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Delayed Initiation of Therapeutic Hypothermia for Outborn Infants is Associated with Adverse Outcomes

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Background/Aims

Neonatal Encephalopathy (NE) is a clinical syndrome occurring between 2-5 per 1000 live births. Therapeutic hypothermia (TH) is a neuroprotective treatment for NE.

Typically, the majority of infants who meet eligibility criteria for TH are born in community hospitals and must be transferred to a tertiary care center for treatment.

We aim to characterize time to TH initiation for infants born at tertiary care centers (inborn) versus outborn infants and determine if delayed initiation is associated with adverse short-term outcomes.

Methods

Retrospective study of infants treated with TH between 2014 and 2018 in two NICUs excluding infants older than 72 hours at TH initiation (14), less than 35 weeks gestational age (5), early termination of TH (1), and absence of encephalopathy (2), and no MRI (11).

Assessment was performed by a blinded neuroradiologist using the mRS scoring system with severe injury defined as a mRS score >9.5 . * Weeke et al (2018), doi:10.1016/j.jpeds.2017.09.043

Primary outcome: Time to initiation of TH compared between inborn and outborn infants.

Secondary outcome: In-hospital mortality, severe MRI injury and/or severe seizure on EEG defined as use of phenobarbital, fosphenytoin and midazolam drip.

Statistical analysis: Baseline differences between inborn and outborn infants were compared using chi-square or Fisher's exact tests for categorical variables and t-tests or their non-parametric equivalents for continuous variables. Logistic regression was used to adjust for confounding.

Table 1. Clinical/Demographic Characteristics*

	Inborn n= 69	Outborn n= 153	p-value
Maternal Characteristics			
Gestational Diabetes (n, %)	14 (20%)	15 (10%)	0.05
Mean Maternal Age (SD)	30.4 (5.9)	27.6 (5.9)	0.001
Delivery Characteristics			
Cesarean section (n, %)	41 (59%)	79 (52%)	0.35
Chest compressions performed (n, %)	10 (15%)	56 (37%)	0.001
Infant Characteristics			
Female Sex (n, %)	31 (45%)	70 (46%)	0.99
Mean birth weight in kg (SD)	3.3 (0.7)	3.4 (0.6)	0.19
Mean Gestational Age in Weeks (SD)	38.5 (2.0)	39.6 (1.7)	<0.001
Median Apgar Score 1 min (# obtained, IQR)	1 [69, 1, 2]	2 [151, 1, 3]	0.06
Median Apgar Score 5 min (# obtained, IQR)	4 [69, 3, 6]	4 [150, 3, 5]	0.70
Median Apgar Score 10 min (# obtained, IQR)	6 [55, 4, 7]	6 [135, 4, 7]	0.53
Cord Gases			
Number of arterial gases obtained (n, %)	55 (80%)	88 (58%)	0.002
Mean arterial pH (SD)	7.04 (0.16)	7.06 (0.18)	0.48
Number of venous gases obtained (n, %)	52 (75%)	82 (54%)	0.003
Mean venous pH (SD)	7.10 (0.17)	7.13 (0.20)	0.47

*Statistically insignificant differences in characteristics not shown here include maternal fever, GBS positive, pre-eclampsia/eclampsia, vacuum assistance, shoulder dystocia, nuchal cord, cord prolapse, placental abruption, uterine rupture, late decelerations on fetal heart monitoring, chorioamnionitis, and prolonged rupture of membranes

Grey Matter Injury on MRI

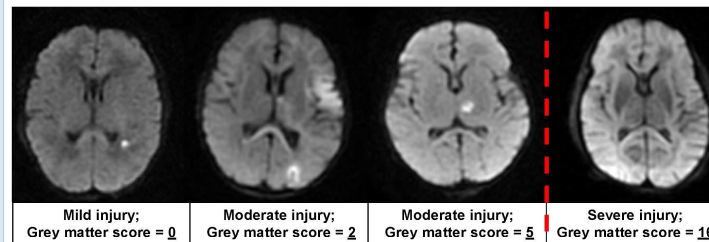


Table 2. Outcomes

	Inborn n= 69	Outborn n= 153	p-value
All infants			
Median Hour of Life TH Initiated (IQR)	1 (1,3)	4 (3,5)	<0.001
Mortality (n, %)	3 (4.3)	21 (13.7)	0.038
Any seizure (n, %)	16 (23.2)	57 (37.5)	0.045
Severe seizure (n, %)	3 (4.3%)	14 (9.2%)	0.28
Severe grey matter injury (n, %)	2 (3)	8 (5.7)	0.62
Mortality, severe seizure, and/or severe grey matter injury (n, %)	7 (10.1)	34 (22.2)	0.039

Results: Encephalopathy Tree Diagram

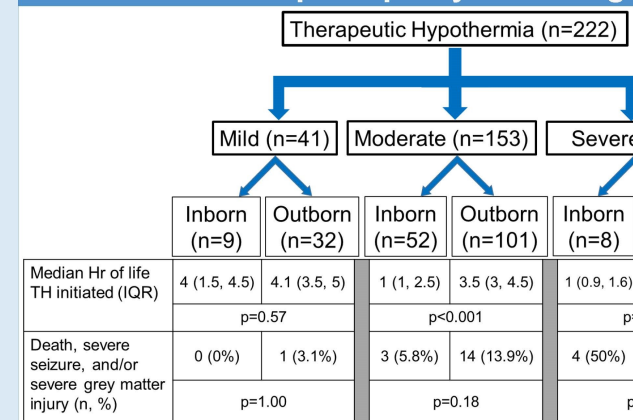


Table 3. Logistic Regression Analysis

Assessing Effect of Confounding on Combined Outcomes: Mortality, Severe Seizure, or Severe Grey Matter Injury

	Predictor Variable	Odds Ratio
Parent Model	Outborn infant	2.53
Extended Model*	Outborn infant	4.95

*Extended model is controlling for confounding from encephalopathy, gestational age, gestational diabetes and sex

Conclusions

- There is significant delay in TH initiation for outborn infants and an associated increase in the odds of death, severe neonatal seizures and/or severe grey matter injury.
- The relationship between delayed TH initiation and adverse outcomes is strongest for those with symptomatic severe encephalopathy.
- Investigation into factors contributing to severe encephalopathy prior to and immediately following birth is urgently needed.

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