Supplementary Online Content

Outcomes of neonatal hypoxic-ischaemic encephalopathy in centres with and without active therapeutic hypothermia: a nationwide propensity score-matched analysis

Shipley LJ¹, Mistry A¹, Sharkey D¹

¹ Division of Child Health and Obstetrics and Gynaecology, School of Medicine, University of Nottingham, UK

Corresponding Author:

Dr Don Sharkey, Academic Child Health, E floor, East Block, University Hospital, Derby Rd, Nottingham, NG72UH, UK. Don.Sharkey@nottingham.ac.uk. Tel no. 44 1158230611.

Content:

Supplementary Table 1 Description of data fields used for determining covariates and outcomes from the National Neonatal Research Database

Supplementary Methods

Supplementary Figure 1 Flowchart of study participants

Supplementary Figure 2 Propensity score distribution (A) and Standardised Bias (B) for infants born in non-cooling centres (control) and those born in cooling centres (treated) both before and after propensity score-matching

Supplementary Figure 3 Propensity score distribution (A) and Standardised Bias (B) for infants born in level 2 non-cooling centres (control) and those born in cooling centres (treated) both before and after propensity score matching

Supplementary Figure 4 Propensity score distribution (A) and Standardised Bias (B) between infants born in a non-cooling centre (control) and those born in a cooling centre (treated) both before and after propensity score-matching excluding those born at home or in midwife led units

Supplementary Table 2 Admission temperature and arrival time following transfer to a cooling centre for infants ≥36 weeks gestational age with moderate or severe HIE who were born in a non-cooling hospital

Supplementary Table 3 Admission temperature and arrival time following transfer to a level 3 CC for infants ≥36 weeks gestational age with moderate or severe HIE who were born in level 2 centres with immediate access to active TH or non-CC

References
Supplementary Table 1. Description of data fields used for determining covariates and outcomes from the National Neonatal Research Database

| Principle Diagnosis at Discharge database entries for HIE Grading |
|-------------------------------------------------------------------|
| **Severe HIE:**                                                   |
| - HIE Grade 3 - Severe Neonatal Encephalopathy                    |
| - Hypoxic ischaemic brain damage ; Severe                         |
| - Severe perinatal asphyxia (with 1 minute Apgar <4)              |
| - Severe Neonatal Encephalopathy - Gr.3                           |
| - Hypoxic Ischaemic Encephalopathy (Gr 3)                         |
| - Severe Neonatal Encephalopathy – Grade 3 HIE                    |
|**Moderate HIE:**                                                  |
| - HIE Grade 2 - Moderate Neonatal Encephalopathy                  |
| - Hypoxic ischaemic brain damage ; Moderate                       |
| - Moderate perinatal asphyxia (with 1 minute Apgar 4-7)           |
| - Moderate Neonatal Encephalopathy - Gr.2                         |
| - Hypoxic Ischaemic Encephalopathy (Gr 2)                         |
| - Moderate Neonatal Encephalopathy - Grade 2 HIE                  |
|**Mild HIE:**                                                     |
| - HIE Grade 1 - Mild Neonatal Encephalopathy                      |
| - Hypoxic ischaemic brain damage ; Mild                           |
| - Mild perinatal asphyxia (with 1 minute Apgar >7)                |
| - Mild Neonatal Encephalopathy - Gr.1                             |
| - Hypoxic Ischaemic Encephalopathy (Gr 1)                         |
| - Mild Neonatal Encephalopathy - Grade 1 HIE                      |
| - Very mild perinatal asphyxia - clinically normal by 24 hours    |
|**Unspecified**                                                   |
| - Birth Asphyxia                                                  |
| - Anoxic Brain Damage                                             |
|**Therapeutic Hypothermia**                                        |
| - Therapeutic Hypothermia                                         |
| - Therapeutic Hypothermia (whole body cooling)                    |
| - Hypothermia Therapeutic                                         |

**Principle procedures during stay entries for identification of Therapeutic Hypothermia**

- Therapeutic Hypothermia
- Therapeutic Hypothermia (whole body cooling)
- Hypothermia Therapeutic

**Demographic and Clinical Variables**
- Gender
- Birthweight
- Gestation in weeks
- Year of Birth
- Onset of Labour
- Presentation of fetus
- Mode of Delivery
- Methods of resuscitation
- Apgar score at 5 minutes
- Nulliparity determined from data field “Number of previous pregnancies”
- Meconium stained liquor
- Maternal Infection determined from data fields “Maternal pyrexia in labour” and “Problems during pregnancy with mother” (maternal UTI /chorioamnionitis/prolonged rupture of membranes)
- Hypotension determined from data fields “Inotropes given”, “Daily drugs”, “Principal diagnosis at discharge”
- Place of birth NHS hospital code
- Place of birth NHS hospital level
- Nitric oxide determined from data fields “Pulmonary vasodilator” and “Principle diagnosis at discharge”
- Persistent pulmonary hypotension determined from data fields “Principal diagnosis at discharge”
- Pre-eclampsia determined from data field problems during pregnancy with mother
- Gestational Diabetes determined from data field “Problems during pregnancy with mother”
- Acute intrapartum events determined from data fields “Problems (obstetric) during pregnancy with mother” (Reduced fetal movements/placental abruption/cord problems/shoulder dystocia) and “Principle diagnosis on discharge”
- Significant resuscitation determined from data field “Methods of resuscitation” (cardiac compressions/intubation/adrenaline/other drugs)
- Respiratory Support device (No support/CPAP/Ventilated/HFOV)

**Outcome Variables**

- Death determined from Destination at Discharge data field. If an infant was discharge “home”, “ward” or “Foster Care” the infants was coded as surviving.
- Seizures determined from “Convulsions today” and “Principle diagnosis at discharge data fields”. Infants were also coded as having seizures if they received anticonvulsants in the “Daily Drugs” data field.
- Number of anticonvulsants determined from “Daily Drugs” data field
- Admission temperature
- Time of admission temperature
- Admission time to neonatal unit
- Length of stay determined from Admission time and Time of discharge data fields

HIE, Hypoxic Ischaemic Encephalopathy; UTI, Urinary Tract Infection; NHS, National Health Service; CPAP, Continuous positive airway pressure; HFOV, High frequency oscillatory ventilation
eMethods

Propensity Score Matching

Propensity score analysis entailed fitting a logistic regression model using a stepwise process and evaluation of potential interactions to determine variables to include in the propensity score. For variables with missing data values were either imputed using Markov chain Monte Carlo method (1) or a separate category was defined indicating non-response. Initially, a priori background variables (gender, gestation, birthweight and birth year) were selected for inclusion into the logistic regression model regardless of their statistical association with the outcome. This baseline model was fitted with addition of one other background variable at a time. The variable with the greatest t ratio was included in the model if >1.0. This process was repeated, until t ratios for all remaining variables were smaller than 1.0. Following this analysis 13 covariates were included. These were:

- Gender
- Birthweight
- Gestation in weeks
- Birth year
- Nulliparity
- Pre-eclampsia
- Maternal infection
- Mode of delivery
- Presentation at birth
- Acute intrapartum events
- Significant resuscitation at birth
- Apgar score at 5 minutes
- Grade of HIE
**Interactions**

Interactions were determined for inclusion into model by ranking the variables in the concluding model by their t ratio and expanding this model by one second-order term at a time. The interaction term was included in the model if t ratio was greater than 2.71, which corresponds to nominal statistical significance at 10% level. No interactions reached this level in our analysis (2).

Propensity scores were estimated using logistic regression based on the selected background variables. A matched sample of untreated and treated infants was created through matching on the logit of the propensity score with caliper width set at 0.05. The propensity strata were trimmed by excluding infants with extreme propensities to minimise residual confounding. A nearest neighbour 1:1 matching algorithm with no replacement was used to form pairs of infants in the CC and non-CC group (3).

**Assessment of balance**

The matching process was evaluated by division of the propensity score into an optimal number of blocks and assessing the within-block equality of means of covariates across the treatment groups. The propensity distribution density was evaluated between control and treated groups both pre and post matching. (Supplementary Figure 2). Additionally, standardised percentage bias for each covariate (formulae as detailed by Rosenbaum and Rubin) after matching was calculated. A covariate was considered balanced if the standardised differences were between -0.2 and 0.2 and standardised mean bias was <5% (4) (5)(Supplementary Figure 2). The resulting model was well balanced with no covariate with a mean bias of >5% and overall mean bias 1.7 with no significant difference between the group (p=0.75).
Sensitivity analyses

Sensitivity analyses were performed between infants born in level 2 non-cooling and cooling centres and between infants born in non-cooling and cooling centres but excluding infants born at home and midwife led units to mitigate potential bias. Further propensity score matching and assessment of balance was undertaken using the above described methodology for these subgroups of infants. Evaluation of model balance is demonstrated in Supplementary Figure 3 and 4.
Supplementary Figure 1. Flowchart of study participants demonstrating the number of infants ≥36 weeks gestational age with moderate or severe hypoxic ischaemic encephalopathy admitted to neonatal units in the UK managed with therapeutic hypothermia

GA, Gestational age; m/s HIE, moderate or severe hypoxic ischaemic encephalopathy; TH, therapeutic hypothermia; NHS, National Health Service

Supplementary Figure 2. Propensity score distribution (A) and Standardised Bias (B) for infants born in non-cooling centres (control) and those born in cooling centres (treated) both before and after propensity score-matching

EmlSCS, Emergency caesarean section; EILSCS, Elective caesarean section; APGAR, Appearance, Pulse, Grimace, Activity and Respiration score; HIE, Hypoxic ischaemic encephalopathy
**Supplementary Figure 3.** Propensity score distribution (A) and Standardised Bias (B) for infants born in level 2 non-cooling centres (control) and those born in cooling centres (treated) both before and after propensity score matching.

![Graph showing propensity score distribution and standardised bias](image)

EmLSCS, Emergency caesarean section; EILSCS, Elective caesarean section; APGAR, Appearance, Pulse, Grimace, Activity and Respiration score; HIE, Hypoxic ischaemic encephalopathy

**Supplementary Figure 4.** Propensity score distribution (A) and Standardised Bias (B) between infants born in a non-cooling centre (control) and those born in a cooling centre (treated) both before and after propensity score-matching excluding those born at home or in midwife led units.

![Graph showing propensity score distribution and standardised bias](image)

EmLSCS, Emergency caesarean section; EILSCS, Elective caesarean section; APGAR, Appearance, Pulse, Grimace, Activity and Respiration score; HIE, Hypoxic ischaemic encephalopathy
Supplementary Table 2. Admission temperature and arrival time following transfer to a cooling centre of infants ≥36 weeks gestational age with moderate or severe HIE who were born in a non-cooling hospital (n=2027).

| Temperature | Age at Admission | Non-cooling centre (n = 611) | Cooling centre (n = 443) |
|-------------|------------------|-------------------------------|--------------------------|
|             | <6 Hours  | 6-12 Hours  | >12 Hours  | <6 Hours  | 6-12 Hours  | >12 Hours  |
| >34°C       | 4.2%      | 11.9%      | 2.4%       | 3.6%      | 11.6%      | 2.5%       |
|             | (n = 86)  | (n = 242)  | (n = 48)   | (n = 22)  | (n = 71)   | (n = 15)   |
| 33-34°C     | 12.7%     | 48.3%      | 6.1%       | 12.9%     | 49.3%      | 5.2%       |
|             | (n = 259) | (n = 979)  | (n = 124)  | (n = 79)  | (n = 301)  | (n = 32)   |
| <33°C       | 2.5%      | 10.3%      | 1.3%       | 2.3%      | 11.9%      | 0.7%       |
|             | (n = 52)  | (n = 209)  | (n = 27)   | (n = 14)  | (n = 73)   | (n = 4)    |

Supplementary Table 3. Admission temperature and arrival time following transfer to a level 3 cooling centre for infants ≥36 weeks gestational age with moderate or severe HIE who were born level 2 centres with immediate access to active therapeutic hypothermia or non-cooling centre.

| Temperature | Age at Admission | Non-cooling centre (n = 611) | Cooling centre (n = 443) |
|-------------|------------------|-------------------------------|--------------------------|
|             | <6 Hours  | 6-12 Hours  | >12 Hours  | <6 Hours  | 6-12 Hours  | >12 Hours  |
| >34°C       | 3.6%      | 11.6%      | 2.5%       | 1.1%      | 8.1%       | 4.3%       |
|             | (n = 22)  | (n = 71)   | (n = 15)   | (n = 5)   | (n = 36)   | (n = 19)   |
| 33-34°C     | 12.9%     | 49.3%      | 5.2%       | 9.9%      | 55.3%      | 3.1%       |
|             | (n = 79)  | (n = 301)  | (n = 32)   | (n = 44)  | (n = 245)  | (n = 58)   |
| <33°C       | 2.3%      | 11.9%      | 0.7%       | 1.1%      | 4.7%       | 2.3%       |
|             | (n = 14)  | (n = 73)   | (n = 4)    | (n = 5)   | (n = 21)   | (n = 10)   |
References

1. Schafer J. Analysis of Incomplete Multivariate Data. Boca Raton: Chapman and Hall/CRC; 1997.

2. Imbens G. Matching methods in practice. J Hum Resour. 2015;50:373-419.

3. Cochran WG, Rubin DB. Controlling bias in Observational Studies: A Review. 1973.

4. Rosenbaum PR. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Statist. 1985;39:33-9.

5. Caliendo M, Kopeinig S. Some practical guidance for implementation of propensity score matching. Journal of Economic Surveys. 2008;22(1):31-72.