Trends in the incidence and management of hypoxic-ischaemic encephalopathy in the therapeutic hypothermia era: a national population study

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ABSTRACT

Objective Hypoxic-ischaemic encephalopathy (HIE) remains a leading cause of neonatal mortality and neurodisability. We aimed to determine the incidence of HIE and management patterns against national guidelines.

Design Retrospective cohort study using the National Neonatal Research Database.

Setting Neonatal units in England and Wales.

Patients Infants 34–42 weeks gestational age (GA) with a recorded diagnosis of HIE.

Main outcomes Incidence of HIE, mortality and treatment with therapeutic hypothermia (TH) were the main outcomes. Temporal changes were compared across two epochs (2011–2013 and 2014–2016).

Results Among 407 462 infants admitted for neonatal care, 12 195 were diagnosed with HIE. 8166 infants ≥36 weeks GA had moderate/severe HIE, 62.1% (n=5069) underwent TH and mortality was 9.3% (n=762). Of infants with mild HIE (n=3394), 30.3% (n=1027) underwent TH and 6 died. In late preterm infants (34–35 weeks GA) with HIE (n=635, 5.2%), 33.1% (n=210) received TH and 13.1% (n=83) died. Between epochs (2011–2013 vs 2014–2016), mortality decreased for infants ≥36 weeks GA with moderate/severe HIE (17.5% vs 12.3%; OR 0.69, 95% CI 0.59 to 0.81, p<0.001). Treatment with TH increased significantly between epochs in infants with mild HIE (24.9% vs 35.8%, p<0.001) and those born late preterm (34.3% vs 46.6%, p=0.002).

Conclusions Mortality of infants ≥36 weeks GA with moderate/severe HIE has reduced over time, although many infants diagnosed with moderate/severe HIE do not undergo TH. Increasingly, mild HIE and late preterm infants with HIE are undergoing TH, where the evidence base is lacking, highlighting the need for prospective studies to evaluate safety and efficacy in these populations.

What is already known on this topic?

- Therapeutic hypothermia is an effective and safe treatment for infants ≥36 weeks gestational age with moderate/severe hypoxic-ischaemic encephalopathy (HIE), improving survival and reducing severe neurodisability.
- There is insufficient evidence to support the use of therapeutic hypothermia for mild HIE or in late preterm infants with HIE.

What this study adds?

- Use of therapeutic hypothermia for moderate or severe HIE has increased over time and is associated with a reduction in mortality.
- A large cohort of infants recorded as having moderate/severe HIE do not receive treatment with therapeutic hypothermia.
- Use of therapeutic hypothermia for mild HIE and in late preterm infants with HIE is increasing despite a lack of efficacy or safety.

INTRODUCTION

Hypoxic-ischaemic encephalopathy (HIE) is the leading cause of mortality and neurodisability in near-term and term babies.[1 2] Therapeutic hypothermia (TH) is an effective, safe treatment for infants ≥36 weeks gestational age (GA) with moderate/severe HIE, improving survival and major neurodisability.[1 3] Following the Total Body Hypothermia (TOBY) cooling trial[4] and the National Institute for Health and Care Excellence guidance in 2010,[5] TH is now the standard of care for infants ≥36 weeks GA with moderate/severe HIE in England and Wales. However, recent data on the current management and outcomes of infants with HIE in the TH era are lacking. The ambitious UK government target of halving brain injury occurring at or soon after birth by 2025 requires an understanding of the current incidence and management of HIE, allowing healthcare providers to target areas most likely to achieve these goals.[6]

There are increasing concerns that infants with mild HIE or those more preterm are also undergoing TH without evidence of benefit.[7–11] A recent UK survey highlighted 75% of cooling centres offered TH to infants with mild HIE.[9] Although infants with mild HIE have an increased risk of mortality and adverse neurological outcomes, there is insufficient evidence to establish any significant benefits or harm with the use of TH in these infants.[7 8] For the preterm population, Azzopardi *et al*[12] reported 3% (n=38) of UK TOBY cooling registrants were 34 or 35 weeks GA with a higher mortality rate (30%) compared with more mature infants (20%). Rao *et al*[10] also found preterm infants who received TH had a higher rate of mortality and white matter injury compared with term infants who received TH. These studies were limited by small numbers.

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The primary aim of this study was to establish the incidence of HIE in the TH era. The secondary aim was to evaluate mortality and changes to TH management.

METHODS

Study population

The National Neonatal Research Database (NNRD) holds prospectively recorded daily clinical data from every infant admitted to UK neonatal units along with outcomes. The NNRD contains an approved clinical database (the National Neonatal Data Set), within the NHS Data Dictionary national electronic data set,[13] and provides newborn brain injury data in the UK.[2] In 2011, approximately 90% of English neonatal units contributed to the NNRD and no units from Wales. From 2012 onwards, all units contributed to the database. Data are screened for errors and amended prior to entry into the database.

Data from the Office for National Statistics (ONS) were used as denominator data (excluding Scotland and Northern Ireland) to calculate national incidence rates of HIE using live birth by GA for each year of the study period.[14]

Data collection

Data were extracted on all infants 34–42 weeks GA who were admitted to neonatal units in England and Wales from 2011 to 2016. Infants with HIE were identified using the 'Principal Diagnosis at Discharge' and 'HIE score' data fields, as diagnosed and inputted by the clinical teams in each centre (online supplemental table 1), and allocated the most severe HIE grade issued during their admission. Infants managed with any TH were identified using the 'Principal Procedures During Stay' or 'Principal Diagnosis at Discharge' or 'Therapeutic Hypothermia' data fields. Infants who did not have a diagnosis of HIE but received TH were not categorised as HIE.

Infants weighing greater than 5500 g (erroneous data) or missing key episode data items (GA, principal diagnosis, place of birth or mortality data) were excluded from the study.

Outcome

The primary aim was the incidence of HIE by live births for England and Wales in the TH era. The secondary aims were to evaluate the management of these infants and mortality and describe any temporal changes.

Statistical analysis

Extrapolation methods based on actual admission numbers and number of cases from 2012 to 2016 when all units contributed to the database were used to estimate the incidence of HIE for 2011 as previously described.[2]

The population incidence rate of HIE per 1000 live births was calculated using NNRD data to identify cases and ONS data for live birth rates per year by GA as the denominator. The study population was divided into two equal epochs (2011–2013 and 2014–2016) to evaluate any changes over time. Infants with moderate/severe HIE who died without undergoing TH were considered with babies who received TH for analysis as these are likely to represent infants who met the cooling criteria but were too sick to undergo treatment or care was reorientated; data for babies who died without undergoing TH are also presented.

For subgroup analyses, infants were further divided into late preterm (34–35 weeks GA) and mild (grade 1) HIE subgroups. Associations between demographic, clinical variables and death were assessed using χ^2 test for categorical data and Mann-Whitney U test for non-normally distributed continuous data. Subgroup characteristics were compared and analysed with univariate analysis and presented as unadjusted OR with 95% CI. All statistical analyses were performed using Stata SE V.15.

RESULTS

A total of 407 462 infants were admitted for neonatal care during the study period. Of these, 12 195 infants had a recorded diagnosis of HIE, giving an incidence of 2.96 per 1000 live births and accounting for 3% of neonatal unit admissions ≥34 weeks GA (online supplemental figure 1). Mortality for all infants with recorded HIE was 7.0% (n=851).

The incidence of moderate/severe HIE in infants ≥36 weeks GA was 2.03 per 1000 (n=8166); 1.26 per 1000 (n=5069) were treated with TH (n=4949) or died without TH treatment (n=120) (table 1, online supplemental table 2). The incidence of moderate/severe HIE in infants ≥36 weeks GA remained similar between epochs (table 1), but TH treatment significantly increased between epochs (54.6% vs 66.6%, p<0.001).

The characteristics of infants ≥36 weeks GA with moderate/severe HIE who did or did not undergo TH were compared

Table 1 Incidence of HIE for the whole study population, infants ≥36 weeks gestational age with moderate/severe HIE and infants ≥36 weeks gestational age with moderate/severe HIE treated with TH

	Any HIE		Moderate/severe HIE and ≥36 gestational weeks at birth					
Year	n	Rate per 1000 live births	n	Rate per 1000 live births	Received TH (n)	Received TH (%)	Received or died without TH (n)	Received or died without TH (%)
2011*	2253 (2320–2372)	3.22 (3.32–3.39)	1592 (1631–1668)	2.33 (2.33–2.39)	694 (704–706)	43.6 (42.3–43.2)	722 (733–735)	45.4 (43.9–45.1)
2012	1916	2.71	1267	1.83	723	57.1	741	58.5
2013	1906	2.81	1213	1.83	806	66.4	823	67.8
2014	2135	3.17	1422	2.16	937	65.9	951	66.9
2015	2104	3.11	1396	2.11	928	66.5	953	68.3
2016	1881	2.77	1276	1.93	861	67.5	879	68.9
Total	12 195	2.96	8166	2.03	4949	60.6	5069	62.1
Epoch 1*	6075 (6142–6194)	2.91 (2.94–2.96)	4072 (4111–4138)	2.00 (2.01–2.03)	2223 (2233–2235)	54.6† (54.0–54.4†)	2286 (2297–2299)	56.1† (55.5–55.9†)
Epoch 2	6120	3.01	4094	2.07	2726	66.6†	2783	68.0†

*Range included to account for 2011 data not available for all hospitals (see the Methods section).
†Significant change between epoch 1 and epoch 2 (p<0.001).
HIE, hypoxic-ischaemic encephalopathy; TH, therapeutic hypothermia.

Table 2 Comparison of antenatal and delivery characteristics of infants ≥36 weeks GA admitted to neonatal units with moderate/severe HIE who received, or died without, TH or did not receive TH

	Infants ≥36 weeks GA with moderate/severe HIE				
Variable	No TH (n=3056)*	Received TH (n=5069)*	Missing n (%)	OR (95% CI)	P value†
Antenatal characteristics					
Diabetes mellitus	19 (0.6)	59 (1.2)	0	1.88 (1.12 to 3.16)	0.02
Gestational diabetes	110 (3.6)	186 (3.7)	0	1.02 (0.80 to 1.30)	0.87
Pre-eclampsia	167 (5.5)	233 (4.6)	0		0.24
Risk factors of early infection‡	788 (25.8)	1116 (22.0)	0	0.81 (0.73 to 0.90)	<0.001
Delivery characteristics					
Gender (male)	1824 (59.7)	2771 (54.7)	3 (<0.01)	0.81 (0.74 to 0.89)	<0.001
GA (weeks)	40 (38–41)	40 (38–41)	0	0.89 (0.82 to 0.97)	<0.001
Birth weight (g)	3379 (2980–3780)	3340 (2950–3760)	0	0.99 (0.98 to 1.00)	0.06
>98th centile	173 (5.7)	289 (5.7)	0	1.01 (0.83 to 1.22)	0.94
Intrapartum events§	238 (7.8)	629 (12.4)	0	1.68 (1.43 to 1.96)	<0.001
Apgar 1 min	3 (2–4)	1 (1–3)	509 (6.2)	0.34 (0.31 to 0.37)	<0.001
Apgar 5 min	6 (5–8)	4 (2–6)	503 (6.2)	0.21 (0.19 to 0.23)	<0.001
Significant resuscitation¶	730 (23.9)	3070 (60.6)	0	4.89 (4.39 to 5.44)	<0.001
Venous cord pH	7.18 (7.04–7.28)	7.13 (6.96–7.25)	2396 (29.5)	0.94 (0.93 to 0.95)	<0.001

Data items diabetes mellitus, gestational diabetes, pre-eclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables were collected using a tick box so it was not possible to accurately determine missing data from absence of a characteristic.
*Data are n (%) or median (IQR).
†Categorical data analysed using χ^2 test; non-normally distributed continuous data analysed using Mann-Whitney U test.
‡Maternal fever, chorioamnionitis, prolonged rupture of membranes and urinary tract infection.
§Cord prolapse, shoulder dystocia, abruption and reduced fetal movements.
¶Chest compression, intubation and drugs.
GA, gestational age; HIE, hypoxic-ischaemic encephalopathy.

(table 2). Overall, 62.1% (n=5069) of infants ≥36 weeks GA with moderate/severe HIE were cooled or died without TH. These infants were significantly more likely to have a background of acute intrapartum events, need for significant resuscitation, lower Apgar scores and lower cord venous pH compared with non-cooled infants. Mortality of infants ≥36 weeks GA with moderate/severe HIE was 9.3% (n=762) and decreased over time between epochs (10.0% vs 8.7%; OR 0.85 (95% CI 0.74 to 0.99), p=0.04). For those undergoing TH (excluding infants who died prior to cooling), there was a significant reduction in mortality between 2011–2013 (n=336, 15.1%) and 2014–2016 (n=297, 10.9%; OR 0.67 (95% CI 0.58 to 0.81), p<0.001). This pattern remained evident after inclusion of infants who died prior to cooling (mortality in epoch 1: 17.5% (n=402); epoch 2: 12.3% (n=355); OR 0.69 (95% CI 0.59 to 0.81), p<0.001). Overall, infants born between 2014 and 2016 had a higher rate of early infection and significant resuscitation (online supplemental table 3).

Infants ≥36 weeks with mild HIE

There were 3394 infants ≥36 weeks GA diagnosed with mild HIE (0.84 per 1000 live births), similar between 2011–2013 (n=1712) and 2014–2016 (n=1682, p=0.57). Mortality was low in this population, with six deaths overall and no difference over time, although infants admitted in 2014–2016 had a higher rate of early infection and significant resuscitation (online supplemental table 4). In total, 1027 (30.3%) were managed with TH and 338 (10.0%) were transported within the first 48 hours from non-tertiary units into a cooling centre. The proportion of infants treated with TH significantly increased over time between 2011–2013 (n=426, 24.9%) and 2014–2016 (n=603, 35.8%, p<0.001).

The characteristics of infants ≥36 weeks GA with mild HIE who did or did not undergo TH were compared (table 3). Those who received TH (including the six infants who died without TH treatment) had a lower birth weight, required more resuscitation, had lower Apgar scores and had lower cord venous pH. Infants with moderate/severe HIE were significantly more likely to have acute intrapartum events, require significant resuscitation and have lower Apgar scores compared with infants with mild HIE (online supplemental table 5).

Late preterm infants (34–35 weeks)

In total, 635 late preterm infants (6.27 per 1000) were diagnosed with any grade HIE (online supplemental table 6); this remained stable through epoch 1 and epoch 2 with 6.00 per 1000 vs 6.55 per 1000, respectively (p=0.27). Of these 81.5% (n=518) had moderate/severe HIE. Late preterm infants treated with TH were significantly more likely to have acute intrapartum events, require significant resuscitation, have lower Apgar scores and have lower cord venous pH (table 4).

Among late preterm infants, 259 (40.8%) were treated with TH (n=210) or died without TH (n=49). This significantly increased between epoch 1 (n=103, 34.3%) and epoch 2 (n=156, 46.6%, p=0.002), although mortality remained unchanged (n=36 (12.0%) vs n=47 (14.0%), p=0.51). The rate of moderate/severe HIE and the associated mortality were greatest in the late preterm population compared with those ≥36 weeks GA (p<0.001; figure 1 and online supplemental table 6). The characteristics between epochs were similar (online supplemental table 7). Overall, mortality in infants with moderate/severe HIE in the late preterm population was 16.0% (n=83) compared with those ≥36 weeks GA at 9.3% (n=762, p=0.005).

Table 3 Comparison of antenatal and delivery characteristics between infants ≥36 weeks GA admitted to neonatal units with mild HIE who received, or died without, TH or did not receive TH

	Infants ≥36 weeks GA with mild HIE				
Variable	No TH (n=2238)*	Received TH (n=1029)*	Missing n (%)	OR (95% CI)	P value†
Antenatal characteristics					
Diabetes mellitus	18 (0.8)	7 (0.7)	0	0.88 (0.37 to 2.12)	0.78
Gestational diabetes	81 (3.5)	26 (2.5)	0	0.72 (0.46 to 1.13)	0.15
Pre-eclampsia	96 (4.1)	33 (3.2)	0	0.77 (0.52 to 1.16)	0.21
Risk factors of early infection‡	441 (18.9)	211 (20.5)	0	1.11 (0.92 to 1.33)	0.27
Delivery characteristics					
Gender (male)	1425 (61.0)	590 (57.5)	1	0.86 (0.74 to 1.00)	0.05
GA (weeks)	40 (39–41)	40 (39–41)	0	0.95 (0.83 to 1.08)	0.43
Birth weight (g)	3410 (3026–3800)	3360 (2965–3740)	0	0.98 (0.97 to 0.99)	0.005
>98th centile	121 (5.2)	33 (3.2)	0	0.61 (0.41 to 0.90)	0.01
Intrapartum events§	170 (7.3)	89 (8.7)	0	1.21 (0.92 to 1.57)	0.17
Apgar 1 min	4 (2–6)	3 (1–5)	152 (4.7)	0.47 (0.41 to 0.54)	<0.001
Apgar 5 min	7 (5–8)	5 (4–7)	141 (4.3)	0.34 (0.30 to 0.40)	<0.001
Significant resuscitation¶	431 (18.4)	433 (42.1)	0	3.21 (2.71 to 3.80)	<0.001
Venous cord pH	7.16 (7.04–7.27)	7.14 (6.99–7.25)	892 (27.3)	0.97 (0.96 to 0.98)	<0.001

Data items diabetes mellitus, gestational diabetes, pre-eclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables were collected using a tick box so it was not possible to accurately determine missing data from absence of a characteristic.
*Data are n (%) or median (IQR).
†Categorical data analysed using χ^2 test; non-normally distributed continuous data analysed using Mann-Whitney U test.
‡Maternal fever, chorioamnionitis, prolonged rupture of membranes and urinary tract infection.
§Cord prolapse, shoulder dystocia, abruption and reduced fetal movements.
¶Chest compression, intubation and drugs.
GA, gestational age; HIE, hypoxic-ischaemic encephalopathy; TH, therapeutic hypothermia.

Table 4 Comparison of antenatal and delivery characteristics of infants 34–35 weeks GA admitted to neonatal units with hypoxic-ischaemic encephalopathy who received, or died without, TH or did not receive TH

	Infants at 34–35 weeks GA with hypoxic-ischaemic encephalopathy				
Variable	No TH (n=366)*	Received TH (n=259)*	Missing n (%)	OR (95% CI)	P value†
Antenatal characteristics					
Diabetes mellitus	10 (2.7)	11 (4.2)	0	1.58 (0.66 to 3.78)	0.30
Gestational diabetes	21 (5.7)	20 (7.7)	0	1.37 (0.73 to 2.59)	0.32
Pre-eclampsia	51 (13.9)	25 (9.7)	0	0.66 (0.40 to 1.10)	0.11
Risk factors of early infection‡	98 (26.8)	64 (24.7)	0	0.90 (0.62 to 1.29)	0.56
Delivery characteristics					
Gender (male)	214 (58.5)	152 (58.7)	1	1.00 (0.73 to 1.39)	0.99
GA (weeks)	35 (34–35)	35 (34–35)	0	1.92 (1.38 to 2.69)	0.01
Birth weight (g)	2250 (2000–2540)	2344 (2080–2640)	0	1.05 (1.01 to 1.08)	<0.01
>98th centile	20 (5.5)	18 (7.0)	0	1.29 (0.67 to 2.50)	0.44
Intrapartum events§	50 (13.7)	58 (22.4)	0	1.82 (1.19 to 2.77)	<0.001
Apgar 1 min	3 (1–5)	1 (0–3)	30 (4.8)	0.23 (0.17 to 0.32)	<0.001
Apgar 5 min	6 (4–8)	3 (1–5)	34 (5.4)	0.18 (0.13 to 0.24)	<0.001
Significant resuscitation¶	113 (30.9)	175 (67.6)	0	4.66 (3.23 to 6.73)	<0.001
Venous cord pH	7.16 (6.95–7.28)	7.06 (6.85–7.25)	226 (36.2)	0.93 (0.90 to 0.97)	0.003

Data items diabetes mellitus, gestational diabetes, pre-eclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables were collected using a tick box so it was not possible to accurately determine missing data from absence of a characteristic.
*Data are n (%) or median (IQR).
†Categorical data analysed using χ^2 test; non-normally distributed continuous data analysed using Mann-Whitney U test.
‡Maternal fever, chorioamnionitis, prolonged rupture of membranes and urinary tract infection.
§Cord prolapse, shoulder dystocia, abruption and reduced fetal movements.
¶Chest compression, intubation and drugs.
GA, gestational age; TH, therapeutic hypothermia.

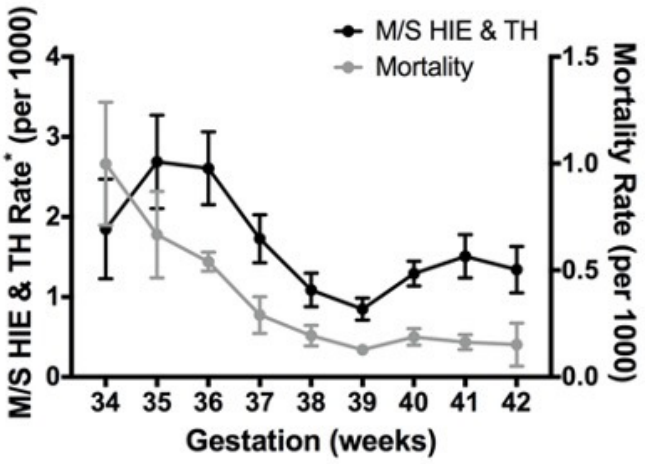

Figure 1 Rate of moderate/severe HIE treated with therapeutic hypothermia and mortality within the study population per 1000 live births at each gestational week. *Data include infants with M/S HIE but were not cooled. HIE, hypoxic-ischaemic encephalopathy; M/S, moderate/severe; TH, therapeutic hypothermia.

DISCUSSION

This large national population-based study has shown the incidence of recorded moderate/severe HIE in infants ≥36 weeks GA remains similar over time, but there has been a reduction in mortality. Based on national guidance for HIE, only 62.1% of eligible infants received TH. Furthermore, we have shown for the first time the increasing number of infants with mild HIE and those born late preterm undergoing TH, without sufficient evidence to support this approach. During the most recent epoch, TH was administered to 36% of infants with mild HIE and 47% of late preterm infants with HIE. These findings are important particularly for late preterm infants where mortality associated with moderate/severe HIE increases with decreasing gestation.

Following publication of the TOBY trial[4] and the national guidance for TH,[5] treatment with TH for moderate/severe HIE in infants ≥36 weeks GA has increased in England and Wales, with a reduction in mortality. Mortality for infants undergoing TH has decreased by more than half since the TOBY study from 23.9%[4] to 15.1% in 2011–2013 and 10.9% in 2014–2016. These findings could reflect changes in practice with earlier recognition and treatment, mild cases being diagnosed as moderate and undergoing TH, as well as improving intensive care management. In our study, 37.9% of infants with recorded moderate/severe HIE did not receive TH. These infants may include those who were too sick to cool or in whom HIE was diagnosed outside the therapeutic cooling window. The clinical decisions for not cooling an eligible infant are not recorded within this database. However, the grading of HIE can be subjective, leading to some clinicians opting not to treat borderline infants, whereas others may have graded these infants as moderate HIE. Likewise, infants may have been incorrectly misclassified as HIE or misdiagnosed as mild and therefore not cooled. Another potential explanation is that TH use was recorded inaccurately or was unrecorded despite being administered; however, TH data are used to reimburse individual hospitals so this data item is usually well recorded. Our findings do, however, potentially suggest a large proportion of eligible infants do not receive TH.

The number of infants with mild HIE undergoing TH has increased over time and their mortality rate is very low. Previous studies of infants with mild HIE demonstrated an increased risk of mortality and adverse neurological outcome.[15–17] However, TH in these infants has not been shown to reduce death or neurodisability,[7 8] although one study reported less brain injury on MRI scans.[18] Management of these infants with TH in the absence of robust evidence risks exposing them to unnecessary treatment with its associated morbidity, such as pain and respiratory support.[19 20] In the UK, TH is mainly undertaken in tertiary centres, increasing the pressure on cot capacity and specialist neonatal transportation services[21] with the need to transfer more infants. Current, ongoing prospective studies (Therapeutic Hypothermia for Infants with Mild Encephalopathy(TIME)[22] and Optimising the Duration of Cooling Therapy in Mild Neonatal Encephalopathy (COMET)[23]) may provide much needed evidence to establish the benefit and safety of TH use for mild HIE.

To our knowledge, this is the largest study to date of late preterm infants with HIE including those treated with TH. Our study has shown preterm infants have a higher incidence rate of moderate/severe HIE diagnosed compared with term infants. The TOBY study demonstrated TH was a safe and effective treatment in infants ≥36 weeks GA,[4] yet TH is increasingly being used in late preterm infants. Other large randomised controlled trials of TH for HIE included infants at 35 weeks GA but did not separately report their outcomes.[19 24 25] The pathophysiology of brain injury in late preterm infants is likely to be different from those at term; Rao *et al*[10] reported a higher incidence of white matter injury and mortality due to the severity of the encephalopathy in late preterm infants. Our study also demonstrated late preterm infants with moderate/severe HIE were four times more likely to die than infants ≥36 week GA (0.80 per 1000 vs 0.19 per 1000 live births), highlighting the need for well-designed prospective randomised controlled studies to evaluate the safety and efficacy in this subgroup.

Strengths and limitations

The study's main strength is the use of national data set from a reliable database of prospective, routinely recorded data.[26] This has allowed analysis with a large sample size and provides an estimate of the incidence of HIE within a national healthcare service. To our knowledge, this study has analysed the largest group of late preterm infants with HIE to date compared with previous studies.[10–12 27 28] Because only 90% of neonatal units contributed to the NNRD in 2011, we calculated the lower and upper estimates of missing data using actual data from admission and HIE rate from 2012 to 2016.[2]

A further strength is the analysis of data after the introduction of a national guideline providing diagnostic criteria for treatment,[5] although we acknowledge clinical evaluation and grading of HIE are subjective and may lead to variations in diagnosis. Furthermore, the database does not hold the individual components of the scoring system, so we were limited by the diagnostic coding of the clinical team caring for the infant. To address the ambition to minimise newborn brain injury in the UK,[6] it would be useful to standardise recorded data with diagnostic criteria and outcomes, allowing more robust national rates and comparisons between centres. Inclusion of additional data fields based on established severity scoring systems (including modified Sarnat score and amplitude-intergrated electroencephalography (aEEG) as specified in UK guidance[29]) could help in standardisation and accuracy of data entry.

The main limitation of studies using large databases is the errors or imprecision in data entry. This is limited through

screening the data for erroneous entries, although this cannot mitigate completely if the data are incorrect at the point of entry. A further limitation is that we do not have neuroimaging results or long-term neurodevelopmental outcome data as these are not recorded in the database or are often incomplete, making analysis unreliable. These outcomes would be of significant interest with such a large data set and are more useful as a measure of brain injury, than the requirement for TH treatment alone, as many infants will have a normal outcome without injury.

CONCLUSION

The use of TH for infants with moderate/severe HIE is increasing and is associated with a reduction in mortality, although a large proportion of potentially eligible infants do not receive treatment. There are also increasing numbers of infants with mild HIE and late preterm infants with HIE undergoing TH outside of the current evidence base. These data highlight the urgent need for initiatives to improve delivery of effective evidence-based practice to all eligible infants and well-designed, prospective studies to evaluate the safety and efficacy in late preterm infants and those with mild HIE.

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Contributors LS and DS made substantial contributions to the concept, planning, design of the study and acquisition of data. LS and DS analysed and interpreted the data. All authors assisted in drafting and editing the manuscript. All authors approved the final version for publication. DS had full access to all the data in the study and takes full responsibility for the integrity of the data and accuracy of the data analysis.

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Competing interests CG has received support from Chiesi Pharmaceuticals to attend an educational conference; in the past 5 years he has been an investigator on received research grants from Medical Research Council, National Institute for Health Research, Canadian Institutes of Health Research, Department of Health in England, Mason Medical Research Foundation, Westminster Medical School Research Trust and Chiesi Pharmaceuticals, and has been an unremunerated member of the Neonatal Data Analysis Unit Board, which oversees the NNRD.

Patient consent for publication Not required.

Ethics approval Ethical approval was given by the London-City and East Research Ethics Committee (REC: 17/LO/1822).

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Supplementary Online Content

Trends in the Incidence and Management of Hypoxic-Ischaemic Encephalopathy in the Therapeutic Hypothermia Era: A national population study

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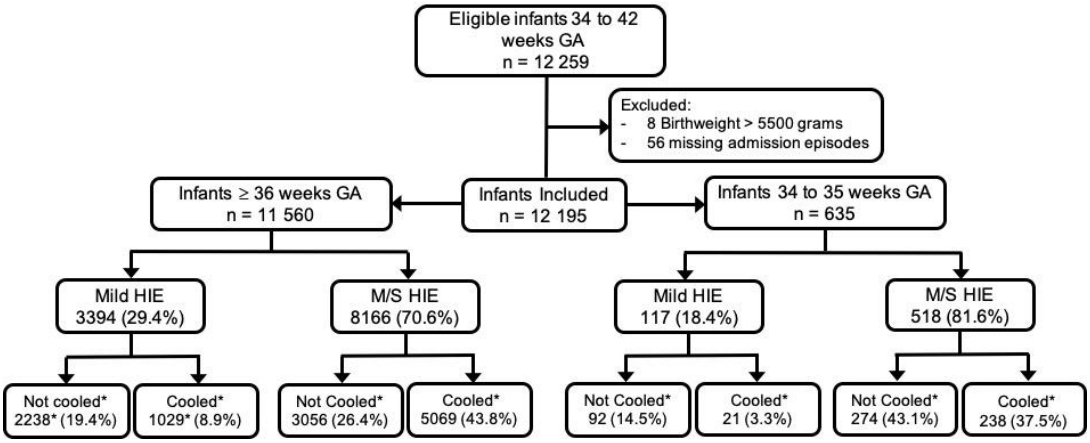
Content:

Supplementary Figure 1. Flowchart of study participants demonstrating included/excluded infants and rate of hypoxic ischaemic encephalopathy for each gestational subgroup



* Therapeutic hypothermia data not available for all infants within each subgroup
GA, gestation age; m/s moderate/severe; HIE, Hypoxic Ischaemic encephalopathy

Supplementary Table 1. National Neonatal Research Database Hypoxic Ischaemic Encephalopathy and Therapeutic Hypothermia data identifiers

Principal Diagnosis at Discharge database entry
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
Principal procedures during stay
Therapeutic Hypothermia - Therapeutic Hypothermia - Therapeutic Hypothermia (whole body cooling) - Hypothermia Therapeutic

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Supplementary Table 2. Comparison of antenatal and delivery characteristics between epochs (2011-13 and 2014-16) for infants ≥36 weeks gestational age with moderate/severe hypoxic ischaemic encephalopathy who died without therapeutic hypothermia

Variables	Number of infants (n=120)*	Missing n (%)
Antenatal Characteristics		
Diabetes mellitus	0	0
Gestational diabetes	4 (3.3)	0
Preeclampsia	2 (1.7)	0
Risk factors of early infection[a]	22 (18.3)	0
Delivery Characteristics		
Gender (male)	61 (50.8)	0
Gestational age (weeks)	39 (37 - 40)	0
Birth weight (grams)	3252 (2840 - 3576)	0
> 98th Centile	3 (2.5)	0
Intrapartum events[b]	13 (10.8)	0
Apgar 1 minute	2 (0 - 5)	9 (7.5)
Apgar 5 minute	5 (1 - 8)	9 (7.5)
Significant resuscitation[c]	58 (38.1)	0
Venous Cord pH	7.23 (7.09 - 7.32)	55 (45.8)
Day of death (days)	0.7 (0.37 - 2.0)	0

* Data are n (%) or median (interquartile range)
[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
[c] Chest compressions, intubation, drugs
Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

Supplementary Table 3. Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants ≥36 weeks gestational age with moderate/severe hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

	Infants ≥36 weeks GA with moderate/severe HIE and TH				
Variables	Epoch 1 (n=2286)*	Missing n (%)	Epoch 2 (n=2783)*	Missing n (%)	p value**
Diabetes mellitus	13 (0.6)	0	46 (1.7)	0	<0.001
Gestational diabetes	63 (2.8)	0	123 (4.4)	0	0.002
Preeclampsia	111 (4.9)	0	122 (4.3)	0	0.43
Risk factors of early infection[a]	384 (16.8)	0	732 (26.3)	0	<0.001
Delivery Characteristics					
Gender (male)	1244 (54.4)	0	1528 (54.9)	0	0.70
Gestational age (weeks)	40 (38 – 41)	0	40 (38 – 41)	0	0.04
Birth weight (grams)	3355 (2958 – 3760)	0	3330 (2940 – 3750)	0	0.29
> 98th Centile	131 (5.7)	0	158 (5.6)	0	0.94
Intrapartum events[b]	278 (12.2)	0	351 (12.6)	0	0.63
Apgar 1 minute	1 (0 – 3)	156 (6.8)	1 (1 – 3)	209 (7.5)	0.37
Apgar 5 minute	4 (2 – 6)	159 (7.0)	4 (2 – 6)	198 (7.1)	0.03
Significant resuscitation[c]	1136 (51.9)	0	1934 (71.3)	0	<0.001
Venous Cord pH	7.11 (6.93 – 7.25)	698 (30.5)	7.13 (6.97 – 7.26)	803 (28.8)	0.009

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia
* Data are n (%) or median (interquartile range)
** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test
[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
[c] Chest compressions, intubation, drugs
Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

Supplementary Table 4. Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants ≥36 weeks gestational age with mild hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

	Infants ≥ 36 weeks GA with mild HIE and TH				
Variables	Epoch 1 (n=426)*	Missing n (%)	Epoch 2 (n=603)*	Missing n (%)	p value**
Antenatal Characteristics					
Diabetes mellitus	1 (0.2)	0	6 (1.0)	0	0.14
Gestational diabetes	8 (1.9)	0	18 (3.0)	0	0.27
Preeclampsia	10 (2.3)	0	23 (3.8)	0	0.19
Risk factors of early infection[a]	69 (16.2)	0	142 (23.5)	0	0.004
Delivery Characteristics					
Gender (male)	243 (57.0)	0	347 (57.5)	0	0.85
Gestational age (weeks)	40 (39 – 41)	0	40 (39 – 41)	0	0.60
Birth weight (grams)	3405 (2970 – 3760)	0	3330 (2950 – 3705)	0	0.10
> 98th Centile	16 (3.8)	0	17 (2.8)	0	0.40
Intrapartum events[b]	37 (8.7)	0	52 (8.6)	0	0.97
Apgar 1 minute	2 (1 – 4)	38 (8.9)	3 (1 – 5)	58 (9.6)	0.02
Apgar 5 minute	5 (4 – 7)	40 (9.4)	6 (4 – 7)	50 (8.3)	0.04
Significant resuscitation[c]	163 (38.3)	0	270 (44.8)	0	0.04
Venous Cord pH	7.14	120 (28.2)	7.14	161 (26.7)	0.78

	(6.98 – 7.25)	(6.99 – 7.25)

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia
* Data are n(%) or median (interquartile range)
** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test
[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
[c] Chest compressions, intubation, drugs
Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

Supplementary Table 5. Comparison of antenatal and delivery characteristics between infants ≥36 weeks with moderate/severe and mild hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

	Infants ≥ 36 weeks GA with M/S versus mild HIE and TH				
Variables	M/S HIE (n=5069)*	Missing n (%)	Mild HIE (n=1029)*	Missing n (%)	p value**
Antenatal Characteristics					
Diabetes mellitus	59 (1.2)	0	7 (0.7)	0	0.17
Gestational diabetes	186 (3.7)	0	26 (2.5)	0	0.07
Preeclampsia	233 (4.6)	0	33 (3.2)	0	0.05
Risk factors of early infection[a]	1116 (22.0)	0	211 (20.5)	0	0.28
Delivery Characteristics					
Gender (male)	2772 (54.7)	0	590 (57.3)	0	0.12
Gestational age (weeks)	40 (38 – 41)	0	40 (39 – 41)	0	<0.001
Birth weight (grams)	3340 (2950 – 3760)	0	3360 (2965 – 3740)	0	0.98
> 98th Centile	289 (5.7)	0	33 (3.2)	0	0.001
Intrapartum events[b]	629 (12.4)	0	89 (8.6)	0	0.001
Apgar 1 minute	1 (0 - 3)	365 (7.2)	3 (1 – 5)	96 (9.3)	<0.001
Apgar 5 minute	4 (2 – 6)	357 (7.0)	5 (4 – 7)	90 (8.7)	<0.001
Significant resuscitation[c]	3070 (60.6)	0	433 (42.1)	0	<0.001
Venous Cord pH	7.13 (6.96 – 7.25)	1501 (29.6)	7.14 (6.99 – 7.25)	281 (27.3)	0.06

GA, Gestational age; m/s, moderate/severe; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia

* Data are n (%) or median (interquartile range)

** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test

[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection

[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements

[c] Chest compressions, intubation, drugs

Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

Supplementary Table 6. Incidence rates for the whole study population by gestational age for any grade of hypoxic ischaemic encephalopathy (HIE), moderate/severe HIE and mortality with moderate/severe HIE

Gestation (weeks)	Any grade HIE (n=12195)	Rate per 1000 live births	M/S HIE & TH (n=5307)	Rate per 1000 live births	Died & M/S HIE (n=843)	Rate per 1000 live births
34	255	6.22	76	1.85	41	1.00
35	380	6.31	162	2.69	40	0.66
36	615	5.04	319	2.61	66	0.54
37	977	3.50	483	1.73	81	0.29
38	1344	2.38	612	1.09	109	0.19
39	1989	1.97	858	0.85	129	0.13
40	3319	2.94	1456	1.29	212	0.19
41	2837	3.63	1163	1.51	144	0.18
42	479	3.49	178	1.34	21	0.15
Total						
34-35 weeks	635	6.27	238	2.35	81	0.80
≥36 weeks	11560	3.03	5069	1.26	762	0.19

M/S, moderate/severe; TH, Therapeutic Hypothermia

Supplementary Table 7. Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants 34 to 35 weeks with hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

	Infants 34 to 35 weeks GA with HIE and TH				
Variables	Epoch 1 (n=103)*	Missing n (%)	Epoch 2 (n=156)*	Missing n (%)	p value**
Antenatal Characteristics					
Diabetes mellitus	1 (1.0)	0	10 (6.4)	0	0.03
Gestational diabetes	6 (5.8)	0	14 (9.0)	0	0.35
Preeclampsia	8 (7.8)	0	17 (10.9)	0	0.40
Risk factors of early infection[a]	24 (23.3)	0	40 (25.6)	0	0.67
Delivery Characteristics					
Gender (male)	60 (58.3)	0	92 (59.0)	0	0.91
Gestational age (weeks)	35 (34 – 35)	0	35 (34 – 35)	0	0.38
Birth weight (grams)	2275 (2030 - 2650)	0	2370 (2122 – 2640)	0	0.14
> 98th Centile	6 (5.8)	0	12 (7.7)	0	0.56
Intrapartum events[b]	21 (20.4)	0	37 (23.7)	0	0.53
Apgar 1 minute	1 (0 – 3)	7 (6.8)	1 (0 – 3)	8 (5.1)	0.79
Apgar 5 minute	4 (1 – 5)	8 (7.8)	3 (1 – 6)	8 (5.1)	0.64
Significant resuscitation[c]	56 (54.4)	0	119 (76.3)	0	<0.001
Venous Cord pH	7.03 (6.85 – 7.23)	40 (38.8)	7.08 (6.85 – 7.26)	60 (38.5)	0.56

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia
* Data are n(%) or median (interquartile range)
** Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test
[a] Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection
[b] Cord prolapse, shoulder dystocia, abruption, reduced fetal movements
[c] Chest compressions, intubation, drugs
Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic