**ID:** 447  
**TITLE:** INCREASING USE OF THERAPEUTIC HYPOTHERMIA FOR HIE OUTSIDE OF THE CURRENT EVIDENCE-BASE: A NATIONAL POPULATION STUDY 2011-2016  
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**CONTENT:**

Hypoxic-ischaemic encephalopathy (HIE) remains a leading cause of mortality and neurodisability in newborns. Therapeutic Hypothermia (TH) has been shown to be a safe and effective treatment in infants ≥36 weeks gestation with moderate/severe (M/S) HIE, as evidenced by TOBY study and NICE guidance. However, there are increasing concerns clinicians are extending TH management to late preterm (LP) infants and those with mild HIE without proven benefits or safety.

We aimed to quantify the national prevalence of HIE, associated mortality and the use of TH in both LP infants and those with mild HIE.

National cohort study using data held in the National Neonatal Research Database from prospectively completed electronic hospital records from infants 34 to 42 weeks gestational age (GA) admitted to neonatal units in England and Wales between 2011 and 2016. Data were collected on infants who were coded as having HIE (Mild or M/S). Office for National Statistics birth data were used to calculate GA prevalence rates per 1000 live births. Data were sub-grouped by GA into two groups, LP (34 to 35 weeks) and ≥36 weeks. Two epochs (2011 to 2013 and 2014 to 2016) were compared to evaluate any temporal changes in practice. Data were analysed using Stata with significance set as p<0.05.

407,462 neonates from 34 to 42 weeks (70,781 LP infants) were admitted to neonatal units during the study period. The rate of HIE in LPs was 6.25/1000 compared to 2.88/1000 in infants ≥36 weeks. Of infants ≥36 weeks GA with HIE (n=11,587), 29% (n=3421) were diagnosed with mild HIE and 30% (n=1027) of these infants underwent TH, increasing significantly from Epoch 1 and 2 (24.7% vs 35.4%, p<0.001).

33% (n=210) of LP infants with HIE underwent TH, again a significant increase between Epoch 1 and 2 (26% vs 39.4%, p<0.001). Overall, LP infants with HIE were significantly more likely to die than those ≥36 weeks (13.1% vs 6.6%, odds ratio 2.11, 95% CI 1.66 - 2.69, p<0.001) and TH did not reduce their risk of death (odds ratio 0.95, 95% CI 0.88-1.03, p=0.25).

In England and Wales, the use of TH in mild HIE and LP infants is increasing with more than 1 in 3 infants now being treated. This risks exposing infants to non-evidence based treatment with potential adverse effects and increasing healthcare costs. The high prevalence of mild HIE overall and the high mortality in LP infants highlights the urgent need for prospective well-designed studies to evaluate safety and efficacy in these populations.

**COI:** None declared
ID: 426
TITLE: MODULATION OF MYELOID CELL POLARIZATION BY THERAPEUTIC HYPOTHERMIA IN NEONATAL HYPOXIC-ISCHAEMIC BRAIN INJURY
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CONTENT:

Hypoxic-ischaemic encephalopathy (HIE), is one of the leading causes of death and disability in children. Therapeutic hypothermia (HT) is the only recommended therapy, which is however limited. A better knowledge of hypothermia’s effector mechanisms is needed to guide the rational design of combination treatments. Inflammation is a major hallmark of HIE pathophysiology involving myeloid cells which reveal a high degree of phenotypic plasticity either participating in progression or resolution of injury-induced inflammation. The purpose of this study was to investigate the impact of HT on the temporal and spatial dynamics of microglia/macrophage cell polarization after neonatal HIE.

Postnatal day 9 (P9) C57BL/6 mice were exposed to hypoxia-ischaemia (HI) through occlusion of the right common carotid artery followed by one hour hypoxia (10% oxygen). Immediately after HI, animals were cooled for 4 hours (HT, Trectal=32°C). Controls (normothermia, NT) were kept on a warming mat to maintain physiological body core temperatures (Trectal=35°C). Brain injury, neuronal cell loss, apoptosis and microglia activation were assessed by immunohistochemistry 1, 3 and 7 days post HI. To analyse a broad set of typical genes associated with both classical (M1) and alternative polarization (M2) phenotypes CD11b+ microglia/macrophages cells were sorted by magnetic activated cell sorting followed by mRNA expression analysis via real time PCR 1, 3 and 7 days post HI.

Acute HT significantly reduced HI-induced brain injury and neuronal loss at 7 days post HI whereas only mild non-significant protection from HI-induced apoptosis was observed at 1 and 3 days post injury. Microglia activation revealed by Iba-1 immunoreactivity was not modulated at 1 day post HI. However, a significant HI-induced upregulation of Iba-1 was observed at 3 days which declined at 7 days. HT did not modulate Iba-1 immunoreactivity at any time point. Gene expression analysis in ex vivo isolated CD11b+ cells demonstrated a strong and significant upregulation of the majority of M1 but also M2 marker genes 1 day after HI, which was significantly reduced by HT. These acute changes following HI were diminished for most of the genes at 3 and 7 days post HI, resulting in no significant differences between HT-treated and normothermia-treated control animals.

These data demonstrate that HT inhibits secondary neuronal degeneration, which is preceded by acute suppression of HI-induced upregulation of pro- and anti-inflammatory genes representing an important effector mechanism of HT, though the early HI-induced mixed gene response in myeloid cells indicates that the traditional M1/M2 classification scheme oversimplifies the concept of distinct inflammatory cell phenotypes in vivo.

COI: None declared.
ID: 728

**TITLE:** NEUROPHYSIOLOGICAL ALTERATIONS DURING THE FIRST 6 HOURS IN INFANTS WITH MILD HYPOXIC ISCHAEMIC ENCEPHALOPATHY.

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**CONTENT:**

Infants with mild Hypoxic Ischaemic Encephalopathy (HIE) currently do not meet selection criteria for Therapeutic Hypothermia (TH) despite having significant levels of disability on follow up. HIE is an evolving process and often it is difficult, in the short time available, to identify which infants would benefit from TH. In the pre-TH era, electroencephalography(EEG) within 6hours of birth was most predictive of outcome and although this has now been altered with TH, EEG continues to play a key role in HIE management.

This study aims to identify and describe features of early EEG (before 6hours of life) in infants with mild HIE and assess their ability to predict neurodevelopmental outcome.

This was a retrospective study of infants with mild HIE from 3 previous prospective studies conducted in tertiary maternity hospitals in Cork, Ireland between 2003-2011. Infants >36weeks gestation with a clinical diagnosis of mild HIE, not undergoing TH with early EEG (before 6hours of life) and heart rate recordings were identified. Control infants were taken from a previous study examining brain activity in normal term infants. EEGs of infants with mild HIE were qualitatively analysed by a neonatal neurophysiologist blinded to outcome. EEGs of infants with mild HIE and controls were quantitatively assessed using multiple features of amplitude, spectral shape and inter-hemispheric connectivity. Quantitative features of the heart rate variability(HRV) analysis were computed for both groups

35 infants with mild HIE (4 of which had an abnormal outcome) and 15 healthy term controls were included in this analysis. Median gestation of infants with HIE was 40.28 [IQR 39.29-41.29] and median birth weight was 2.52kg [IQR 3.14-3.75kg]. Qualitative EEG analysis of infants with mild HIE showed that 45.7% had absent/poor sleep wake cycling, 57.1% had diffuse delta waves and 25.7% were discontinuous. Quantitative EEG analysis revealed significant differences in spectral shape between infants with mild HIE and controls (Table 1). HRV analysis revealed no difference between the groups. When assessing outcome, range-EEG (rEEG) median (p=0.046), rEEG lower margin (p=0.046) and spectral flatness (p=0.031) were associated with abnormal neurodevelopmental outcome at 24 months. Qualitative EEG features and HRV did not correlate with outcome.

Previous studies report that 25% of infants born with mild HIE have significant disability at follow up. Quantitative analysis of early EEG revealed significant differences between control infants and infants with mild HIE. Incorporation of early quantitative EEG features could be considered in future trials of TH in infants with mild HIE to aid the objective identification of cases.

**IMAGES:**

https://www.eiseverywhere.com/eiselectv3/v3/events/351149/submission/files/download?fileID=d68c0cff487bbfa55db056a10e009200-MjAxOS0wNSM1Y2UyNyY2QwYTvhh

Quantitative EEG features in Infants with mild HIE compared with control population.
COI: None declared
ID: 787
TITLE: ROLE OF INFLAMMATORY BIOMARKERS IN CEREBROSPINAL FLUID IN NEWBORNS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY
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CONTENT:

Inflammation plays a crucial role in the pathogenesis of hypoxic-ischemic injury in newborns. Temporal evolution and impact of the inflammatory cascade have been shown in preclinical models. The measurement of biomarkers which correlate with inflammation may be an approach to its characterization in human neonates. β2 microglobulin (β2m) and Neopterin in cerebrospinal fluid (CSF) have been used as surrogate biomarkers of central nervous system inflammation. The aim of this study was to describe the behavior of β2m and Neopterin in CSF in newborns with hypoxic-ischemic encephalopathy (HIE) and to study the association with brain injury in MRI and neurodevelopmental outcomes.

Infants with HIE born in Sant Joan de Déu and Clinic Hospitals (Barcelona) in a two-year period were prospectively included. The severity of the HIE was classified within 6 hours of life. Infants with moderate or severe HIE received whole-body cooling. β2m and Neopterin were measured in study patients in CSF obtained 12-72 hours after birth and in a control group of newborns with suspicion of sepsis that was finally ruled out. β2m and Neopterin correlated with brain injury on MRI (Rutherford score) evaluated by 2 blinded researchers and with neurodevelopmental outcomes at 2 years assessed by Bayley Scale of Infant Development III (BSID III). The relationship between biomarkers and MRI and BSID III scores was assessed using Spearman’s rank correlation coefficient and ROC curves.

Fifty-five neonates were included and biomarkers were determined in CSF in 36. There were 10 infants with mild, 11 with moderate and 15 with severe HIE. Ten patients died. The median values of β2m and Neopterin were 3 mg/L and 46 nmol/L, respectively, both significantly higher than in controls. Only two infants had β2m levels higher than 7 mg/L and only 5 infants had Neopterin levels higher than 200 nmol/L, and all of them had severe HIE. Association between levels of β2m and Neopterin and the severity of HIE and outcomes are described in table 1. Cutoff values of β2m of 3.07 mg/L and Neopterin of 46 nmol/L predicted the composite outcome of death or score <85 in any BSID III domain with a specificity of 91% and 100% and a sensitivity of 76% and 100%.

CSF β2m and Neopterin are raised in infants with HIE, indicating the activation of the inflammation cascade. Infants with severe damage show higher levels. Interestingly, very high levels correspond invariably to severe HIE, but not all infants with severe HIE show high levels, which may reveal diverse mechanisms of injury in HIE. The characterization of inflammation supports further research into anti-inflammatory therapy as cooling coadjuvant.

IMAGES:
https://www.eiseverywhere.com/eselectv3/v3/events/351149/submission/files/download?fileID=6348c9eaa0c02da80ce3c1bb02518586-MjAxOS0wNSM1Y2UyNjY2Y2U1YWZh
COI: None declared