Early Granulocyte Inflammatory Biomarkers in Newborn Babies with Moderate or Severe Hypoxic Ischemic Encephalopathy

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Background

- Hypoxic ischemic encephalopathy (HIE) occurs when an infant's brain is deprived of oxygenated blood flow during the perinatal period
- This event triggers a cascade of ischemia-reperfusion injury, often resulting in brain injury, mortality, or lifelong disabilities
- The mechanisms of HIE injury are both multiphasic and multifactorial, with initial ischemic cell death followed by secondary energy failure and a surge of inflammation
- Pre-clinical data from animal models suggest that granulocyte-mediated pathways involving neutrophils and microglia contribute significantly to this inflammatory process

Objective

To assess plasma levels of granulocyte biomarkers in infants with moderate to severe HIE within the first 10 hours of life

Methods

Study Design: Phase-II randomized, placebo-controlled trial (NCT05778188)

Population:

- 23 infants with moderate (n=18) or severe (n=5) HIE
- Mean gestational age: 38 weeks
- Mean weight: 3133g

Sample Collection: Plasma collected within the first 10 hours of life before administration of any investigational product (pre-dose)

Markers Analyzed (by enzyme-linked immunosorbent assay [ELISA]):

- Myeloperoxidase (MPO)
- Neutrophil Elastase (NE)
- Cell-free DNA (marker for neutrophil extracellular traps)

Controls: Healthy adult plasma used as negative control

Confounding factors: Excessively hemolyzed samples were excluded from analysis

Statistical Analysis:

- Unpaired t-test with Welch's correction for unequal variance
- Healthy adult controls vs. pre-dose plasma of moderate and severe HIE infants were compared

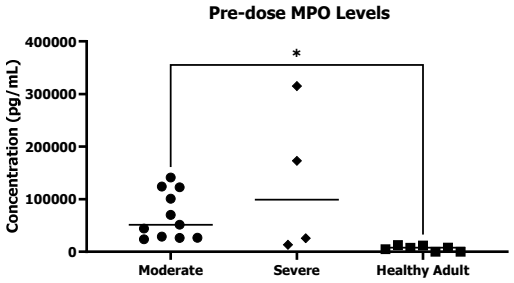

Figure 1. MPO levels in plasma of infants with moderate or severe HIE, prior to administration of investigational product (pre-dose). Plasma from healthy adults was used as a negative control. Horizontal lines represent median value of each group. * denotes p<0.01 comparing moderate HIE vs. healthy adults.

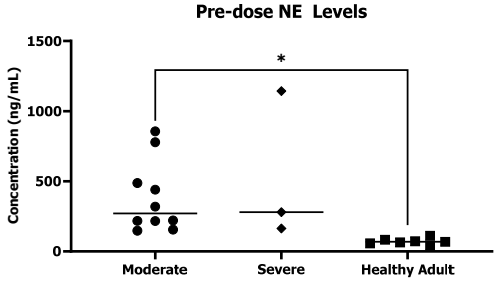

Figure 2. Neutrophil elastase concentration in plasma of infants with moderate or severe HIE, prior to administration of investigational product (pre-dose). Plasma from healthy adults was used as a negative control. Horizontal lines represent median value of each group. * denotes p<0.01 comparing moderate HIE vs. healthy adults

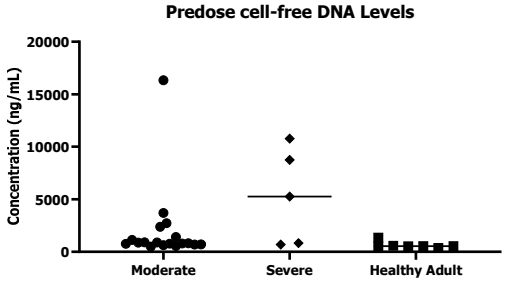

Figure 3. Cell-free DNA levels in plasma of infants with moderate or severe HIE, prior to administration of investigational product (pre-dose). Plasma from healthy adults was used as a negative control. Horizontal lines represent median value of each group

Results

MPO Levels: Moderate HIE infants: 6.7-fold increase vs. healthy adults (P = 0.0009); severe HIE infants: 1.9 times higher than moderate HIE infants

Neutrophil Elastase Levels: Moderate HIE: 4.0-fold increase vs. healthy adults (P = 0.0038)

Cell-free DNA: Moderate HIE: 1.6 times higher vs. healthy adults; severe HIE: 6.2 times higher vs. moderate HIE

Table of Key Findings

	N	Fold Increase (median)	p-value
MPO, moderate HIE	11	6.7	0.0009
MPO, severe HIE	4	1.9	n/a
NE, moderate HIE	10	4.0	0.0038
NE, severe HIE	3	1.0	n/a
Cell-free DNA, moderate HIE	18	1.6	n/s
Cell-free DNA, severe HIE	5	6.2	n/a

Conclusions

- Infants with moderate HIE have elevated levels of myeloperoxidase and neutrophil elastase in the first 10 hours of life, suggesting significant granulocyte-mediated inflammation
- These preliminary results highlight the potential role of granulocytes in the pathophysiology of ischemia-reperfusion injury in neonatal HIE, warranting further investigation

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