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Cerebral regional oxygen saturation trends in infants with hypoxic-ischemic encephalopathy

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ABSTRACT

Background: Neurological outcomes in neonatal hypoxic-ischemic encephalopathy (HIE) continue to be suboptimal despite therapeutic hypothermia (TH). Cerebral near-infrared spectroscopy provides real-time regional oxygen saturation ($CrSO_2$) that may be a marker of adverse MRI findings and neurodevelopmental outcomes.
Aim: The aim of this study was to examine the value of $CrSO_2$ monitoring in infants with HIE undergoing TH.
Study design and subjects: In this prospective study, $CrSO_2$ was continuously recorded in 21 infants with HIE admitted for TH.
Outcome measures: Brain MRI signal abnormalities at 2 weeks were scored in individual brain region and classified as none/mild, moderate and severe. 13 infants completed Bayley Scales of Infant Development (BSID) testing at 18–24 months.
Results: Between 24 and 36 h of life, there was a significant increase in odds of having moderate-severe brain MRI abnormalities with higher absolute $CrSO_2$ values. Per 10% increase in absolute $CrSO_2$, the odds ratio for moderate-severe brain MRI abnormalities was greatest at 30 h (OR 3.78; confidence intervals (CI): 1.23–11.6, $p = 0.011$). $CrSO_2$ increased more rapidly in infants with greater injury seen on MRI (0.20/h for MRI scores 0/1, by 0.48/h for MRI score 2, and by 0.68/h for MRI score 3, $p = 0.05$). At 30 h, absolute $CrSO_2$ correlated significantly with abnormal MRI findings in basal ganglia (92% vs. 78%, $p = 0.001$), white matter (88% vs. 76%, $p = 0.01$), posterior limb of internal capsule (92% vs. 78%, $p = 0.001$), and brain stem (94% vs. 80%, $p = 0.03$) but not with cortical injury (86% vs. 80%, $p = 0.17$). Higher $CrSO_2$ beyond 24 h correlated with greater odds of worse BSID scores.
Conclusions: Increasing $CrSO_2$ is associated with moderate-severe brain injury as assessed by MRI. Higher absolute CrSO2 values during TH correlates with subcortical injury on MRI and poor neurodevelopmental outcomes in infants with HIE undergoing TH. $CrSO_2$ can inform providers seeking early identification of patients at risk of worse injury who may benefit from further intervention.

1. Introduction

Therapeutic hypothermia (TH), now standard of care in neonatal hypoxic-ischemic encephalopathy (HIE), is currently offered within 6 h of birth [1]. It is unclear how far beyond the initial 6 h the window of benefit from initiation of TH extends [2,3]. In cases where the infant is remote from a hospital equipped to provide TH or identification of encephalopathy occurs late, secondary cerebral injury may be ongoing and the newborn may benefit from TH or emerging adjuvant neuroprotective strategies [4,5] even beyond the conventional window of 6 h after birth. A real-time continuous measurement of cerebral oxygenation could help identify such infants.

Near-infrared spectroscopy (NIRS) measures regional perfusion and oxygenation to provide a cerebral regional oxygen saturation ($CrSO_2$) reading. Brain metabolism, cerebral blood flow, and systemic oxygenation affect $CrSO_2$ [6,7]. Reduction in brain metabolism leads to a

Abbreviations: HIE, Hypoxic-ischemic encephalopathy; NIRS, Near-infrared spectroscopy; TH, Therapeutic hypothermia; BSID, Bayley Scales of Infant Development; $CrSO_2$, Cerebral regional oxygen saturation; OR, Odds ratio; FTOE, Fractional tissue oxygen extraction

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decrease in oxygen extraction and increases $CrSO_2$ [6,7]. If systemic oxygenation and hemoglobin are relatively stable, fluctuations in $CrSO_2$ are likely due to changes in brain perfusion or oxygen extraction [8,9]. In either scenario, a high $CrSO_2$ would indicate cerebral blood flow in excess of need for cerebral metabolism (luxury perfusion). TH is believed to ameliorate reperfusion injury through its effect on cerebral metabolism [10], and thus would be expected to stabilize or decrease $CrSO_2$. High $CrSO_2$ in infants during hypothermia is associated with poor outcomes [7,11] and may suggest presence of luxury perfusion. Thus, changes in $CrSO_2$ could be informative regarding the emerging balance of perfusion and neuronal injury. A rising $CrSO_2$ would indicate worsening injury or increasing reperfusion.

The aim of this study was to examine the value of continuous monitoring of $CrSO_2$ in infants with HIE undergoing TH. We hypothesized that rising $CrSO_2$ in infants with HIE during TH suggests presence of luxury perfusion and correlates with worse cerebral injury seen on MRI and with poor neurodevelopmental outcomes.

2. Methods

Between July 2011 and December 2012, infants > 36 weeks gestational age with moderate to severe encephalopathy undergoing therapeutic hypothermia for 72 h according to the institutional protocol at were prospectively considered for enrollment upon clincal decision for TH. The Vanderbilt University Institutional Review Board approved the protocol and written informed consent was obtained from the parents/legal guardians. Institutional criteria for TH are: > 36 weeks gestational age with moderate to severe encephalopathy and at least one of the following: Apgar score < 5 or continued need for resuscitation at 10 min after birth, or acidosis defined as either umbilical cord pH or any arterial pH < 7.0, or a base deficit > 16 mmol/L (or base excess < − 16 mmol/L) within 60 min of birth (arterial or venous blood). Exclusion criteria were prenatally diagnosed syndrome and metabolic disorder incompatible with survival.

Once TH was initiated, a single infant/neonatal NIRS sensor (5100 INVOS™ system, Covidien/Medtronic, U.S., FDA approved) was applied to the mid-frontal region for 48 h. The sensor was applied over a transparent mesh non-stick wound dressing (Mepitel®, Mölnlycke, Sweden) [12] and then connected to a Vital Sync™ monitor (Covidien/Medtronic, U.S.), a device which assimilates physiologic data from multiple bedside monitors. Every day, the sensor was briefly lifted for inspection of skin integrity as per NICU protocol.

$CrSO_2$ was measured every 30 s for until 54 h after birth to allow for a minimum of 48 h of monitoring during TH. Hourly mean of absolute $CrSO_2$ values was calculated and hereafter any mention of $CrSO_2$ refers to the mean of hourly absolute values. Change in absolute $CrSO_2$ over time provided the rate of rise of $CrSO_2$.

HIE was clinically graded based on neurologic exam as Sarnat stage 1,2, or 3 [13,14] upon admission to the NICU. Due to a change in the institutional hypothermia protocol, the first seven infants received head cooling with a cooling cap (Cool-Cap®, Olympic/Natus, U.S., FDA approved) while the remaining patients received whole body cooling.

Brain MRI scans were done in the second week of life. T1 and T2 weighted MRI scans were graded by a pediatric neuro-radiologist blinded to the infants clinical presentation at five regions (basal ganglia, posterior limb of the internal capsule, white matter, cortex and brainstem) from 0 to 3 with 0 representing no injury, while 1, 2, 3 described mild, moderate and severe injury respectively [15–18]. Each infant was assigned a score based on the worst grade of injury at any given location on MRI.

Neurodevelopmental outcomes were assessed between 18 and 24 months using Bayley Scales of Infant Development (BSID) (3rd Edition). To ensure compliance, the clinic staff made multiple phone calls and mailed reminders to the families.

2.1. Statistical analysis

Infants were assigned to one of three groups based on the degree of MRI abnormalities: none/mild, moderate, or severe MRI abnormalities. Median and quartiles were calculated for the demographic variables (gestational age, birth weight, Apgar scores, cord pH, neonatal pH, initial lactate levels) and hourly mean of absolute $CrSO_2$ values in the three groups. Differences in demographic variables by MRI severity were tested using Kruskal-Wallis (continuous variables) or Pearson's test (categorical variables). Hourly means of absolute $CrSO_2$ over time by overall injury grade were summarized using spaghetti plots showing individual and group-average trends over time. Proportional odds ordinal regression was used to estimate the odds of having a worse score in each of the domains of Bayley testing with a 10% increase in absolute $CrSO_2$ at hourly intervals. Separate models were fit using each hourly $CrSO_2$ as the predictor, and the odds-ratios (OR) with 95% confidence intervals (CI) were plotted versus time to identify the hour(s) after birth which most strongly correlated with MRI abnormalities. Rate of rise of $CrSO_2$ was also compared among infants with various degrees of MRI injury and BSID outcomes. Secondary analysis was also conducted to determine if $CrSO_2$ correlated with regional MRI injuries. Wilcoxon signed rank tests were used to test for differences in $CrSO_2$ by injury severity (none/mild versus moderate/severe) at each of the five regions.

3. Results

3.1. Patient characteristics (Table 1)

28 infants with HIE admitted for TH were enrolled in the study. NIRS data in the first 48 h and MRI in the second week were available in 21. Two infants died prior to MRI, 3 infants had sub-optimal MRI scans due to excessive motion, and in one infants there was a technical problem with the NIRS machine. Another infant was excluded after developing extensive extra-axial, parenchymal and intraventricular hemorrhages subsequent to maternal trauma prior to labor. Nine of the 21 infants had seizures and received anti-seizure medications, which included phenobarbital, fosphenytoin, levetiracetam and oxcarbamazepine. The NIRS sensor was well tolerated under TH and no adverse events related to continuous monitoring were reported. No significant difference was found between the infants who underwent head cooling

Table 1
Demographic variables by MRI grade of injury. Continuous variables are summarized by the median (25th–75th percentile).

MRI grade of injury	0 or 1	2	3	*p*-value
N	*N* = 8	*N* = 6	*N* = 7	
GA[b] (weeks)	39 (38–40)	40(39–40)	39(39–40)	0.47
Birth weight, Kg	3.1(2.9–3.5)	3.3(3.2–3.3)	3.3(3.2–3.4)	0.83
Apgar at 1 min	2 (1–3)	2(1–2)	1(0–1)	0.039
Apgar at 5 min	4(4–5)	4(3–5)	2(1–3)	0.1
Sarnat stage				
1	6	3	2	0.34[a]
2	2	3	4	
3	0	0	1	
Cord pH	7.0(6.8–7.1)	6.8(6.8–6.9)	7.0(6.7–7.1)	0.62
Neonatal pH	7.2(7.1–7.2)	7.2(7.0–7.2)	7.0(7.0–7.2)	0.88
Initial Lactate	6.9(5.1–8.2)	6.4(5.1–7.2)	13.7(13.6–17.3)	0.21
Ionotrope use	0	1	3	
iNO	0	1	2	
Anti-seizure meds	3	3	3	
Sedatives(morphine/versed)	0	1	1	

Kruskal-Wallis test unless otherwise specified.
[a] Pearson test.
[b] GA – Gestational age.