Cardiac, renal and liver function in neonates with Hypoxic Ischemic Encephalopathy treated with Therapeutic Hypothermia

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Introduction

- **Hypoxic-ischemic encephalopathy (HIE)** is a condition in which perinatal asphyxia (PA)—prolonged hypoxia before, during, or after birth—leads to neuronal injury, causing extensive central nervous system (CNS) damage and possibly death.
- **Up to 15-20% of infants diagnosed with HIE die in the postnatal period**, and an additional 25% develop severe neurological deficits, including motor, auditory, or visual dysfunction, epilepsy, and cerebral palsy.[1] Hypoxia secondary to perinatal asphyxia can lead to multiorgan dysfunction in addition to CNS damage.
- **Therapeutic hypothermia (TH)** has become a standard of care for asphyxiated neonates. It has proven to be beneficial in minimizing the CNS damage that causes HIE. Cooling of an infant's core temperature to 33-34°C for 72 hours improves neurological outcomes at 18 months of age in asphyxiated neonates.[2,3]
- **Cardiac dysfunction** has been noted in 62% of neonates with HIE.[4]
- **Kidney and liver injury** have also been shown to be a consequence of PA and may present in infants with HIE[5,6,7], but whether this is a significant predictor of mortality or severity of neurological outcomes is inconclusive.

Objective

- To evaluate cardiac, renal and liver function in neonates with HIE treated with TH and to determine whether various biochemical/functional parameters of cardiac, renal, and hepatic function are significant predictors of mortality.

Methods

Study Population: 47 neonates diagnosed with HIE and treated with TH in a level IV NICU, divided into groups based on:

- **Gestational age (GA)**: Late Preterm (n=8) and Term (n=39)
- **Size at Birth**: Small-for-gestational age (SGA; n=12), appropriate-for-gestational age (AGA; n=30) and Large-for-gestational age (LGA; n=5)
- **Outcome**: Alive (n=40) and Deceased (n=7).

Cardiac function parameters: Ejection Fraction (EF), Shortening Fraction (SFx), and end-diastolic left ventricle internal diameter (LVIDd) and blood pressure (BP) were obtained from the reports of echocardiograms. Blood pressure was also retrieved from EMR. EF was calculated via the Teichholz formula.[8]

Biochemical Parameters: The following parameters were extracted from EMR at 24, 48, 72 and 96 hours (±4 hours) after birth: Troponin I, CK-MB, AST, ALT, Alk Phos, Lactic Acid (LA), Creatinine (Cr), BUN, and Urine Output (UO).

Glomerular filtration rate (GFR) was calculated using Brion et al's formula for estimating neonatal GFR.[9]

Statistical analysis: One-way ANOVA and Pearson correlation analyses were used to compare continuous variables between the independent groups. Fisher exact test was used for categorical variables.

Results

Cardiac Function Parameters

- There was no significant difference in cardiac function parameters (EF, SFx, or LVIDd) between the alive and deceased groups (p>0.05). *See Table 1*

Parameter	Alive	Deceased	Significance
Ejection Fraction (%)	72.8 ± 8.3	69.8 ± 6.0	p = 0.40
LVIDd (cm)	1.7 ± 0.2	1.8 ± 0.2	p = 0.19
Shortening Fraction (%)	38.9 ± 6.8	36.6 ± 4.2	p = 0.40

Table 1. Echocardiogram parameters associated with HIE Infant Survival and Mortality (Mean ± SD)

Cardiac Function Parameters (cont.)

- No significant correlation was found between echocardiogram parameters (EF, LVIDd, or SFx) and any measured biomarker of cardiac (Troponin I and CK-MB), renal (BUN, Cr BUN/Cr, GFR), or hepatic (ALT, AST, Alk Phos, LA) injury (p>0.05).

Creatinine

- Mean serum **Creatinine** was significantly higher in the deceased group than the alive group at 24, 48, 72, and 96 (±4) hours after birth (p<0.005). *See Figure 1*

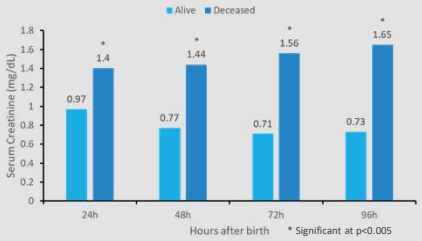

Figure 1. Mean serum creatinine levels at 24, 48, 72, and 96h after birth.

Glomerular Filtration Rate (GFR)

vi. Mean **GFR** was significantly lower in the deceased group than the alive group at 24, 48, 72, and 96 (±4) hours after birth (p<0.05). *See Figure 2.*

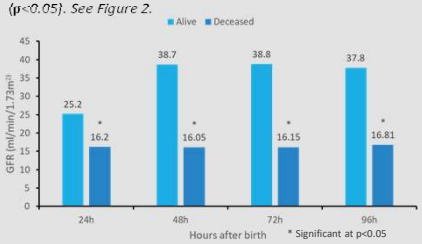

Figure 2. Mean GFR at 24, 48, 72, and 96h after birth.

Results

Urine Output

- Mean **Urine Output** was significantly lower in the deceased group than the alive group at 48, 72, and 96 (±4) hrs after birth (p<0.05) but was *not* significantly lower at 24h. *See Figure 3*

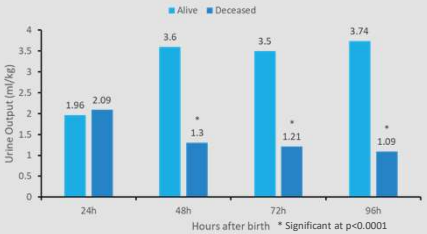

Figure 3. Mean urine output at 24, 48, 72, and 96h after birth.

BUN

- Mean serum **BUN** was not significantly different at any time point between the alive and deceased groups (p<0.05). *See Figure 4*

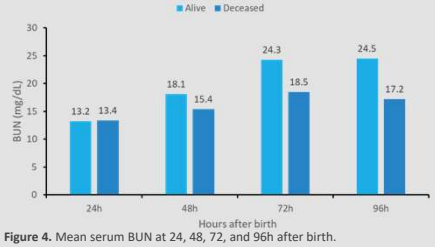

Figure 4. Mean serum BUN at 24, 48, 72, and 96h after birth.

Liver Function Parameters

- Mean serum ALT, AST, and Lactic Acid were significantly higher in the deceased group than the alive group at 24 hours *(see Table 2)*, (p<0.05).

Parameter	Alive	Deceased	Significance
24h ALT (U/L)	87.0 ± 98.6	359.4 ± 216.9	p < 0.00001
24h AST (U/L)	207.6 ± 296.9	1214.0 ± 847.7	p < 0.00001
24h Alk Phos (U/L)	142.8 ± 38.7	165.3 ± 105.5	p = 0.33
24h Lactic Acid (mmol/L)	2.9 ± 1.5	8.6 ± 4.9	p = 0.000013

Table 2. 24h Liver function parameters associated with HIE Infant Survival and Mortality (Mean ± SD)

Gestational Age

- There was no significant difference in cardiac, renal, or liver function parameters between the Late Pre-Term and Full-Term groups (p>0.05) or the SGA, AGA, and LGA groups (p>0.05).

Discussion

- Cardiac function parameters from echocardiograms (EF, SFx, LVIDd) did not significantly correlate with changes in biomarkers for renal and hepatic function.
- As a result, decreases in renal and hepatic function in neonates with HIE may be influenced more by the neonate's inherent systemic response to hypoxia than cardiac dysfunction alone.

Conclusions

- Cardiac, renal, and liver function parameters did not significantly differ based on gestational age or by weight for gestational age.
- Markers of renal and hepatic function may be predictive of survival in neonates with HIE being treated with therapeutic hypothermia.

Limitations

- There were disparities in the number of subjects in each group; for example, the Alive group had 40 subjects while the Deceased group had just 7.
- Approval will be requested to expand the study to include additional neonates treated for HIE up to 2020. This would improve the power of the study.

References

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