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Neonatal Therapeutic Hypothermia for Neonatal Encephalopathy: Mortality and Neurodevelopmental Outcome

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Abstract

Aim

To study the mortality and neurodevelopmental outcome of infants with neonatal encephalopathy (NE) who required therapeutic hypothermia (TH).

Methods

All infants requiring TH between Jan 2009 – Dec 2016 at a single NICU were included. Data was obtained from clinical notes, MRI brain reports, The Bayley Scales of infant and toddler development-III (BSIDIII).

Results

127 infants received TH. 12 infants died. Of the 115 surviving infants, 75 (65%) were male with a median birthweight of 3.54 kg and median gestation of 40 weeks. Brain MRIs of the surviving cohort were normal in 91 (81%) infants. The Bayley's score showed that the number (%) of infants below the normal range (≤ 89) was: Motor:15/112 (13.9%), Cognitive: 17/112 (15.7%), Speech & Language: 33/112 (33.3%). When the babies are subdivided into those with normal and abnormal brain MRIs the proportion with scores ≤89 are:

Normal MRI: Motor - 8.9%, Cognitive - 8.9%, Speech & Language - 26.9%.
Abnormal MRI: Motor - 30.4%, Cognitive – 39.1%, Speech & Lang – 47.8%.

Conclusion

In this series of infants with NE requiring TH there was a preponderence of male infants: 78 vs 49. Among those who died there was a preponderence of females: 9 vs 3. The neonatal mortality rate in our series (9.4%) is similar to the Irish national data. The majority of infants had a satisfactory BSID-III score and a normal MRI brain report. The brain MRI is predictive of neurodevelopmental outcome.

Introduction

Hypoxic-ischaemic encephalopathy (HIE) is one of the most common neurological disorders of the perinatal period, and a major cause of significant morbidity and mortality in childhood.[1,] It has an incidence of 1.5 to 2.5 per 1000 live births in developed countries.[2] HIE, can, if significant, trigger a cascade of neuronal injury, leading to neonatal encephalopathy (NE) with resultant long-term neurological sequelae.

Therapeutic hypothermia (TH) has emerged as the international gold standard of care for neonates with moderate or severe encephalopathy.[3,] A Cochrane Systematic Review (2013) concluded that TH in term and late preterm infants with HIE resulted in a statistically significant and clinically important reduction in mortality and neuro-disability at 18 months of age.[4]

The Bayley Scales of Infant and Toddler Development [5] (Bayley-lll) and brain Magnetic Resonance Imaging (MRI), have predominantly been used to assess, predict and counsel about neurodevelopmental outcomes in these newborns.[6]

We have reviewed all neonates requiring TH in our unit over an eight-year period. Our primary outcome was to describe the short-term and medium-term neurodevelopmental outcomes [using the Bayley Scales of Infant and Toddler Development (Bayley-lll) [7]] and neuro-radiological findings (using the Barkovich MR Scoring System [8]) of the surviving neonates.

Methods

This was a retrospective descriptive study of all neonates who received TH for neonatal encephalopathy at a single, level 3 NICU over an eight-year period (January 2009 – December 2016).

Infants received TH according to the established hospital TH Protocol. The National Neonatal TH Candidacy Checklist outlines the criteria for initiation of TH used at this neonatal unit.[9]

Clinical psychology, medical and nursing databases were used to identify all infants who received TH at this centre over the study period. Medical charts were reviewed to provide clinical and demographic data. Infants were classified in the medical notes as having a mild, moderate or severe encephalopathy based on clinical Sarnat assessment. This data was extracted and recorded. Bayley-lll scores for the study population were retrieved from clinical psychology records. The Bayley Assessment Scores were performed by a clinical psychologist (MS) at 2 years corrected gestational age. The MRI brain reports of this infant cohort were sourced from a combination of medical charts and electronic radiology records. These were reviewed and classified using the validated Barkovich MR Scoring System by a Consultant Paediatric Radiologist (VD).

The collected data was anonymised and entered on a Microsoft Excel spreadsheet. The data was analysed using descriptive statistics.

Results

A total of 127 neonates received therapeutic hypothermia over the eight-year study period. Twelve neonates (9.4%) died shortly after birth.

Characteristics of infants who died

Twelve infants died in the neonatal period., at a median of 5.5 days. Of these, 3 infants (25%) were male. The median birth weight was 3545g (IQR 767). The median gestation was 40 weeks (IQR 2). Median apgar scores at 5, 10, 15 and 20 minutes were 0 (IQR 2), 2 (IQR 3.25), 3 (IQR 5.25) and 5 (IQR 2.5) respectively. Mean cord gases were pH 6.8, BE -18, pH 7.0, BE -15. Nine infants (75%) required inotropic support. Eight infants (67%) had clinical and electrographically detected seizures. All infants had a severe encephalopathy based on Sarnat examination. Six infants (50%) had an MRI brain at a median of 2.5 days. All had extensive basal ganglia and watershed injuries.

The characteristics of the surviving infants is shown in Table 1.

Table 1. Neonatal Encephalopathy requiring Therapeutic Hypothermia - Characteristics of Surviving Infants [Number of patients (%)]

Total number of surviving infants	115
Male gender	75 (65.2)
Birth weight (median), (Interquartile range)	3540g (820)
Gestation (median), (Interquartile range)	40 weeks (2) N=1 received therapeutic hypothermia at 33 weeks gestation, n=114 were ≥ 35 weeks
Apgar scores (median), (Interquartile range)	
At 1 minute	2 (2.25)
At 5 minutes	4 (4)
At 10 minutes	5(4)
At 20 minutes	5 (2)
Cord gases (mean)(SD)	Arterial: pH 7.06 (0.17), BE -11 (5.01), Venous: pH 7.12 (0.15), BE -10 (4.31)
Inotropic support	22 (19.1)
Clinical seizures	54 (46.9)
Electrographically detected seizures	53 (46.1)
Grade of Encephalopathy (based on clinical examination)	
Mild	15 (13.0)
Moderate	88 (76.5)
Severe	9 (7.8)
Not recorded	3 (2.6)

The Bayley Scales of Infant and Toddler Development

All surviving neonates (n=115) were referred for a Bayley-lll (See table 2). A Bayley-lll score was available for 108 infants (93.9%). Of the remaining 7 patients, 5 patients were lost to follow up and 2 patients were unsuitable for assessment due to uncooperative behaviour. The Bayley-lll was performed at 2 years corrected gestational age by a clinical psychologist.

Table 2. Bayley III Scales of Infant and Toddler Development of Neonates with encephalopathy requiring Therapeutic Hypothermia [Number of patients (%)]

Total no. of patients, n=108

Composite Score	Cognition	Language	Motor	Motor Scaled Score	Gross Motor	Fine Motor
Above Average Range (≥110)	39 (36.1)	33 (30.5)	46 (42.6)	≥1 SD above the mean	12 (11.1)	43 (39.8)
Normal Range (90-109)	52 (48.1)	38 (35.2)	47 (43.5)	Normal range (8-12)	79 (73.1)	56 (51.9)
Below Average Range (≤89)	17 (15.7)	36(33.3)	15 (13.9)	≤1 SD below the mean	16 (14.8)	8 (7.4)
Not recorded		1 (0.9)		*Not recorded*	1 (0.9)	1 (0.9)

Of the 15 infants with a mild encephalopathy, 93% (n=14), 80% (n=12) and 86% (n=13) had ≥ average scores for cognitive, language and motor scores respectively. One infant did not have a Bayley-lll score recorded. Regarding the 88 infants with a moderate encephalopathy, 80% (n=70), 61% (n=54) and 83% (n=73) had ≥ average cognitive, language and motor scores respectively. One infant did not have a Bayley-lll score performed. One infant only had cognitive and motor scores recorded.

With regards to those neonates described as having severe encephalopathy (n=9, 7.82%), median Apgar scores of 0 at 1 minute, 1 at 5 minutes, 6 at 10 minutes and 3.5 at 20 minutes were recorded. Mean cord gases (arterial pH 6.9 (SD 0.21), Base Excess -14 (SD 6.77), venous pH 7.1 (SD 0.24), Base Excess -12 (SD 8.24)) were noted. Seven infants (78%) required inotropic support. Seven infants (78%) had clinical and electrographically detected seizures.

BSID-III scores were available for the nine infants with severe encephalopathy (100%). Four patients (44%) had below average composite cognitive scores, three of which had scores in the 'Extremely low' range. The remainder (n=5) had scores in the 'Average' (n=3), 'High Average'(n=1) or 'Very Superior' range (n=1). Six patients (n=6, 66.7%) had Below Average composite language scores, four of which had scores in the 'Extremely Low' range. The remainder, (n=3) had scores in the 'High Average' range. Regarding assessment of motor skills, four patients (44%) had Below Average composite scores, three of which had scores in the 'Extremely Low' range. The remainder (n=5) had scores in the 'Average' (n=3), 'High Average' (n=1) and 'Very Superior' (n=1) range.

Barkovich Scoring System of MRI Brain Reports

MRI reports were obtained for 112 of 115 surviving patients (97.4%). Three reports (2.6%) were unable to be retrieved. MRI Brain imaging was carried out at median of 6.5 days. (See table 3)(Next Page)

Table 3. Barkovich Scoring System of MRI Brain reports [Number of patients (%)]	
Basal ganglia	
Normal	99 (88.4)
Mild abnormality (Abnormal signal in the thalamus / Abnormal signal in thalamus and lentiform nucleus)	9 (8)
Severe abnormality (Abnormal signal in thalamus, lentiform nucleus, and perirolandic cortex / More extensive involvement	4 (3.6)
Watershed	
Normal	95 (84.8)
Mild Abnormality (Single focal infarction / Abnormal signal in anterior or posterior watershed white matter	5 (4.5)
Severe Abnormality (Abnormal signal in anterior or posterior watershed cortex and white matter / Abnormal signal in both anterior and posterior watershed zones / More extensive cortical involvement	12 (10.7)
Basal ganglia/Watershed	
Normal	91 (81.2)
Mild Abnormality **(**Abnormal signal in basal ganglia or thalamus / Abnormal signal in cortex	14 (12.5)
Severe Abnormality Abnormal signal in cortex and basal nuclei (basal ganglia or thalami) / Abnormal signal in entire cortex and basal nuclei	7 (6.3)

In total, 89 infants (79.5%) had normal MRI brain reports. Thirteen out of 15 infants with mild encephalopathy had an available MRI brain report, all of which were normal. An MRI brain report was available for 87 out of 88 infants with moderate encephalopathy. Of these, 82% (n=72) were normal. An MRI report was available for all infants (n=9) with a severe encephalopathy. Four out of 9 infants (44.4%) with severe neonatal encephalopathy had a normal MRI brain.

A Bayley-lll score was available for 84 out of 89 neonates with normal MRI brain reports (94.3%) (See table 4)(Next Page). Of the remainder (n=5), one patient was uncooperative for assessment, 4 patients were lost to follow up. Regarding the neonates with abnormal MRI findings (n=23, 20.5%), Bayley Assessment Scores were available for 21 patients (91.3%). One infant was uncooperative for developmental assessment. One patient was lost to follow up.

Table 4. BSID-III Score of Infants stratified according to MRI Brain results [Number of patients (%)]

Composite Score	**Cognition**		**Language**		**Motor**	
MRI Brain Result	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**
	(n=89)	**(n=23)**	**(n=89)**	**(n=23)**	**(n=89)**	**(n=23)**
Above Average Range (≥110)	33 (37)	5 (21.7)	30 (33.7)	3 (13)	39 (43.8)	5 (21.7)
Normal Range (90-109)	43 (48.3)	7 (30.4)	30 (33.7)	6 (26)	37 (41.6)	9 (39.1)
Below Average Range (≤89)	8 (8.9)	9 (39.1)	24 (26.9)	11 (47.8)	8 (8.9)	7 (30.43)
Not recorded	5 (5.6)	2 (8.7)	5 (5.6)	3 (13)	5 (5.6)	2 (8.7)

Discussion

In the 115 surviving infants requiring TH, the majority had a normal MRI brain and a satisfactory neurodevelopmental outcome. The diffusion-weighted MRI was predictive of a normal Bayley-lll assessment at 2 years of age. A sub-cohort of neonates who had normal MRI brain reports had isolated Speech and Language issues in the infantile period. Subtle changes in the language centres are perhaps not identifiable by MR imaging. Early referral to Speech and Language therapy should be considered for neonates requiring TH. This is supported by previous studies.[10,11]

Our study is strengthened by the large patient cohort that was reviewed. Furthermore, two reliable and validated assessment tools were used for analysis – the Bayley-lll, and the Barkovich MRI Scoring System. All but 7 infants had a Bayley-lll assessment. MRI reports were available for 112 surviving infants (97.4%). A single clinical psychologist and consultant radiologist carried out the Bayley-lll assessments and Barkovich scoring respectively, thus eliminating the risk of inter-observer variability.

Noteworthy, the majority of infants requiring TH were male (n=75, 65.2%). This was also reflected in the Irish National Report on neonatal TH (2018).[12] In 2018, two-thirds of the infants who received TH in Ireland were male (76.8%; n=53). Male sex has previously been identified as a risk factor for NE in the literature.[13] The mechanisms underlying this sex difference are poorly understood.[14,15] Although the majority of infants requiring TH in our study were male, only 25% (n=3) of the neonatal deaths were male. A higher mortality rate for female infants requiring TH was also reported nationally. Between 2016-2018 in Ireland, 14.5% of females requiring TH died (n=11) versus 9.8% of males (n=13).

The neonatal mortality rate in our series of 127 infants was 9.4%. This is similar to the Irish national data from 2018 (mortality rate 6.1%). In contrast, the mortality rates for the control group in the TOBY study[7], the NICHD[16] study and ICE study[17] were 25.7% 24%, and 25% respectively. Advances in NICU care over the last decade may account for these differences. The Bayley-lll scores were satisfactory in the overall patient cohort, in each of the core developmental domains. Eighty-four percent of neonates (n=91) had cognitive scores in the average or above average range.

The TOBY study reported that 70% (n=81) of their cohort undergoing TH had cognitive scores in the normal range. Of note, a cut-off composite score of ≥85 was used to define 'Average' in their study.

Chalak et al [18] conducted a prospective cohort study of infants requiring TH in Texas, U.S (2005-2011). Ninety neonates received TH. Similar to our study, moderate encephalopathy was described in 80 (89%) infants, while severe encephalopathy occurred in 10 infants (11%). Bayley-lll scores were available for 62 infants at a mean ± SD age of 20 ± 2.9 months. In comparison to our study, 53% (n=33) had average or above average cognitive scores versus 84% (n=91) in our study. Average or above average language scores were reported for 56% (n=35) versus 66% (n=71) in our cohort. Sixty-eight percent (n=42) had average or above average motor scores versus 86% (n=93) in our population. Of note, a cut-off composite score of ≥85 was used to define 'Average' in their study. We have described the 'Average' score as ≥90. As this study was conducted prior to our study (2005-2011), one could postulate that advancements in NICU care may potentially account for these differences.

MRI is widely used to predict outcomes in neonatal encephalopathy.[19,20,21] One can extrapolate from our data that if an infant has normal brain imaging, their chances of having normal cognitive, language and motor outcomes at 2 years corrected gestational age are 85%, 67% and 85% respectively. This data provides useful prognostic information. It also emphasises the importance of Speech and Language Therapy in the management of these neonates.

In conclusion, we have described the neurodevelopmental outcomes and neuro-radiological findings of infants with NE requiring TH in a single, Level 3 NICU over an eight-year period. This study will enable more accurate prognostication of neuro-developmental outcomes and correlation with MRI Brain findings for health-care professionals, patients and their families.

List of Abbreviations used:
HIE - Hypoxic Ischaemic Encephalopathy
MRI - Magnetic Resonance Imaging
TH – Therapeutic Hypothermia
Bayley-lll - Bayley Scales of Infant and Toddler Development – 3rd edition
NICU – Neonatal Intensive Care Unit

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

Ethical Approval:
Ethical approval was obtained from the National Maternity Hospital Ethics Committee.

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