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# Prognostic Uncertainty During Therapeutic Hypothermia and Hemodynamic Instability- the Link between Vasoactive Therapies and Adverse Outcomes in the Neonatal Intensive Care Unit

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*"Evaluate whether hemodynamic instability, defined as the need for vasoactive support, predicts vital signs, cerebral near-infrared spectroscopy (cNIRS), mechanical ventilator support, biochemical parameters, and neurodiagnostics in neonates with moderate-severe Hypoxic Ischemic Encephalopathy (HIE). "*

**Abstract:**

*BACKGROUND: Evaluate whether hemodynamic instability, defined as the need for vasoactive support, predicts vital signs, cerebral near-infrared spectroscopy (cNIRS), mechanical ventilator support, biochemical parameters, and neurodiagnostics in neonates with moderate-severe Hypoxic Ischemic Encephalopathy (HIE).*

*METHODS: A retrospective cohort study of thirty-four newborns diagnosed with moderate-severe HIE from 2010 to 2013 at a quaternary NICU with neurodevelopmental assessments until 2016. Data points were extracted from electronic medical records and chart review. The dataset was analyzed to compare primary and secondary outcomes between two groups, patients with vasoactive agents (n=18) and without vasoactive agents (n=16). The primary outcome compared primary hemodynamic parameters (heart rate, blood pressures) and cerebral NIRS. Secondary outcomes were differences in mechanical ventilation, laboratory indices, and neurodiagnostics.*

*RESULTS: There were no statistically significant differences between heart rate, blood pressure, or oxygen delivery as measured by cerebral NIRS (6,12, 24, 48, and 72 hours time points after birth) in babies with and without vasoactive support. Neonates with vasoactive requirements during therapeutic hypothermia had higher hypoxemia severity, higher blood lactate, lower albumin, and hemoglobin, and required prolonged ventilation (P=0.027). Additionally, they were 30% more likely to have abnormal background EEG with a low voltage pattern (p <0.05). Moderate or severe brain injury on MRI at 10-12 days was seen in almost 50% of the patients exposed to vasoactive support. Despite these important differences at NICU discharge, neurodevelopmental delays (Bay- ley III scaled and composite scores) at six months were not significantly worse in the newborns exposed to vasoactive medications during cooling.*

*CONCLUSION: It is critical to study the benefits and risks of medical interventions for hemodynamic instability and assess for feedback on whether therapy is meeting the intended goal of appropriate oxygen delivery. Vasoactive medication requirement in neonates with moderate-severe HIE predicts or perhaps contributes to adverse outcomes at NICU discharge. Prognosticating risks for neurocognitive deficits beyond infancy thus remains an important research question in pediatrics.*

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***Keywords**: Hypoxic Ischemic Encephalopathy, primary hemodynamic parameters, therapeutic hypothermia, mechanical ventilation, vasoactive therapies*

*"Critically ill neonates are at risk for irreversible neurocognitive deficits after a sentinel perinatal event in the setting of moderate-severe Hypoxic Ischemic Encephalopathy. Respiratory failure, life-threatening events requiring cardiopulmonary resuscitation, and shock often occur during the early neonatal period."*

**Introduction:**

Critically ill neonates are at risk for irreversible neurocognitive deficits after a sentinel perinatal event in the setting of moderate-severe Hypoxic Ischemic Encephalopathy. Respiratory failure, life-threatening events requiring cardiopulmonary resuscitation, and shock often occur during the early neonatal period. The serious hemodynamic derangements that can occur in a baby with a high level of illness and moderate-severe HIE are systemic hypotension, myocardial dysfunction, and shock (1-4). In current neonatal critical care practice, there is heterogeneity in the management of early hemodynamic instability, and vasoconstrictors are commonly utilized despite evidence of a paradoxical reduction in

| Time In hours | Blood gas | No Vasoactives group | | | | Vasoactives group | | | | P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Mean (SD)** | **Min** | **Med** | **Max** | **Mean (SD)** | **Min** | **Med** | **Max** | |
| 6 | Mean pH | 7.23 (0.13) | 6.89 | 7.25 | 7.41 | 7.17(0.13) | 6.85 | 7.19 | 7.33 | 0.251 |
| | Min pH | 7.23(0.14) | 6.88 | 7.25 | 7.41 | 7.14(0.19) | 6.61 | 7.19 | 7.33 | 0.205 |
| | Mean pCO2 | 41.34(20.33) | 19.10 | 36.70 | 91.90 | 35.58(14.71) | 13.40 | 36.70 | 63.00 | 0.416 |
| | Min pCO2 | 40.48 (20.57) | 19.10 | 33.10 | 91.90 | 34.11(15.17) | 9.00 | 34.20 | 63.00 | 0.377 |
| 12 | Mean pH | 7.15(0.19) | 7.00 | 7.02 | 7.46 | 7.20(0.12) | 7.00 | 7.19 | 7.35 | 0.426 |
| | Min pH | 7.14(0.19) | 7.00 | 7.00 | 7.46 | 7.18(0.14) | 7.00 | 7.18 | 7.35 | 0.502 |
| | Mean pCO2 | 36.05(7.53) | 24.00 | 35.95 | 52.40 | 41.72(14.69) | 19.00 | 42.03 | 78.70 | 0.189 |
| | Min pCO2 | 34.39(8.88) | 19.00 | 35.20 | 52.40 | 38.83(13.61) | 17.90 | 38.50 | 78.70 | 0.306 |
| 24 | Mean pH | 7.19(0.14) | 7.00 | 7.19 | 7.42 | 7.22(0.10) | 7.00 | 7.22 | 7.41 | 0.544 |
| | Min pH | 7.10(0.16) | 7.00 | 7.00 | 7.41 | 7.11(0.14) | 7.00 | 7.00 | 7.39 | 0.767 |
| | Mean pCO2 | 34.10(7.69) | 22.70 | 32.30 | 50.67 | 41.87(10.03) | 26.88 | 38.70 | 56.75 | 0.032 |
| | Min pCO2 | 31.78(6.16) | 22.00 | 29.00 | 44.10 | 38.06(8.5) | 24.20 | 36.70 | 55.00 | 0.036 |
| 48 | Mean pH | 7.24(0.14) | 7.00 | 7.23 | 7.54 | 7.19(0.11) | 7.00 | 7.19 | 7.42 | 0.234 |
| | Min pH | 7.10(0.2) | 7.00 | 7.00 | 7.54 | 7.02(0.06) | 7.00 | 7.00 | 7.26 | 0.151 |
| | Mean pCO2 | 36.82(6.46) | 23.70 | 37.88 | 48.70 | 40.25(7.51) | 24.57 | 41.55 | 51.03 | 0.211 |
| | Min pCO2 | 33.15(7.68) | 21.20 | 33.20 | 48.40 | 34.77(8.25) | 16.00 | 34.40 | 50.00 | 0.597 |
| 72 | Mean pH | 7.17(0.19) | 7.00 | 7.13 | 7.47 | 7.27(0.13) | 7.06 | 7.30 | 7.47 | 0.122 |
| | Min pH | 7.11(0.19) | 7.00 | 7.00 | 7.47 | 7.11(0.18) | 7.00 | 7.00 | 7.45 | 0.971 |
| | Mean pCO2 | 42.11(8.45) | 30.80 | 40.00 | 55.80 | 40.38(5.97) | 34.03 | 38.18 | 54.43 | 0.556 |
| | Min pCO2 | 39.75(6.34) | 29.40 | 39.00 | 49.00 | 36.91(7.64) | 20.70 | 36.00 | 51.70 | 0.330 |

*Table 1. Mean and minimum blood gas pH and $pCO_2$ mm Hg mm(mmHg)*

cardiac output.

In addition to immediate injury, HIE can be associated with impaired oxygen delivery, systemic hypotension, and cerebral ischemia followed by reperfusion injury to the brain. Cerebral ischemia has been linked to adverse perinatal events and impaired cerebrovascular autoregulation in neonates (4, 5). However, it is complicated to estimate the fluctuations of cerebral blood flow that occur during the acute stages of shock, hemodynamic instability, and respiratory illness (6-9). We investigated whether predictive factors were hidden within the large amount of data generated, concomitantly with the variable medical therapies utilized for infants with HIE in the first seventy-two hours after birth. Our primary hypothesis was that cerebral NIRS and hemodynamic parameters would predict brain injury. The study's secondary outcome was that babies receiving vasoactive infusions during cooling would have more adverse outcomes either correlating or perhaps exacerbated by treatment.

| Time Point | Variable | All (N = 34) | | No Vasoactives | | Vasoactives | | P Value |
|---|---|---|---|---|---|---|---|---|
| | | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | |
| 0-24 hours | Platelet Count (*$10^9$/L) | 34 | 176.06 (70.00) | 16 | 213.22 (69.36) | 18 | 143.04 (53.04) | 0.0022 |
| | Lactic Acid (mmol/L) | 30 | 7.37 (4.40) | 14 | 5.78 (3.94) | 16 | 8.77 (4.41) | 0.0622 |
| | Albumin (g/dL) | 34 | 2.35 (0.46) | 16 | 2.60 (0.38) | 18 | 2.13 (0.42) | 0.0017 |
| | Hemoglobin (g/dL) | 34 | 15.25 (2.83) | 16 | 16.68 (2.00) | 18 | 13.98 (2.89) | 0.0037 |
| | Troponin (ng/ml) | 33 | 1.50 (3.48) | 15 | 1.20 (3.84) | 18 | 1.75 (3.24) | 0.6551 |
| | Sodium (mEq/L) | 34 | 135.37 (3.26) | 16 | 134.78 (2.86) | 18 | 135.89 (3.58) | 0.3308 |
| | Glucose (mg/dL) | 34 | 131.93 (62.49) | 16 | 118.04 (45.41) | 18 | 144.27 (73.62) | 0.2273 |
| | ANC # (manual) | 32 | 11540.28 (5613.90) | 15 | 14062.30 (5522.37) | 17 | 9314.96 (4811.75) | 0.0143 |
| | Creatinine (mg/dL) | 34 | 1.18 (0.44) | 16 | 1.18 (0.57) | 18 | 1.18 (0.29) | 0.9972 |
| | Calcium (mg/dL) | 34 | 8.57 (0.62) | 16 | 8.74 (0.66) | 18 | 8.42 (0.55) | 0.1287 |
| | Prothrombin time (sec) | 21 | 21.01 (10.73) | 8 | 16.52 (3.51) | 13 | 23.77 (12.77) | 0.0727 |
| 24-48 hours | Platelet Count | 29 | 151.08 (55.70) | 13 | 164.12 (70.33) | 16 | 140.49 (39.60) | 0.2943 |
| | Lactic Acid | 27 | 3.88 (3.11) | 10 | 2.34 (1.27) | 17 | 4.79 (3.53) | 0.0164 |
| | Albumin | 26 | 2.18 (0.41) | 10 | 2.48 (0.47) | 16 | 1.99 (0.23) | 0.0107 |
| | Hemoglobin | 29 | 15.89 (2.44) | 13 | 17.34 (2.30) | 16 | 14.71 (1.89) | 0.0022 |
| | Troponin | 7 | 1.04 (1.92) | 2 | 0.08 (0.11) | 5 | 1.42 (2.21) | 0.4554 |
| | Sodium | 29 | 135.52 (5.44) | 14 | 136.26 (4.83) | 15 | 134.83 (6.04) | 0.4897 |
| | Glucose | 32 | 89.32 (25.42) | 15 | 93.32 (22.73) | 17 | 85.79 (27.77) | 0.412 |
| | ANC # (manual) | 25 | 10291.75 (6147.53) | 10 | 13137.45 (5837.85) | 15 | 8394.62 (5765.16) | 0.0568 |
| | Creatinine | 32 | 1.20 (0.73) | 15 | 1.15 (0.71) | 17 | 1.25 (0.76) | 0.7299 |
| | Calcium | 32 | 8.68 (0.61) | 15 | 8.68 (0.54) | 17 | 8.67 (0.68) | 0.9842 |
| | Prothrombin time | 24 | 21.96 (5.40) | 8 | 20.18 (5.71) | 16 | 22.85 (5.20) | 0.2622 |
| 48-72 hours | Platelet Count | 26 | 129.54 (60.91) | 12 | 159.13 (73.21) | 14 | 104.18 (33.16) | 0.0301 |
| | Lactic Acid | 22 | 2.84 (2.34) | 8 | 1.64 (0.92) | 14 | 3.52 (2.65) | 0.0266 |
| | Albumin | 23 | 2.31 (0.48) | 12 | 2.53 (0.49) | 11 | 2.08 (0.34) | 0.0201 |
| | Hemoglobin | 25 | 15.95 (3.14) | 11 | 17.97 (2.12) | 14 | 14.36 (2.93) | 0.0023 |
| | Sodium | 29 | 135.52 (5.44) | 14 | 136.26 (4.83) | 15 | 134.83 (6.04) | 0.4897 |
| | Glucose | 29 | 88.64 (22.79) | 14 | 88.1 (14.95) | 15 | 89.16 (28.82) | 0.9013 |
| | ANC # (manual) | 21 | 6699.25(3444.86) | 8 | 7435.50 (2125.63) | 13 | 6246.17 (4069.27) | 0.4565 |
| | Creatinine | 29 | 1.12 (0.96) | 14 | 0.86 (0.78) | 15 | 1.37 (1.07) | 0.1577 |
| | Calcium | 29 | 9.03 (0.82) | 14 | 9.19 (0.78) | 15 | 8.88 (0.85) | 0.3204 |
| | Prothrombin time | 34 | 26.18 (11.64) | 16 | 21.93 (8.36) | 18 | 29.95 (13.01) | 0.0429 |

*Table 2. Laboratory diagnostics references in sections*

Equipoise is beneficial to research in this field as the links between comprehensive vasopressor indications, and blood pressure thresholds that represent the individualized limits of cerebral autoregulation are unclear (10-12). The hemodynamic parameters chosen in our study are currently being researched as possible indicators of newborn cerebrovascular pressure autoregulation, i.e., heart rate, systolic, diastolic, mean blood pressure, and cerebral NIRS (12-15). We explain the relevance of our findings in context to currently available research for newborn cerebrovascular autoregulation in full-term babies with moderate-severe brain injury.

*Objectives:* To evaluate whether hemodynamic instability, defined as the need for vasoactive support, predicts vital signs, cerebral NIRS, mechanical ventilator support, laboratory indices, EEG, brain MRI findings, and early neurodevelopmental indices in neonates with moderate-severe HIE. The primary aim was to study the differences between primary hemodynamic parameters and cerebral NIRS in patients with and without exposure to continuous vasoactive medications during their seventy-two hours after birth. The clinically relevant data included in this study were, selected medications (analgesics, anti-seizure therapies, postnatal steroids, inhaled nitric oxide), cardiac troponin I, the established biomarker of myocardial injury, laboratory test results, and neurodiagnostic assessments deemed as a standard of care for therapeutic hypothermia at the study center.

***"Only a few neonatal research centers in the USA have correlated cerebral NIRS with blood pressure (16). The secondary aim was to analyze the differences in mechanical ventilator support, biochemical parameters, and neurodiagnostic assessments between the newborns requiring and not requiring vasoactive support during their first seventy-two hours in the NICU. "***

Only a few neonatal research centers in the USA have correlated cerebral NIRS with blood pressure (16). The secondary aim was to analyze the differences in mechanical ventilator support, biochemical parameters, and neurodiagnostic assessments between the newborns requiring and not requiring vasoactive support during their first seventy-two hours in the NICU.

**Study methods**

**Design and Data sources:** A retrospective cohort study of thirty-four neonates diagnosed with

moderate-severe Hypoxic Ischemic Encephalopathy from 2010 to 2013 at a regional children's hospital with neurodevelopmental follow-ups until 2016. This period was chosen as cerebral NIRS was a routinely used diagnostic tool in infants receiving TH, allowing time for early neurodevelopmental follow-up. Data points were extracted from electronic medical records and supplemented by a chart review.

*Setting*: All the study subjects were out-born and transferred to the quaternary NICU to receive therapeutic hypothermia and any inhaled Nitric oxide or ECMO.

*Participants*: The study was approved by the deidentified study center, Institutional Review Board. Patients were excluded if EMR data was unavailable. A data analyst, with the guidance of the principal investigator, designed and executed the search strategy for the EMR, including relevant laboratory results, bedside monitoring data, and patient demographics. This data was augmented through chart review to generate a vasoactive score and extract EEG background and brain MRI findings. ICD codes were searched through medical records for the code HIE, cooling, and therapeutic hypothermia. An initial thirty-seven patients in the NICU at the study center were screened as potential subjects. Three patients were excluded as they did not meet the criteria for cooling at the time. Thirty-four patients were included as they had computerized documentation of receiving therapeutic hypothermia for moderate-severe HIE in the study period. Moderate and Severe encephalopathy was defined based on the 2003 AAP and ACOG criteria (17). An Olympic cool cap was utilized for administering therapeutic hypothermia during the selected time period at the study center. All the patients had their rectal temperatures maintained at 34.5°C ± 0.5°C (34.0-35.0°C) for the duration of hypothermia. Primary hemodynamic data, vasoactive medication dosages, and relevant clinical data were available for all the subjects. The primary outcomes (Heart rate, Blood Pressure, and cNIRS) were analyzed at five-time points.

The respiratory components of the secondary outcomes included the duration of mechanical ventilator support and oxygenation index. Biochemical parameters were trended across three-time points (0-24 hours, 24-48 hours, and 48-72 hours). EEG during cooling was reported either as an evolving pattern or finalized across seventy-two hours. Brain MRI was obtained 10-12 days after birth and included in the data analysis as normal, mild, or moderate to severe injury based on the radiologist's report. Neurodevelopmental assessments after NICU discharge were conducted at the study center and included Bayley III scaled and composite scores from 6 months to 24 months. The number of patients limited statistical power in the review period. The sample size was not calculated as the study design was planned as a retrospective cohort to clarify selected physiologic aspects of clinical decision-making.

Primary hemodynamic data, vasoactive medication information, and relevant clinical information were available for all subjects. Approximately 65% of patients had cerebral NIRS recordings during cooling. One patient did not have an EEG, and five died without brain MRI before their demise. Seven patients expired in the NICU, and one patient died at two years of age.

Neurodevelopmental outcomes were analyzed for the twenty-three patients with high-risk infant follow-up clinic visits at the study center from 6 months to 2 years of age. The median birth weight was 3.15 kilograms (IQ 2.6–3.56), 68% of the patients were male, and there were four late preterm infants in the cohort between 35-36 weeks of gestational age.

***"Neurodevelopmental outcomes were analyzed for the twenty-three patients with high-risk infant follow-up clinic visits at the study center from 6 months to 2 years of age."***

*Vasoactive score/index:* Vasoactive medication information was available in the chart review for all the study subjects. The study subjects were categorized into two groups, exposed or not exposed to continuous vasoactive medications at the time of statistical analysis due to limited variation in the pressor score.

| Variable | Category | All (N = 34) Mean (SD)/ Frequency (Percent) | No Vasoactives (N = 16) Mean (SD)/ Frequency (Percent) | Vasoactives (N = 18) Mean (SD)/ Frequency (Percent) | P Value |
|---|---|---|---|---|---|
| Ventilator Duration (days) | | 5.00 (4.35) | 3.31 (2.68) | 6.50 (5.03) | 0.027 |
| EEG Background | Missing/Not Done | 4 (11.76) | 2 (12.50) | 2 (11.11) | 0.045 |
| Burst suppression | | 9 (26.47) | 7 (43.75) | 2 (11.11) | |
| Continuous low voltage | | 20 (58.82) | 7 (43.75) | 13 (72.22) | |
| Flat | | 1 (2.94) | 0 (0.00) | 1 (5.56) | |
| EEG Seizure | Missing/Not Done | 1 (2.94) | 0 (0.00) | 1 (5.56) | 0.708 |
| | Absence | 23 (67.65) | 12 (75.00) | 11 (61.11) | |
| | Presence | 10 (29.41) | 4 (25.00) | 6 (33.33) | |
| Sarnat Stage | Missing | 2 (5.88) | 1 (6.25) | 1 (5.56) | 0.450 |
| | 2 | 10 (29.41) | 6 (37.50) | 4 (22.22) | |
| | 3 | 22 (64.71) | 9 (56.25) | 13 (72.22) | |
| Mortality Before NICU Discharge | Alive | 27 (79.41) | 14 (87.50) | 13 (72.22) | 0.405 |
| | Death | 7 (20.59) | 2 (12.50) | 5 (27.78) | |
| MRI(A/B) | Not Done | 5 (14.71) | 2 (12.50) | 3 (16.67) | 0.108 |
| Normal MRI-Mild injury | | 20 (58.82) | 12 (75.00) | 8 (44.44) | |
| Moderate-Severe injury | | 9 (26.47) | 2 (12.50) | 7 (38.89) | |
| EEG evolution | Not Done | 1 (2.94) | 0 (0.00) | 1 (5.56) | 1.00 |
| | Only Seizures | 3 (8.82) | 2 (12.50) | 1 (5.56) | |
| Normal -Mild | | 7 (20.59) | 3 (18.75) | 4 (22.22) | |
| Moderate- Severe | | 23 (67.65) | 11 (68.75) | 12 (66.67) | |

*Table 3. Exploratory Outcomes- Mechanical ventilation duration and NICU neurodiagnostics*

The abbreviation VAS denotes patients in the vasoactive exposed group, and non-VAS denotes patients with a vasoactive score of 0/no exposure to vasoactive infusions. Each baby was assigned a Vasoactive score/index that accounted for the vasoactive medications considered clinically indicated by the treating team for hypotension and cardiorespiratory illness in the transitional period, i.e., the first seventy-two hours after birth. A score of 0 denoted no utilization of vasoactive infusions, 1-Dopamine less than 10 mcg/kg/min or Epinephrine less than 0.1 mcg/kg/min; Score 2-Dopamine 10-20 mcg/kg/mt, Epinephrine 0.1-0.2 mcg/kg/mt, more than one vasoactive infusion; Score 3-Milrinone (M), Vasopressin (VP) or ECMO/ECLS.

Eighteen patients with a score of 1, 2, or 3 were assigned to the vasoactive group for the analysis. Sixteen patients with a vasoactive index score of 0 were in the group of newborns not exposed to vasoactive medications. Seven neonates expired before NICU discharge, and the criterion for their inclusion was either exposure or no exposure to vasoactive medications in the first seventy-two hours after birth.

STATISTICAL ANALYSIS: Mean with standard deviation (SD) were presented for each primary outcome at each time point on the entire population. Mean with SD were also presented for each group separately. Primary outcomes were compared between two groups by a two-sample two-sided t-test at each time point.

The false discovery rate (FDR) was used to adjust for multiple comparisons. Variables with

consistent significant p values across all three time periods were highlighted. Secondary outcomes were compared between two groups by a two-sample two-sided t-test at each time point except oxygenation index. Wilcoxon's two-sample test was utilized to compare the oxygenation index due to the severe skewness. MRI grade and ventilator duration were compared between two groups for exploratory outcomes by a two-sample two-sided t-test. Comparisons of EEG background (A/B/C), EEG seizure presence, Sarnat stage, and mortality before NICU discharge were by Fisher exact test.

MISSING DATA AND MORTALITY DATA:

Seven neonates admitted to the study center's NICU for cooling died before discharge. One baby died after CPR in the NICU, and six patients died after redirection to exclusive palliative care. One patient died at two years of age after NICU discharge. Cerebral

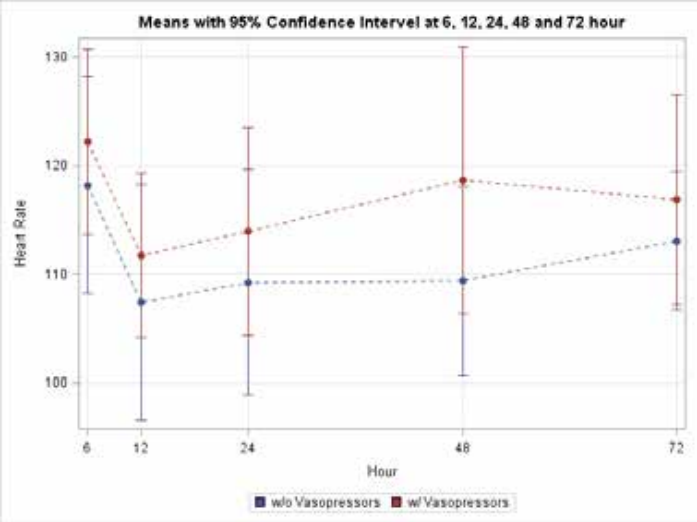



*Figure 1*

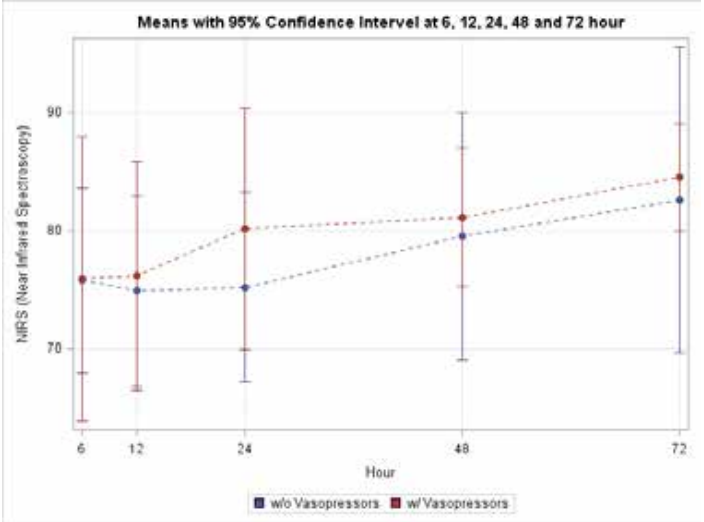
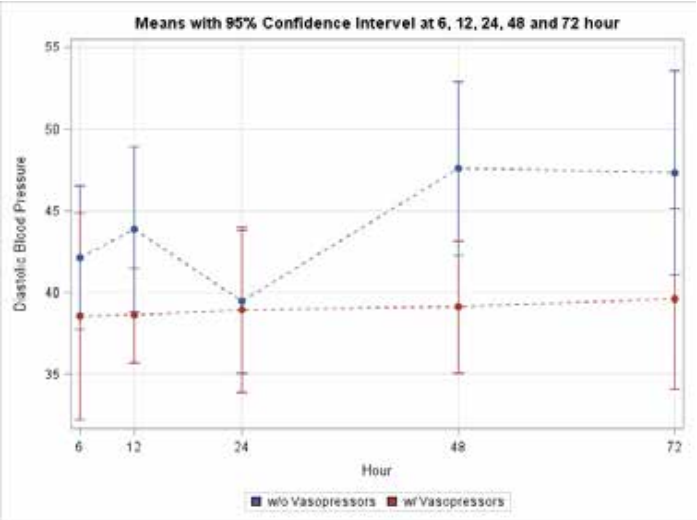



*Figure 2*

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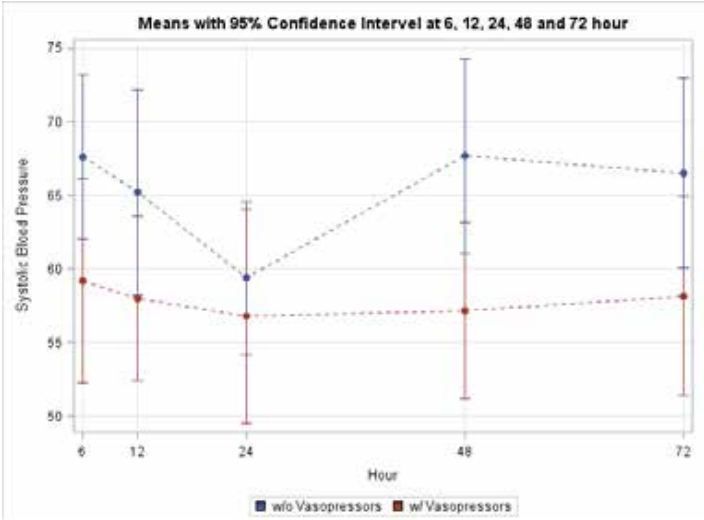


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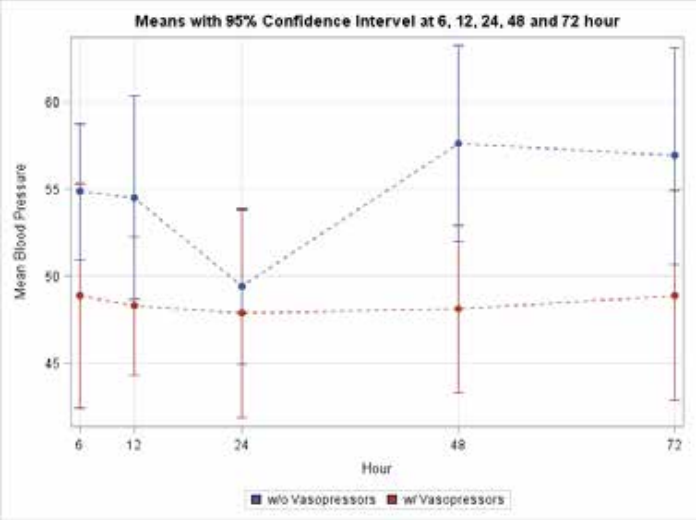


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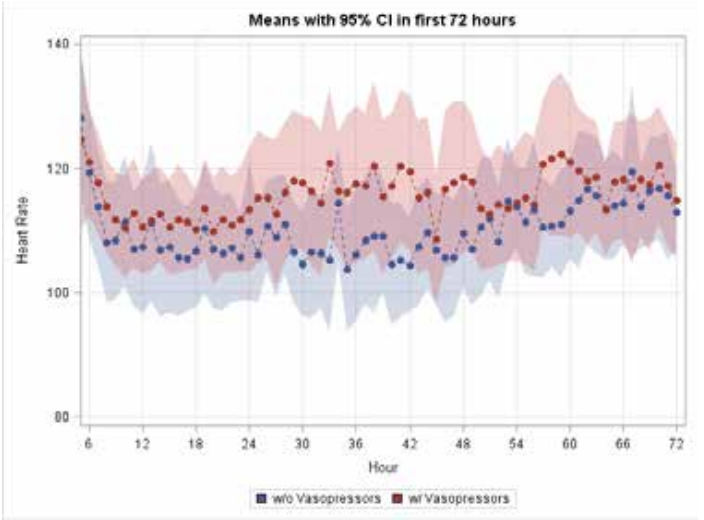


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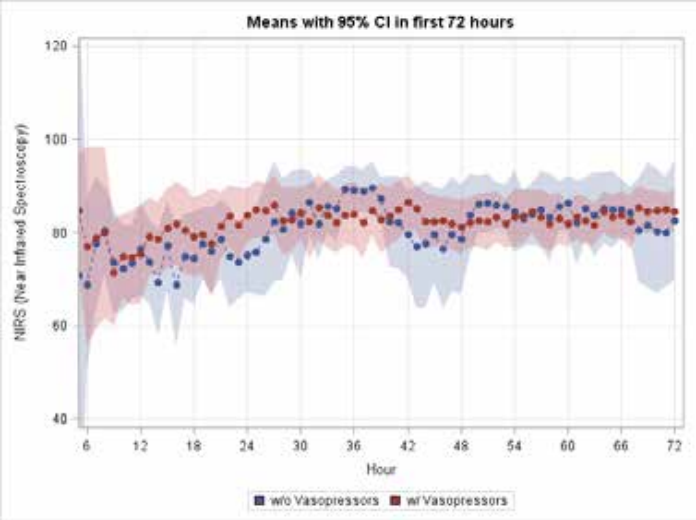


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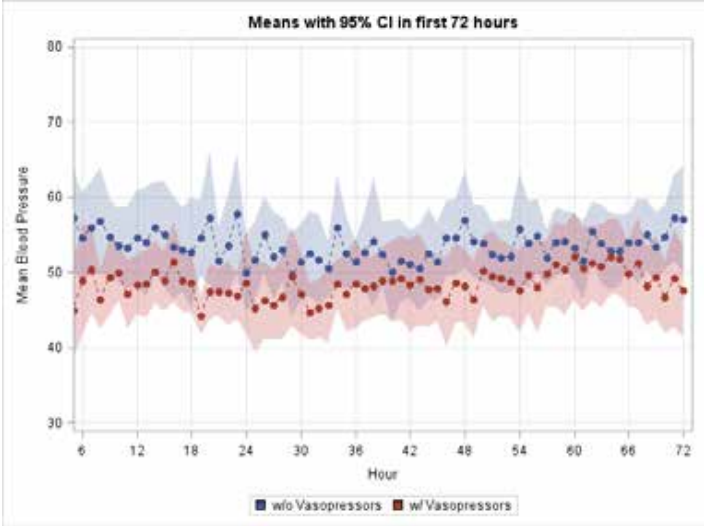


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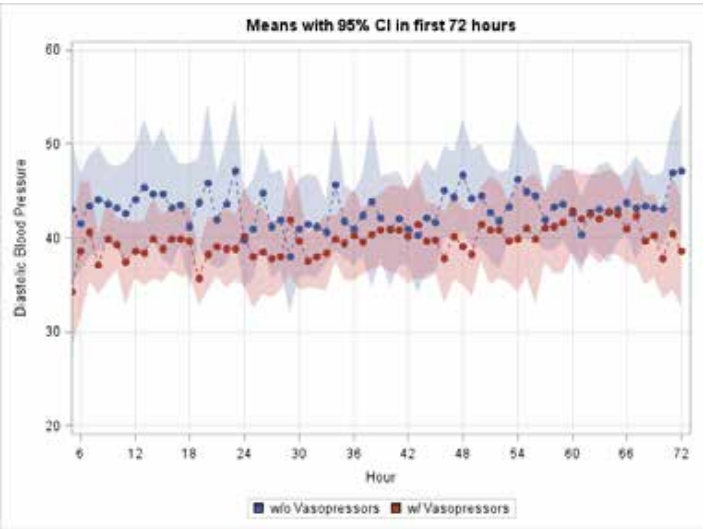


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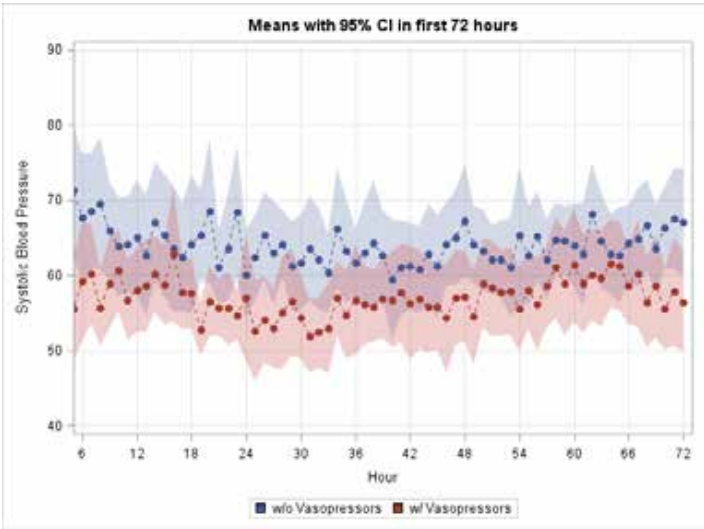


*Figure 10*

*Figure Legends: Blue graph is non -VAS group and red graph is VAS group for each figure.*
*Figure 1- The trend of mean heart rate with 95% confidence interval (CI) at 6, 12, 24, 48 and 72-hours.*
*Figure 2- The trend of mean C-NIRS with 95% confidence interval (CI) at 6, 12, 24, 48 and 72-hours.*
*Figure 3- The trend of mean diastolic blood pressure with 95% confidence interval (CI) at 6, 12, 24, 48 and 72-hours.*
*Figure 4- The trend of mean with 95% confidence interval (CI) at 6, 12, 24, 48 and 72-hour for systolic blood pressure.*
*Figure 5- The trend of mean with 95% confidence interval (CI) at 6, 12, 24, 48 and 72-hour for mean blood pressure.*
*Figure 6- The trend of continuous hourly heart rate mean values within the first seventy-two hours.*
*Figure 7- The trend of continuous hourly mean values for C-NIRS.*
*Figure 8- The trend of continuous hourly mean values for mean blood pressure.*
*Figure 9- The trend of continuous hourly mean values for diastolic blood pressure.*
*Figure 10- The trend of continuous hourly mean values for systolic blood pressure.*
*Figure 11- The trend of mean with confidence intervals for oxygenation index (OI) within the first seventy-two hours.*

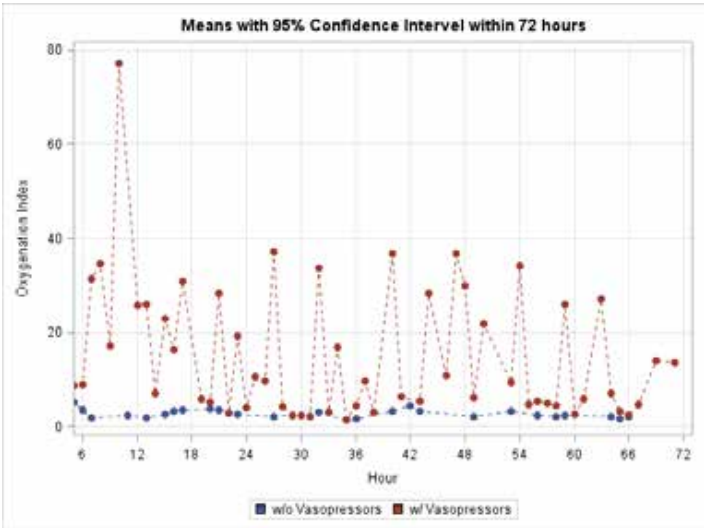


*Figure 11*

NIRS recordings were available for twenty-four patients during cooling, fourteen in the VAS group and ten in the non-VAS group. EEG was done in thirty-three of the thirty-four patients.

One baby in the vasoactive group required ECLS/VA-ECMO and survived to NICU discharge. In regard to the mortality data for patients requiring vasoactive agents, two patients, each with vasoactive scores of 1 and 3, and one patient with a VAS score of 2, died in the NICU. In the group without exposure to vasoactive therapies, two patients died before NICU discharge.

Among the twenty-seven patients surviving to NICU discharge, twenty-three patients had early neurodevelopmental assessments at the study center. While the majority of the babies had their six months Bayley III ND assessments, by two years of age, only 1/3 of the children followed up at the high-risk infant follow-up clinic. Thirteen patients had HRIF assessments at 24-28 months of age, five patients at 14-16 months and five patients had only one visit at 6.5 months of age. The recorded information included chronologic age, age equivalent data, scaled scores, and composite scores for 1. Cognitive 2. Composite language 3. Receptive language 4. Expressive language 5. Composite motor 6. Fine motor, 7. Gross motor. Developmental milestones were described as advanced, normal, and delays-mild, moderate, and severe.

RESOLUTION OF INCOMPLETE DATA: Any missing or unclear data points from computer extraction were resolved by chart review, and all ventilator and blood gas values were validated by secondary review. If the hemodynamic or laboratory measurements were missing for a targeted hour, the value at the closest hour was used within a (-4, +4) hour range. If there was no measurement collected within the 8-hour range, that was treated as missing data. Non-invasive blood pressure was used only if arterial blood pressure (umbilical or peripheral arterial line) was missing. 38% of babies had missing NIRS at all five timepoints in the non-VAS group (after the imputation with the closest time point). The missing rate of NIRS was 22-28% (22% for the 24th and 48th hour and 28% for the rest three timepoints) in the VAS group. The missing rate of the other primary outcomes ranges from 0-9% across the five timepoints.

***"There were no significant differences in primary outcomes between the two groups at all five timepoints after FDR adjustment."***

**Study results:**

PRIMARY OUTCOMES: There were no significant differences in primary outcomes between the two groups at all five timepoints after FDR adjustment. Figures 1-5 illustrate 1. The trend of mean with 95% confidence interval (CI) at 6, 12, 24, 48, and 72-hour for each primary outcome, i.e., Heart rate, Blood pressure (systolic, diastolic, mean), and c-NIRS and, Figures 6-10 illustrate 2. The trend of continuous hourly mean values within the first seventy-two hours for each

primary outcome.

SECONDARY OUTCOMES

Respiratory support, laboratory measurements, and neurodiagnostics:

Mean, minimum, and maximum for mechanical ventilator support were generated during the following time period, 0-6/6-12/12-24/24-48/48-72 hours. Respiratory support measurements: Oxygenation Index (OI) was not collected in the original data set. OI was manually calculated as 100*FiO2*MAP/PaO2. Blood pH was generated from Arterial/Venous/Capillary blood pH. If multiple blood pH types were collected simultaneously, we chose the type based on the following preference: 1. Arterial; 2. Venous; 3. Capillary. Blood partial pressure CO2 (pCO2) and blood arterial partial pressure O2 (pa02) were also generated similarly to blood pH with the same order of preference.

We analyzed the median (with 25 Th. -75 Th. tiles) number of available raw data points per subject during each time period for each outcome. Most summary measurement statistics (mean, minimum, and maximum) were generated on only 1-2 data points in each subject per time period, especially for laboratory tests. The biochemical parameters included albumin, cardiac troponin (nTnI), calcium, creatinine, hemoglobin, hepatic enzymes (ALT/SGPT, AST/SGOT), lactic acid-blood gas, magnesium, phosphorus, platelet count, prothrombin time (PT), random blood glucose, sodium, and absolute neutrophil count (ANC). Exploratory outcomes included MRI grade, ventilator duration, EEG background (A/B/C), EEG seizure presence, Sarnat stage, and Bayley III scaled and composite scores. Similarly, for the laboratory measurements, each subject's mean, minimum, and maximum were calculated during 0-24/24-48/48-72 hours. All of the below analysis was based on these summary statistics.

***"Neonates with moderate to severe HIE and vasoactive requirements were more likely to have a higher burden of hypoxemic illness and require prolonged ventilation, approximately two additional days (P=0.027). The oxygenation index was significantly higher during 6-24 hours (p<0.05) (Figure 11)."***

Neonates with moderate to severe HIE and vasoactive requirements were more likely to have a higher burden of hypoxemic illness and require prolonged ventilation, approximately two additional days (P=0.027). The oxygenation index was significantly higher during 6-24 hours (p<0.05) (Figure 11). The two groups had no consistent differences in blood pH and blood partial pressure CO2 (pCO2) (Table 1). In the first three days, the group treated with vasoactive agents had higher lactic acid, lower hemoglobin, and lower albumin (Table 2).

The patients exposed to vasoactive agents were also 30% more likely to have abnormal background EEG with low voltage patterns during therapeutic hypothermia and showed either moderate or severe brain injury on MRI at 10-12 days after birth. Before their demise, three patients had moderate-severe brain injury on MRI, and one had moderate-severe brain injury per head ultra-

| Month | Variable | All (N = 34) | | No Vasoactives | | Vasoactives | | P Value |
|---|---|---|---|---|---|---|---|---|
| | | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | |
| 6 | Cognitive Composite | 21 | 96.43 (15.42) | 11 | 94.09 (20.47) | 10 | 99.00 (6.99) | 0.4679 |
| | Cognitive scaled | 21 | 9.29 (3.08) | 11 | 8.82 (4.09) | 10 | 9.80 (1.40) | 0.4679 |
| | Language Composite | 21 | 91.86 (11.99) | 11 | 88.36 (14.89) | 10 | 95.70 (6.48) | 0.1594 |
| | Receptive Language Scaled | 21 | 8.90 (2.64) | 11 | 8.27 (3.04) | 10 | 9.60 (2.07) | 0.2609 |
| | Expressive Language Scaled | 21 | 8.29 (1.95) | 11 | 7.73 (2.33) | 10 | 8.90 (1.29) | 0.1754 |
| | Motor Composite | 20 | 84.70 (19.24) | 10 | 87.70 (19.41) | 10 | 81.70 (19.62) | 0.5006 |
| | Fine Motor Scaled | 21 | 8.43 (3.59) | 11 | 8.36 (3.93) | 10 | 8.50 (3.37) | 0.9333 |
| | Gross Motor Scaled | 20 | 6.10 (3.70) | 10 | 6.80 (3.88) | 10 | 5.40 (3.57) | 0.4119 |
| 14 | Cognitive Composite | 17 | 90.88 (16.61) | 8 | 86.88 (20.34) | 9 | 94.44 (12.61) | 0.3649 |
| | Cognitive scaled | 17 | 8.00 (3.41) | 8 | 7.38 (4.07) | 9 | 8.56 (2.83) | 0.4939 |
| | Language Composite | 17 | 86.29 (15.43) | 8 | 82.63 (18.98) | 9 | 89.56 (11.64) | 0.3722 |
| | Receptive Language Scaled | 17 | 8.18 (2.96) | 8 | 7.13 (3.23) | 9 | 9.11 (2.52) | 0.1752 |
| | Expressive Language Scaled | 17 | 7.06 (2.86) | 8 | 6.88 (3.56) | 9 | 7.22 (2.28) | 0.8118 |
| | Motor Composite | 17 | 85.41 (31.01) | 8 | 75.75 (35.14) | 9 | 94.00 (25.83) | 0.2375 |
| | Fine Motor Scaled | 17 | 8.65 (4.37) | 8 | 7.25 (4.13) | 9 | 9.89 (4.43) | 0.2251 |
| | Gross Motor Scaled | 17 | 7.41 (4.08) | 8 | 6.50 (3.89) | 9 | 8.22 (4.29) | 0.4022 |
| 24 | Cognitive Composite | 12 | 87.08 (18.76) | 5 | 84.00 (16.73) | 7 | 89.29 (21.10) | 0.6529 |
| | Cognitive scaled | 12 | 7.42 (3.75) | 5 | 6.80 (3.35) | 7 | 7.86 (4.22) | 0.6529 |
| | Language Composite | 12 | 87.42 (15.42) | 5 | 88.40 (22.12) | 7 | 86.71 (10.42) | 0.8621 |
| | Receptive Language Scaled | 12 | 8.58 (2.39) | 5 | 8.20 (3.49) | 7 | 8.86 (1.46) | 0.6609 |
| | Expressive Language Scaled | 12 | 7.08 (3.23) | 5 | 7.80 (4.09) | 7 | 6.57 (2.70) | 0.5421 |
| | Motor Composite | 12 | 88.92 (22.15) | 5 | 90.80 (26.63) | 7 | 87.57 (20.53) | 0.8166 |
| | Fine Motor Scaled | 12 | 8.17 (4.00) | 5 | 8.20 (4.76) | 7 | 8.14 (3.76) | 0.9819 |
| | Gross Motor Scaled | 12 | 8.08 (3.78) | 5 | 8.60 (4.51) | 7 | 7.71 (3.50) | 0.7085 |

*Table 4. Neurodevelopmental Indices- Mean and SD values*

sound. Amongst the three patients without brain MRI prior to their death in the NICU, one 39-week EGA baby with IUGR was determined to have suffered brain death. In context to the severity of EEG findings in the babies who died before NICU discharge, two patients had a burst suppression pattern, and one had a flat line/ isoelectric pattern (Table 3). One patient in the non-VAS group died at two days of age from respiratory failure and had persistent metabolic acidosis with a pH of less than 7.0. Brain MRI was not done for this neonate, and a burst suppression pattern was noted on the EEG along with clinical assessments of a devastating neurologic exam. The means of Bayley III composite cognitive and language scores were 99 (CI 6.99; n=10) and 95.7 (SD 6.48) in the VAS group; in the non-VAS group, 94.09 (SD 20.47; n=11) and 88.36 ( CI SD=14.89) respectively. The motor composite scores were 87.7 (CI 19.4; n=11) and 81.7 (CI 19.62; n=10) in non-VAS and VAS respectively. At six months, the majority of the patients had normal to mild developmental delays, and there were no statistically significant differences in between the two groups (Table 4).

***" At six months, the majority of the patients had normal to mild developmental delays, and there were no statistically significant differences in between the two groups (Table 4)."***

**DISCUSSION:**

1. PRIMARY HEMODYNAMIC PARAMETERS:

The influence of vasopressors' positive chronotropic effects on cerebral blood flow and cerebrovascular autoregulation during cooling is unclear. In our study, the babies exposed to vasoactive medications had lesser systolic, diastolic, and mean BPs, albeit this was not statistically significant between the two groups

(Figures 3-5, 8-10). Additionally, the VAS group's diastolic BP was lowest at twenty-four to forty-eight hours but did not reach statistical significance (Figures 3 and 9). It is uncertain whether these findings were impacted either by the sample size, transient vasoactive effects, or the clinical practice of titrating dosages in response to the observed alterations of vasopressors on the systemic vasculature. Our observation of lower mean BP is similar to a recent publication that the mean arterial BP in neonates with moderate/severe HIE treated with dopamine during cooling was significantly lower than controls (18).

***"Our observation of lower mean BP is similar to a recent publication that the mean arterial BP in neonates with moderate/severe HIE treated with dopamine during cooling was significantly lower than controls (18)."***

Sinus bradycardia is commonly observed during therapeutic hypothermia and is discussed as protective against evolving ischemic stress (2, 19, 20). Our study showed no differences in the heart rate measured between VAS and non-VAS patients across each time point ( Figures 1, 6). Heart rate and Blood Pressure are included in the Neonatal Pain, Agitation, and Sedation Scale (N-PASS). Nursing staff in the study center referenced N-PASS, and physicians prescribed pharmacologic analgesia as needed. It was impossible to extrapolate the effect of seizure activity on heart rate retrospectively.

***"Our data showed that babies exposed to vasoactive therapies had an early and sustained improvement in hypotension, as evidenced by the comparable blood pressures at the measured time points separated by 6-12 hours."***

Ascertaining if the burden of cardiovascular illness in a severely asphyxiated newborn is predominantly hypovolemic shock, cardiogenic shock, or septic shock can be challenging in retrospective clinical research. Our data showed that babies exposed to vasoactive therapies had an early and sustained improvement in hypotension, as evidenced by the comparable blood pressures at the measured time points separated by 6-12 hours. Importantly, babies requiring vasoactive agents had lower hemoglobin, particularly in the first twenty-four hours, suggesting that a perinatal sentinel event that led to blood loss in the maternal-fetal unit could have been a diagnostic consideration retrospectively. Low albumin indicates that our cohort of patients had a hemodynamic compromise with endothelial injury. Aberrations of vasculature permeability and function could have placed these babies more at risk for systemic hypotension requiring vasopressor therapies. Cardiac troponin I is considered a reliable biomarker of myocardial dysfunction (21-23). In a retrospective study on babies with perinatal asphyxia, the optimal cTnI cutoff value for mortality was 8.1 ng/ml; the median cTnI concentration was 3.1 ng /ml among the twenty-one non-surviving infants, significantly higher compared with the median 0.18 ng/ml observed in the 157 overall survivors (24).

Cardiac troponin levels were measured in 78% of our entire cohort, and the highest cTnI values were in the first 24 hours among the VAS patients. These findings were higher than previously published ranges suggested as cutoff, for 1. Perinatal hypoxia (0.15 microgram/L) predicts myocardial damage but is lower for 2 - predicting the risk of early mortality (4.6 microgram/L), albeit not statistically significant (Table 2). Our results should be interpreted with the limitation that thirty-three patients had troponin measurements for the first 24 hours, and less than one-third of these patients had recorded troponin measurements at the 48 and 72-hour's timepoints. Peripartum onset of myocardial dysfunction and cardiopulmonary resuscitation in the delivery room could have been important factors that influenced the first set of troponin measurements (25).

Delineating which babies were born in the setting of intraamniotic inflammation was not possible. However, none of the babies had confirmed early onset neonatal sepsis. The ANC count was not statistically significant between the two groups. This may suggest that our cohort's pathophysiologic cascade of multi-systemic illness could have been attributed to an abrupt vascular perinatal event rather than sepsis. Serum sodium and serum creatinine were not significantly different between the two groups (Table 2). The hourly clinical management decisions included not administering excess crystalloid boluses and adjusting sodium intake in the intravenous hydration fluids carefully. The indications for echocardiograms were: 1. Vasoactive requirement, 2. Prior to initiating inhaled nitric oxide, 3. Escalating ventilator or vasopressor requirements, or 4. Refractory/worsening metabolic acidosis. During the study period, the standard of clinical care for babies with a hemodynamic crisis at this regional neonatal ECLS center involved a 1-2 ECMO doctor decision-making process to ensure consistency in the treatment of hypotension and cardiorespiratory illnesses.

***"The seven babies who expired prior to NICU discharge had devastating brain injuries on clinical assessments, and their early disease trajectory was complicated by either hypoxemic respiratory failure or no meaningful response to escalating vasopressor support along with postnatal steroid therapies."***

The seven babies who expired prior to NICU discharge had devastating brain injuries on clinical assessments, and their early disease trajectory was complicated by either hypoxemic respiratory failure or no meaningful response to escalating vasopressor support along with postnatal steroid therapies. ECMO was deemed a

potentially inappropriate therapy and not in the baby's best interest on a case-by-case basis in conjunction with structured family meetings (26).

2. BURDEN OF HYPOXEMIC ILLNESS AND pCO2 DYSREGULATION in HIE:

Oxygen supply and transport are the critical components of medical therapies that optimize tissue level functions and recovery in neonatal cardiorespiratory illnesses and shock. The burden of hypoxemic illness indicated by oxygenation index (OI) in our patients was higher in the VAS group, especially during the first 6-24 hours after birth ($p<0.05$) (figure 11). Oxygen carrying capacity may also have been impacted during the acute phases of respiratory failure in the babies with hemodynamic instability as indicated by lesser hemoglobin in the first twenty-four hours postnatally (Table 2).

Persistent pulmonary hypertension is an important morbidity in patients after perinatal injury (27). Four babies in this study required inhaled nitric oxide for persistent pulmonary hypertension (n=3 in the VAS group). It was impossible to clarify how a combination of a pulmonary vasodilator (iNO) and vasoactive impacted oxygen delivery to the myocardial tissue and brain. The pCO2 measurements (Table 1) were not significantly different between the two groups, even though babies exposed to vasoactive agents had higher hemodynamic instability and stayed longer on mechanical ventilation. Isolated recordings of hypocapnia (pCO2 lesser than 30 mm Hg) for individual patients did not contribute to a statistically significant factor to explain differences either in MRI findings or predicting risks of early neurodevelopmental delays be- tween the two groups in our cohort. However, it is plausible that the risk of ischemic brain injury in the VAS group was increased by higher lactate levels altering cerebral tissue oxygen extraction and pCO2 vasoreactivity.

***"However, it is plausible that the risk of ischemic brain injury in the VAS group was increased by higher lactate levels altering cerebral tissue oxygen extraction and pCO2 vasoreactivity."***

3. DIAGNOSTIC CONSIDERATIONS OF THE MONITORING MODALITIES AND BIOCHEMICAL INDICES:

3.A. CEREBRAL NIRS: The standard of neuroprotective care for moderate-severe HIE at the time of this study was initiating therapeutic hypothermia within six hours after birth. There was no established time point or clinical parameter for informing medical providers regarding the evolution of ischemia-reperfusion phases into the irreversible process of apoptotic brain injury during cooling. Reperfusion is an injurious pathophysiologic process, often described as the phase of cerebral hyperperfusion that follows a latent or hypoperfusion phase in newborns impacted by a sentinel hypoxic ischemic perinatal event. It is uncertain if luxury perfusion is the trigger or the unavoidable effect of hyperperfusion and hyperoxia in the cascade of cellular derangements and worsening neurological injury (28).

Cerebral NIRS can be utilized as a non-invasive diagnostic tool for oxygen delivery and possibly identify if a baby is at risk for cerebral injury. The widespread practical application of this modality has been hindered by the lack of defined lower and upper limits for neonates and insufficient research data (29). A commonly referenced range of c-NIRS is 55-85%, based on studies in preterm infants (30). A well-appearing newborn born at term gestational age after an uncomplicated delivery can have a c-NIRS trajectory of 40-50% at birth to almost 78% in the first two days, followed by a plateau to 55-85% by 3-6 weeks of age (31). The neonatal research studies regarding neonatal brain injury and CrSO2 have explicated aspects such as higher values associated with adverse outcomes and multiple factors affecting cerebral blood flow such as heart rate, mean blood pressure, pC02, systemic oxygen saturation, and B. Glucose (31-37). Previous research in infants with severe HIE and worse outcomes has demonstrated CrSO2 values in the range of 77-84% (34). Consistently elevated rScO2 levels during the seventy-two hours of cooling can be attributed to decreased oxygen consumption, lower metabolic rate either from cooling or pathologic, secondary neuronal loss from apoptosis, and any unintended effects of sedative medications (8).

***"Consistently elevated rScO2 levels during the seventy-two hours of cooling can be attributed to decreased oxygen consumption, lower metabolic rate either from cooling or pathologic, secondary neuronal loss from apoptosis, and any unintended effects of sedative medications (8). "***

Systematic consideration of multiple etiologies and interventions can benefit the setting of significant disturbances in the C-NIRS baseline values or cutoff values of <60% and >90%. The timeframe for observing rising c-NIRS values in selected publications ranged be- tween 4-72 hours post birth in neonates with moderate-severe HIE (34, 35). In our study, there was no difference in the c-NIRS values between the patients not exposed to vasoactive agents and those exposed to vasoactive therapies (Figures 2, 7). The location of the c-NIRS optode monitor on an infant's scalp can influence the recorded values by measuring selected regional oxygen saturations. Extending the breadth of the actual probe to the occipital-temporal areas could hypothetically enhance prognostic information regarding which areas of the newborn brain are at the most risk for evolving injury. Reperfusion injury is vital for evaluating the risks of irreversible neurological deficits after a sentinel perinatal event that deprived the newborn's brain of oxygen and essential metabolites. The pathophysiologic cascade of biochemical and vascular responses in the setting of moderate-severe HIE can contribute to the evolution of significant brain injury. The existing clinical evidence that investigates the utility of C-NIRS as a prognostic marker for severity of MRI findings in cooled infants is limited due to the small numbers of patients and the absence of an integrated diagnostic profile with co-existing data such as mean BP, respiratory support, and biochemical indices (36, 37).

Time-trended measurements of cerebral NIRS across seventy-

two hours did not independently correlate either with the severity of brain injury on MRI or exposure to vasoactive medications in our study. The abnormal neurodiagnostics, as evidenced by low voltage EEG background patterns and moderate-severely abnormal brain MRIs in the VAS group along with clinical observations of higher oxygenation index, initial lower hematocrits, and elevated lactate levels in may suggest that those infants indeed suffered some of the sequelae of secondary cellular injury and luxury cerebral perfusion. EEG and brain MRI are important tools of a clinician's neurodiagnostic approach while caring for this vulnerable population.

***"The abnormal neurodiagnostics, as evidenced by low voltage EEG background patterns and moderate-severely abnormal brain MRIs in the VAS group along with clinical observations of higher oxygenation index, initial lower hematocrits, and elevated lactate levels in may suggest that those infants indeed suffered some of the sequelae of secondary cellular injury and luxury cerebral perfusion."***

3. B. EEG: We described the EEG features in our study population by the following descriptions (38)-1. Background activity-a. burst suppression (discontinuous activity throughout and with or without reactivity), b. continuous low voltage and c. flat trace; 2. Seizures; 3. Evolution of EEG over 72 hours normal or mildly abnormal; moderately abnormal; severely abnormal

A new piece of neurodiagnostic information from our study is finding a continuous low voltage pattern that was moderately severely abnormal in babies exposed to vasoactive therapies. EEG evidence of seizures was not significantly different in the two groups. All the subjects were documented as Sarnat stage 3 or Sarnat stage 2, changing to Sarnat stage 3 during the first seventy-two hours of postnatal life (Table 3). Anti-epileptic drug therapy was prescribed for 50% of the patients in the entire cohort with almost 90% phenobarbital exclusively, and two patients required a combination of phenobarbital and levetiracetam. A few of the confounding factors with EEG patterns of brain activity in our study population could be the utilization of opiates for analgesia, or/and diazepam for agitation, and the effects of hypothermia. Per the symptom-based-needs assessment approach at the time of clinical care, 32% of the neonates were exposed to Opiate (Fentanyl or Morphine Sulfate), and 24% received Diazepam continuous infusion for the following indications-analgesia, agitation, PPHN crisis, or achieve better synchrony with mechanical ventilation for babies with a high level of respiratory illness. An empiric continuous intravenous opiate infusion was not the standard of analgesic care for neonates undergoing therapeutic hypothermia in the study center during 2010-2013. Our research suggests that empiric anti-seizure therapy may not be indicated at the beginning of therapeutic hypothermia for every neonate with moderate-severe HIE. In conjunction with the pediatric neurologist's recommendations, a judicious case-by-case approach can help neonatologists choose the beneficial and appropriately indicated medical therapies for these infants.

3.C. MRI**:** Hypoxia-ischemia in newborns typically results in one of two characteristic patterns of brain injury: (1) Watershed-distribution pattern involving inter-vascular boundary-zone white matter, plus cortical gray matter when severe, and (2) Basal ganglia-distribution pattern involving deep grey nuclei, hippocampi, and perirolandic cortex, with further cortical involvement when severe. The neuropathology of brain injury in moderate-severe HIE can be summarized as 1. Selective neuronal necrosis may occur from cerebral ischemia, with deprivation of oxygen and glucose followed by reperfusion and the cascade of metabolic events. This can be caused by a severe and abrupt injury that diffusely affects the cerebral cortex, deep nuclei, and brain stem. Moderately severe asphyxia can be seen in the situation with slowly evolving hypoxia, acidosis followed by late deceleration of the fetal heart rate, diminished cardiac output, hypotension, and the cerebral ischemic pattern of injury in the cerebral cortex. 2. Parasagittal brain injury that has been known to occur in 40-60% of asphyxiated term infants. In addition to border zones/watersheds or end-fields of major arteries, other distal fields, like the posterior occipital region, can get affected (5).

Brain MRI was done 10-12 days after birth and reviewed by the pediatric radiologists at the study center. In this retrospective analysis of MRI reports, the extent of brain injury was described as either A. normal MRI and mild injury and B-Moderate-severe white matter injury, stroke, intraparenchymal hemorrhage, or presence of cerebral sinovenous thrombosis and sagittal sinus thrombosis. Normal to mild injury was predominantly seen in the non-VAS group (86%; n=12/14). Almost 50% of the patients in the VAS group had moderate-severe MRI evidence of brain injury (n=7/15) (Table 3). Previous research has demonstrated both increased incidence of MRI brain injury and no significantly elevated risk of severe brain injury in babies with HIE requiring vasopressors (3,18).

***"Almost 50% of the patients in the VAS group had moderate-severe MRI evidence of brain injury (n=7/15) (Table 3). Previous research has demonstrated both increased incidence of MRI brain injury and no significantly elevated risk of severe brain injury in babies with HIE requiring vasopressors (3,18)."***

Five neonates expired without brain MRI. Two patients had a head ultrasound prior to their demise in the NICU. Their early neonatal illness course was complicated by devastating neurologic clinical assessments, hemodynamic instability (despite escalating vasoactives), or persistent hypoxemic respiratory failure refractory to maximally dosed inhaled nitric oxide. Shared decision-making with the goal of exclusive palliative care was the main step toward compassionate extubation in those patients (26).

4. EXTENDING THE CLINICAL TRAJECTORY TO EARLY NEURODEVELOPMENTAL OUTCOMES

A comprehensive way of addressing the implications of moderate-severe HIE will include respiratory and cardiovascular disease trajectories, neurodiagnostics, and early childhood neurodevelopmental outcomes (39-41). Moderate or severe disabilities can occur in approximately 30% of patients, mostly with severe HIE, along with significant cognitive deficits restricting a child's ability to function independently (40, 41). The first study integrating neurodevelopmental outcomes at eighteen months of age and school age for children who received TH with cool cap showed that favorable neurodevelopmental outcomes assessed at eighteen months of age had a predictive value for normal functional assessments at 7-8 years (42). The largest data set (CHND) to date of developmental outcomes analyzed in infants after hypothermia for HIE described two models for predicting death or neurodevelopmental impairment as early as the first few hours after birth. The severity of HIE and specific patterns of EEG and MRI brain injury were associated with death and neurodevelopment impairment. The important caveat was that a composite outcome of death or NDI assumed that the babies who died after withdrawal of artificial life support would most likely suffer from later death or NDI (43).

Our study discussed early neurodevelopmental outcomes (motor, receptive language and expressive language) from six months to two years to better understand the clinical trajectory. Normal to mild delays were the predominant descriptive assessments for the entire cohort. Neurodevelopmental delays at six months were not significantly different in the VAS and non-VAS groups (Table 4).

**Limitations:**

Fluid resuscitation and volume challenge details were not included in the data extraction. This avoided the confounding effects of inaccurate data entry as all the neonates in our study center were outborn. However, early neonatal sodium and creatinine levels were not significantly different in the two groups of this cohort. Platelet levels significantly differed between the two groups for the first 0-24 and the last 48-72 hours. This study was not designed to extract information on blood product administration or delayed cord clamping. The observation of lower platelets in the vasoactive exposed group could have been either a false positive or that those patients received a platelet transfusion between 24 and 48-hour time points. A recent systematic review and meta-analysis for predicting neurodevelopmental outcomes in moderate and severe HIE showed that early MRI was more predictive than MRI performed after the first week of postnatal life (39). As mentioned previously, our study described brain MRI findings at 10-12 days; perhaps an earlier MRI may have had different findings regarding the extent of brain injury. The other limitations of this retrospective study were the lack of general adaptive and socioemotional components and almost 60% fewer follow-up assessments at two years.

***"Cerebral hemodynamics and neurovascular coupling (cerebrovascular responses to brain metabolism) are important concepts to elucidate in the newborn brain."***

**Conclusions:**

Cerebral hemodynamics and neurovascular coupling (cerebrovascular responses to brain metabolism) are important concepts to elucidate in the newborn brain. Derangements in metabolic processes at both intracellular and extracellular levels can potentially affect cerebral hemodynamics and autoregulatory thresholds after acute perinatal injury. During the acute phases of neonatal illnesses, thoughtful and compassionate communication regarding a family's values and individualized perspectives on life and childhood are essential. Concurrently, exploring better ways to understand the closely linked physiologic factors after birth may enhance prognosticating outcomes (41). The physiology of newborn cerebral autoregulation can be clarified by analyzing multiple factors with pathophysiologic relevance, i.e., alterations in primary hemodynamic parameters, changes in cerebral perfusion pressure, and biochemical and hematological parameters. Targeted neonatal echocardiograms, time and frequency domain heart rate variability, continuous cerebral NIRS recordings, key biomarkers, and neurodevelopmental data beyond infancy are a few examples of the precision medicine-based research tools that may improve prognostication challenges for neonatal brain injury and hemodynamic instability.

***References:***


1. *Leone TA, Finer NN. Shock: a common consequence of neonatal asphyxia. J Pediatr. 2011 Feb;158(2 Suppl):e9-12. doi: 10.1016/j.jpeds.2010.11.005.*
2. *Giesinger RE, Bailey LJ, Deshpande P, McNamara PJ.et al. Hypoxic-Ischemic Encephalopathy and Therapeutic Hypothermia: The Hemodynamic Perspective. The Journal of Pediatrics. 2017 Jan;180:22-30.e2. doi: 10.1016/j.jpeds.2016.09.009.*
3. *Mohammad K. Hemodynamic instability associated with increased risk of death or brain injury in neonates with hypoxic ischemic encephalopathy. Journal of Neonatal-Perinatal Medicine. 2016;9:357-62.*
4. *Balushi A, Barbosa Vargas S, Maluorni J, Sanon PN, Rampakakis E, Saint-Martin C, et al. Hypotension and Brain Injury in Asphyxiated Newborns Treated with Hypothermia. Am J Perinatol. 2018;35:31-8.*
5. *Volpe's Neurology of the Newborn.Neurology of the Newborn. 2008 (10): 288-295.https://doi.org/10.1016/C2010-0-68825-0.*
6. *Lee JK, Poretti A, Perin J, Huisman TAGM, Parkinson C, Chavez-Valdez R, et al. Optimizing Cerebral Autoregulation May Decrease Neonatal Regional Hypoxic-Ischemic Brain Injury. Dev Neurosci. 2017;39(1-4):248-256. doi: 10.1159/000452833. Epub 2016 Dec 16.*
7. *Burton VJ, Gerner G, Cristofalo E, Chung SE, Jennings JM, Parkinson C. A pilot cohort study of cerebral autoregulation and 2-year neurodevelopmental outcomes in neonates with hypoxic-ischemic encephalopathy who received therapeutic hypothermia. BMC Neurol. 2015 Oct 20;15:209. doi: 10.1186/s12883-015-0464-4.*
8. *Howlett JA, Northington FJ, Gilmore MM, Tekes A, Huisman TA, Parkinson C. Cerebrovascular autoregulation and neurolog- ic injury in neonatal hypoxic-ischemic encephalopathy.Pediatr Res. 2013 Nov;74(5):525-35. doi: 10.1038/pr.2013.132. Epub 2013 Aug 13.*
9. *Vutskits L. Cerebral blood flow in the neonate. Paediatr An-*

aesth. 2014 Jan;24(1):22-9. doi: 10.1111/pan.12307.
10. El-Dib M, Soul JS. Monitoring and management of brain hemodynamics and oxygenation. Handb Clin Neurol. 2019;162:295-314. doi: 10.1016/B978-0-444-64029-1.00014-X. PMID: 31324316.
11. Shellhaas RA, Kushwaha JS, et al. An Evaluation of Cerebral and Systemic Predictors of 18-Month Outcomes for Neonates With Hypoxic Ischemic Encephalopathy. J Child Neurol. 2015 Oct;30(11):1526-31. doi: 10.1177/0883073815573319.
12. Thewissen L, Caicedo A, Lemmers P, Van Bel F, Van Huffel S, Naulaers G. Measuring Near-Infrared Spectroscopy Derived Cerebral Autoregulation in Neonates: From Research Tool Toward Bedside Multimodal Monitoring. Front Pediatr. 2018 May 14;6:117. doi: 10.3389/fped.2018.00117. PMID: 29868521; PMCID: PMC5960703.
13. Shellhaas RA, Thelen BJ, Bapuraj JR, Burns JW, Swenson AW, Christensen MK, Wiggins SA, Barks JD. Limited short-term prognostic utility of cerebral NIRS during neonatal therapeutic hypothermia. Neurology. 2013 Jul 16;81(3):249-55. doi: 10.1212/ WNL.0b013e31829bfe41. Epub 2013 Jun 14. PMID: 23771483; PMCID: PMC3770165.
14. Sood BG, McLaughlin K, Cortez J. Near-infrared spectroscopy: applications in neonates. Semin Fetal Neonatal Med. 2015 Jun;20(3):164-72. doi: 10.1016/j.siny.2015.03.008.
15. Peng S, Boudes E, Tan X, Saint-Martin C, Shevell M, Wintermark P. Does near-infrared spectroscopy identify asphyxiated newborns at risk of developing brain injury during hypothermia treatment?. Am J Perinatol. 2015 May;32(6):555-64. doi: 10.1055/s-0034-1396692.
16. Massaro AN, Lee JK, Vezina G, Glass P, O'Kane A, Li R, et al. Exploratory Assessment of the Relationship Between He- moglobin Volume Phase Index, Magnetic Resonance Imaging, and Functional Outcome in Neonates with Hypoxic-Ischemic Encephalopathy. Neurocrit Care. 2021 Aug;35(1):121-129. doi: 10.1007/s12028-020-01150-8. Epub 2020 Nov 20. PMID: 33215394; PMCID: PMC8134623.
17. American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy and Cerebral Palsy, Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology. Washington, DC American College of Ob- stetricians and Gynecologists 2003;1-85.
18. Pazandak C, McPherson C, Abubakar M, Zanelli S, Fairchild K, Vesoulis Z.Blood Pressure Profiles in Infants With Hypoxic Ischemic Encephalopathy (HIE), Response to Dopamine, and Association With Brain Injury.P Front Pediatr. 2020 Aug 26;8:512. doi: 10.3389/fped.2020.00512.
19. Armstrong K, Franklin O, Sweetman D, Molloy EJ. Cardiovascular dysfunction in infants with neonatal encephalopathy. Arch Dis Child. 2012 Apr;97(4):372-5. doi: 10.1136/ adc.2011.214205.
20. Vesoulis ZA, Rao R, Trivedi SB, Mathur AM. The effect of therapeutic hypothermia on heart rate variability. J Perinatol. 2017 Jun;37(6):679-683. doi: 10.1038/jp.2017.42.
21. Vijlbrief DC, Benders MJ, Kemperman H, van Bel F, de Vries WB. Cardiac biomarkers as indicators of hemodynamic adapta- tion during postasphyxial hypothermia treatment. Neonatology. 2012;102(4):243-8. doi: 10.1159/000339117.
22. Metzler M, Govindan R, Al-Shargabi T, Vezina G, Andescavage N, Wang Y, et al. pattern of brain injury and depressed heart rate variability in newborns with hypoxic ischemic encephalopathy. Pediatr Res. 2017 Sep;82(3):438-443. doi: 10.1038/pr. 2017.94.
23. Sweetman D, Armstrong K, Murphy JF, Molloy EJ. Cardiac biomarkers in neonatal hypoxic ischaemia. Acta Paediatr. 2012;101(4):338-343. doi:10.1111/j.1651-2227.2011.02539.x
24. Montaldo P, Rosso R, Chello G, Giliberti P. Cardiac troponin I concentrations as a marker of neurodevelopmental outcome at 18 months in newborns with perinatal asphyxia. J Perinatol. 2014;34(4):292-295. doi:10.1038/jp.2014.1.
25. Liu X, Chakkarapani E, Stone J, Thoresen M. Effect of cardiac compressions and hypothermia treatment on cardiac troponin I in newborns with perinatal asphyxia. Resuscitation. 2013;84(11):1562-1567. doi:10.1016/j.resuscitation.2013.07.003.
26. Perugu S, Cleary JP. Referral for Extracorporeal Life Support in newborns with Hypoxic Ischemic Encephalopathy-Framework for integrating Bioethics and Palliative care outreach education. Pediatric Ethiscope:The Journal of Pediatric Bioethics. 2018 June;31 (1):10-18.
27. Lakshminrusimha S, Shankaran S, Laptook A, McDonald S, Keszler M, Van Meurs K, et al. Pulmonary Hypertension Associ- ated with Hypoxic-Ischemic Encephalopathy-Antecedent Characteristics and Comorbidities. J Pediatr. 2018 May;196:45-51.e3. doi: 10.1016/j.jpeds.2017.12.055.
28. Greisen G. Cerebral blood flow and oxygenation in infants after birth asphyxia. Clinically useful information? Early Hum Dev. 2014 Oct;90(10):703-5. doi: 10.1016/j.earlhumdev.2014.06.007.
29. Hunter CL, Oei JL, Suzuki K, Lui K, Schindler T. Patterns of use of near-infrared spectroscopy in neonatal intensive care units: international usage survey. Acta Paediatr. 2018 Jul;107(7):1198-1204. doi: 10.1111/apa.14271.
30. Alderliesten T, Dix L, Baerts W, Caicedo A, van Huffel S, Naulaers G, et al. Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates. Pediatr Res. 2016;79(1-1):55-64. doi:10.1038/pr.2015.186.
31. Dix LM, van Bel F, Lemmers PM. Monitoring Cerebral Oxygenation in Neonates: An Update. Front Pediatr. 2017 Mar 14;5:46. doi: 10.3389/fped.2017.00046.
32. Toet MC, Lemmers PM, van Schelven LJ, van Bel FCerebral oxygenation and electrical activity after birth asphyxia: their relation to outcome. Pediatrics. 2006;117(2):333-339. doi:10.1542/peds.2005-0987.
33. Kooi EM, van der Laan ME, Verhagen EA, Van Braeckel KN, Bos AF. Cerebral oxygenation is associated with neurodevelopmental outcome of preterm children at age 2 to 3 years. Dev Med Child Neurol. 2015;57(5):449-455. doi:10.1111/dmcn.12622.
34. Chock VY, Variane GFT, Netto A, Van Meurs KP. NIRS improves hemodynamic monitoring and detection of risk for cerebral injury: cases in the neonatal intensive care nursery. J Matern Fetal Neonatal Med. 2020;33(10):1802-1810. doi: 10.1080/14767058.2018.1528223.
35. Lemmers PM, Zwanenburg RJ, Benders MJ, de Vries LS, Groenendaal F, van Bel F, et al. Cerebral oxygenation and brain activity after perinatal asphyxia: does hypothermia change their prognostic value? Pediatr Res. 2013;74:180-5.
36. Weber F, Scoones GP. A practical approach to cerebral near-infrared spectroscopy (NIRS) directed hemodynamic

*management in noncardiac pediatric anesthesia. Paediatr Anaesth. 2019;29(10):993-1001. doi:10.1111/pan.13726.*

37. *Basu SK, Kaiser JR, Guffey D, Minard CG, Guillet R, Gunn AJ; CoolCap Study Group.Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. Arch Dis Child Fetal Neonatal Ed 2016;101:F149–F155. doi: 10.1136/archdischild-2015-308733.*
38. *Awal MA, Lai MM, Azemi G, Boashash B, Colditz PB. EEG background features that predict outcome in term neonates with hypoxic ischaemic encephalopathy: A structured review. Clin Neurophysiol. 2016 Jan;127(1):285-296. doi: 10.1016/j.clinph.2015.05.018.*
39. *Ouwehand S, Smidt LCA, Dudink J, Benders MJNL, de Vries LS, Groenendaal F, et al. Predictors of Outcomes in Hypoxic-Ischemic Encephalopathy following Hypothermia: A Meta-Analysis. Neonatology. 2020;117(4):411-427. doi: 10.1159/000505519.*
40. *Natarajan G, Pappas A, Shankaran S. Outcomes in childhood following therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy (HIE). Seminars in perinatology. 2016;40(8):549-555. doi: 10.1053/j.semperi.2016.09.007.*
41. *Natarajan G, Laptook A, Shankaran S. Therapeutic Hypothermia: How Can We Optimize This Therapy to Further Improve Outcomes?. Clin Perinatol. 2018;45(2):241-255. doi:10.1016/j.clp.2018.01.010.*
42. *Guillet R, Edwards AD, Thoresen M, Ferriero DM, Gluckman PD, Whitelaw A, et al. Seven- to eight-year follow-up of the CoolCap trial of head cooling for neonatal encephalopathy. Pediatr Res **71,** 205–209 (2012). https://doi.org/10.1038/pr.2011.30.*
43. *Peeples ES, Rao R, Dizon MLV, Johnson YR, Joe P, Flibotte J, Hossain T, et al. Children's Hospitals Neonatal Consortium Hypoxic-Ischemic Encephalopathy Focus Group. Predictive Models of Neurodevelopmental Outcomes After Neonatal Hypoxic-Ischemic Encephalopathy. Pediatrics. 2021 Feb;147(2):e2020022962. doi: 10.1542/peds.2020-02296.*

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