cooling era, one study reported that severe hyeroxemia (PaO2>200 mmHg) was associated with increased odds of adverse outcome (OR 3.85) in newborns with intrapartum asphyxia.[11] A similar association was found in infants qualifying for TH, such that a PaO2>100 mmHg within the first hour of life corresponded to a 4-fold increased risk of HIE and a more than 2-fold greater incidence of hypoxic injury on MRI among those with moderate-severe HIE.[17] Likewise, high fractional inspired O2 concentrations within the first few hours of life, often prior to attainment of blood gases, is also associated with increased risk of adverse outcome.[18] Hence PO2, like PCO2, warrants close monitoring to maintain partial pressures at appropriate levels.

Thankfully regulating PO2 is relatively easily achieved clinically. Continuous oximetry on the right hand (pre-ductal) beginning immediately following delivery is a standard component of neonatal resuscitation. Blended oxygen should be available and resuscitation initiated with room air. Once stabilized, maintaining pre-ductal oxygen saturations between 90-97% should neither heighten the risk of developing pulmonary hypertension nor increase the degree of secondary injury attributable to oxidative stress.[19] Experience would suggest that monitoring both pre- and post-ductal saturations in these infants is wise.

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With the advent of TH, clinicians caring for infants with neonatal encephalopathy were afforded the first effective therapy capable of reducing the secondary injury from a presumed hypoxic-ischemic insult. During the recovery phase, evolving changes in respiratory control and pulmonary mechanics represent an additional opportunity for clinical intervention aimed at maximizing recovery. Maintenance of eucapnia and normoxemia, therefore, should be envisioned as "essential expectations" in the care of these infants. These simple goals are achievable with appropriate monitoring, attention to detail, and individualized respiratory support.

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## Conflicts of interest

Author declares there are no conflicts of interest.

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