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Influence of timing of initiation of therapeutic hypothermia on brain MRI and neurodevelopment at 18 months in infants with HIE: a retrospective cohort study

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ABSTRACT

Objective To examine the influence of timing of initiation of therapeutic hypothermia (TH) on brain injury on MRI and on neurodevelopmental outcomes at 18 months.

Design Retrospective cohort study.

Setting Tertiary neonatal intensive care unit in Ontario, Canada.

Patients Ninety-one patients with hypoxic ischaemic encephalopathy (HIE) were included, 54 in the early TH group and 37 in the late TH group.

Intervention Whole-body hypothermia administered for 72 hours, initiated either before 3 hours of life (early TH) or between 3 and 6 hours of life (late TH).

Main outcome measures Brain injury on MRI after TH (assessed by two neuroradiologists), and neurodevelopmental outcomes at 18 months old.

Results TH was initiated at a median time of 1.4 hours (early TH) and 4.4 hours (late TH). Sixty-four neonates (early TH=36, late TH=28) survived and completed neurodevelopmental assessment at 18 months. Neonates in the early TH group received more extensive resuscitation than neonates in the late TH group (p=0.0008). No difference was observed between the two groups in the pattern or severity of brain injury on MRI, or in the neurodevelopmental outcomes at 18 months. The non-survivors (n=16) had lower Apgar scores at 10 min, more extensive resuscitation, suffered from more severe HIE and had significantly more abnormal cerebral function monitoring.

Conclusion In this retrospective cohort study, TH initiated early was associated neither with a difference in brain injury on MRI nor better neurodevelopmental outcomes at 18 months.

INTRODUCTION

Hypoxic ischaemic encephalopathy (HIE) occurs in 1–2 per 1000 live births and is associated with mortality and long-term neurodevelopmental disabilities.[1–4] Therapeutic hypothermia (TH) decreases mortality and neurodevelopmental impairment at 18–24

What is known about the subject?

► Therapeutic hypothermia (TH), initiated <6 hours of life, is the standard treatment for infants with moderate to severe hypoxic ischaemic encephalopathy.
► Preclinical studies show that TH is more effective when started very early, although little clinical data exist in support.

What this study adds?

► The pattern and severity of brain injury on MRI was not different between the early (< 3 hours) and late (3 – 6 hours) TH groups.
► Early initiation of TH was not associated with a significant difference in moderate to severe neurodevelopmental impairment at 18 months old.

months.[3 5–7] Brain MRI helps provide diagnostic and prognostic information regarding neurodevelopmental outcomes at 18–24 months.[4 8]

Based on the inclusion criteria of large randomised controlled trials (RCT), the current recommendation is to start TH before 6 hours of life.[2 9 10] This therapeutic window corresponds to the latent period of HIE, where there is a transient recovery of oxidative metabolism and the possibility to prevent secondary energy failure.[11] The secondary failure is the main phenomenon responsible for neuronal loss and is characterised by cytotoxic failure, mitochondrial failure and accumulation of excitotoxins.[12]

While many preclinical studies showed that an earlier initiation of TH improves neuroprotection,[11 13 14] only one clinical cohort study showed that early TH (<3 hours after

Table 1 Characteristics of the cohort of eligible patients

	Early TH (n=54)	Late TH (n=37)	P value
C-section, n (%)	35 (64.8)	16 (43.2)	0.04
Male sex, n (%)	31 (57.4)	23 (62.2)	0.7
Gestational age, mean (SD)	39.0 (1.7)	39.1 (1.4)	0.7
BW (kg), mean (SD)	3.35 (0.65)	3.31 (0.55)	0.8
Resuscitation score, median (IQR)	5 (5–6)	4 (4–5)	0.001
Apgar score at 10 min, median (IQR)	4 (3–5)	4 (4–6)	0.1
Arterial cord blood pH, mean (SD)	6.9 (0.2)	7.0 (0.2)	0.2
Who initiated TH? n (%)			<0.0001
Centre before advice	25 (46.3)	3 (8.1)	
Centre after advice	19 (35.2)	11 (29.7)	
Transport team	9 (16.7)	18 (48.6)	
NICU	1 (1.9)	5 (13.5)	
How was TH initiated?* n (%)			0.5
Passive	38 (71.7)	19 (59.4)	
Passive, followed by cold packs	12 (22.6)	10 (28.6)	
Cold packs	3 (5.7)	3 (8.6)	
Time of referral to CHEO (hours), median (IQR)	1.3 (0.8–1.7)	2 (1.4–4)	0.0003
Time of arrival of transport team, median (IQR)	2.3 (1.8–3.3)	4.6 (3–5.9)	<0.0001
Time of initiation of TH, median (IQR)	1.4 (0.6–2)	4.4 (4–6.4)	<0.0001
Time to target temperature, median (IQR)	4.3 (3.1–6.7)	7.4 (6.4–8.9)	0.007
Degree of encephalopathy before TH			0.03
Normal or Sarnat 1, n (%)	14 (25.9)	11 (29.7)	
Sarnat 2, n (%)	23 (42.6)	23 (62.2)	
Sarnat 3, n (%)	12 (31.5)	3 (8.11)	
Abnormal cerebral function monitoring†			0.2
Discontinuous	6 (14)	5 (17.2)	
Burst suppression	7 (16.3)	7 (24.1)	
Low amplitude or flat trace	9 (20.9)	1 (3.4)	
Seizures	29 (59.2)	20 (40.8)	1.0
Death	13 (24.1)	3 (8.1)	0.05

*For patients with TH initiation before their admission to NICU (53 patients in early TH and 32 patients in late TH).
†Cerebral Function Monitoring performed in 43 patients in early TH and 29 patients in late TH.
BW, birth weight; CHEO, Children's Hospital of Eastern Ontario; C-section, caesarean section; NICU, neonatal intensive care unit; TH, therapeutic hypothermia.

birth) was associated with better motor outcomes at 18 months of age.[15] Our objective was to examine the effects of early TH (started ≤3 hours of life) on the pattern and severity of brain injury on MRI and neurodevelopmental outcomes in a regional cohort of infants with HIE. We hypothesised that infants, where TH was initiated earlier, would have less severe brain injury and less severe neuro-developmental impairment.

METHODS

Study design and population

We performed a retrospective cohort study of infants who received TH at the Children's Hospital of Eastern Ontario (CHEO) between October 2009 and December 2016.

CHEO is a university-affiliated level 3 outborn unit, with 400 admissions per year. Institutional eligibility for TH aligns with the 2018 Canadian Paediatric Society's position statement[9] and includes babies born at ≥35 weeks' gestational age and <6 hours with: (1) evidence of intrapartum asphyxia and (2) evidence of moderate to severe encephalopathy. Intrapartum asphyxia was defined as either: (A) cord or early postnatal pH ≤7.00 or base deficit ≥16 or (B) pH 7.01–7.15 or base deficit −10 to −15.9 with an acute perinatal event and at least one of: Apgar score ≤5 at 10 min or need for positive pressure ventilation or resuscitation at 10 min.

Whole-body hypothermia (target core temperature of 33.0°C–34.0°C) was achieved with a servo-controlled blanket device (Blanketrol III). Neonates were monitored with cerebral function monitoring (BrainZ Instruments, New Zealand) from their admission to neonatal intensive care unit (NICU) and for the duration of the TH, which was administered for 72 hours unless there was a clinical indication to stop therapy. Babies were grouped into: early TH (started ≤3 hours of life) or late TH (started >3 hours of life but ≤6 hours).

MR data acquisition

Newborns were scanned after TH (median 5 days of life). The MRI scans were performed using a 1.5 T (Sigma HD, General Electric Healthcare Technologies, Waukesha, WI, USA) or 3 T (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) MRI system. No anaesthesia was used. The standard clinical imaging protocol included T1 and T2-weighted images, diffusion-weighted images and MR spectroscopy obtained at the left basal ganglia.

The MRI images were assessed jointly by two paediatric neuroradiologists, blinded to clinical grade of encephalopathy and the outcome. Analysis of the severity and pattern of brain injury on MRI was performed using two previously validated scoring systems: the National Institute of Child Health and Human Development (NICHD)[16] and the modified Barkovich scoring system.[17] Interobserver reliability was previously assessed and showed good agreement (91%).

As described in recent reports,[1 16 18] moderate to severe brain injury was defined as a score of ≥2 in the basal ganglia/thalami, or a score ≥3 in the watershed area (Barkovich scoring system), or a score ≥2A in the NICHD scoring system.

Data collection

For each baby, clinical data regarding prenatal, perinatal, postnatal and neonatal follow-up information

were collected. The amount of resuscitation at birth was summarised by a previously described resuscitation score graded from 1 to 6: 1=no intervention, 2=blow by oxygen, 3=endotracheal suctioning, 4=bag mask positive pressure ventilation, 5=endotracheal intubation with positive pressure ventilation, 6=endotracheal intubation with ventilation and medication.[19] Postnatal variables included severity of encephalopathy in the first 6 hours of life, before initiating TH (Sarnat score)[20] as reported in the patient chart, time of arrival of transport team at referral hospital, time to initiation of cooling and to target temperature, clinical seizures, death and abnormal cerebral function monitoring background (defined as discontinuous, burst suppression, low amplitude or flat trace). The cerebral function monitoring background was established based on patient chart review and was reviewed by one of the investigators (BL) in case of ambiguity. Neonatal follow-up variables focused on moderate to severe impairment at 18 months.

Follow-up

Surviving infants were assessed in our neonatal follow-up clinic at 18 months. The assessment is based on a combination of the Ages and Stages Questionnaire, Third Edition (ASQ-3) reported by parents and observed by a physician, along with a medical evaluation and a neurological examination. The infants were previously evaluated with a hearing screening test performed at 4 and 10 months, and ophthalmology examination at 9 months.

The ASQ is an age-specific developmental screening questionnaire assessing five developmental areas: communication, fine motor, gross motor, problem-solving and personal-social. A child is defined as developmentally delayed when ≥2 of their score is 2 SD below the mean in any of the domain.[21] Previous studies have demonstrated that the ASQ is valid, economical and is extremely effective to detect severe neurodevelopmental disability in infants after HIE.[22] For the purpose of this study, global developmental delay was defined by a score of 2 SD below the mean in three or more domains or 2 SD below the mean in two domains, along with a score of 1 SD below the mean in one other domain. Moderate to severe impairment was defined as confirmed cerebral palsy, deafness, blindness or severe visual impairment or global developmental delay.

Patient and public involvement

Patients were not directly involved in the design of this study.

Statistical analysis

Clinical variables were compared using the Fisher's exact test for categorical variables, t-tests for continuous variables, or the Wilcoxon rank-sum test for non-parametric continuous variables. MRI findings were compared between groups using Fisher's exact test. Relationships between MRI patterns of injury and outcomes were assessed using Cochran-Armitage trend tests, or the

Fisher's exact test, where appropriate. The relationship between timing of initiation of TH and outcomes was assessed using a multivariable logistic regression adjusting for severity of encephalopathy at baseline. This relationship was also analysed using timing of initiation of TH as a continuous predictor.

An instrumental variable (IV) approach was also used as an alternative way to correct for confounding.

The level for statistical significance was set a priori at <0.05. All statistical analyses were performed using R statistical software V.3.4.2.[23]

RESULTS

One hundred patients were admitted to our centre for TH during the study period. Nine were rewarmed early as they did not fulfil TH criteria (n=8) or presented with contraindications to TH (n=1). Therefore, 91 neonates were included in the study, 54 in the early TH and 37 in the late TH group (figure 1). In the early TH group, caesarean section delivery was more common, resuscitation was more extensive, more neonates suffered from severe encephalopathy and more neonates died (table 1). Additionally, for neonates in the early group, TH was more often initiated by the birthing centre before advice from a neonatologist and referral to CHEO was done earlier.

Sixteen neonates (17.6%) in the cohort died; 13 in the early TH group and 3 in the late TH group. The perinatal variables were similar across the two groups of non-survivors (online supplementary table 2). Compared with the survivors, the non-survivors (n=16) had lower Apgar scores at 10 min (p=0.02), more extensive resuscitation, suffered from more severe HIE on clinical exam (p<0.001) and had significantly more abnormal cerebral function monitoring (p<0.001) (online supplementary table 3).

Among the 75 neonates who survived to discharge, a neurodevelopmental assessment was completed at 18 months for 64 neonates (85%). The descriptive data for these patients, according to the timing of TH, are presented in table 2. Again, the two groups were different with more extensive resuscitation and a trend towards more severe encephalopathy in the early group. Despite more severe encephalopathy in the early TH group, no difference was observed between groups in the pattern and severity of brain injury, on either of the scoring tools (table 3). Twenty-one of the 64 patients (33%) exhibited abnormal neurodevelopment at 18 months, of which 12 presented with moderate to severe impairment (online supplementary table 6).

Logistic regression analyses using TH initiation time as a dichotomous predictor (≤3 hours vs >3 hours), and controlling for severity of encephalopathy, revealed no significant differences between groups for moderate to severe impairment. A subgroup analysis excluding patients with severe HIE also showed no difference between early and late TH for neurodevelopmental
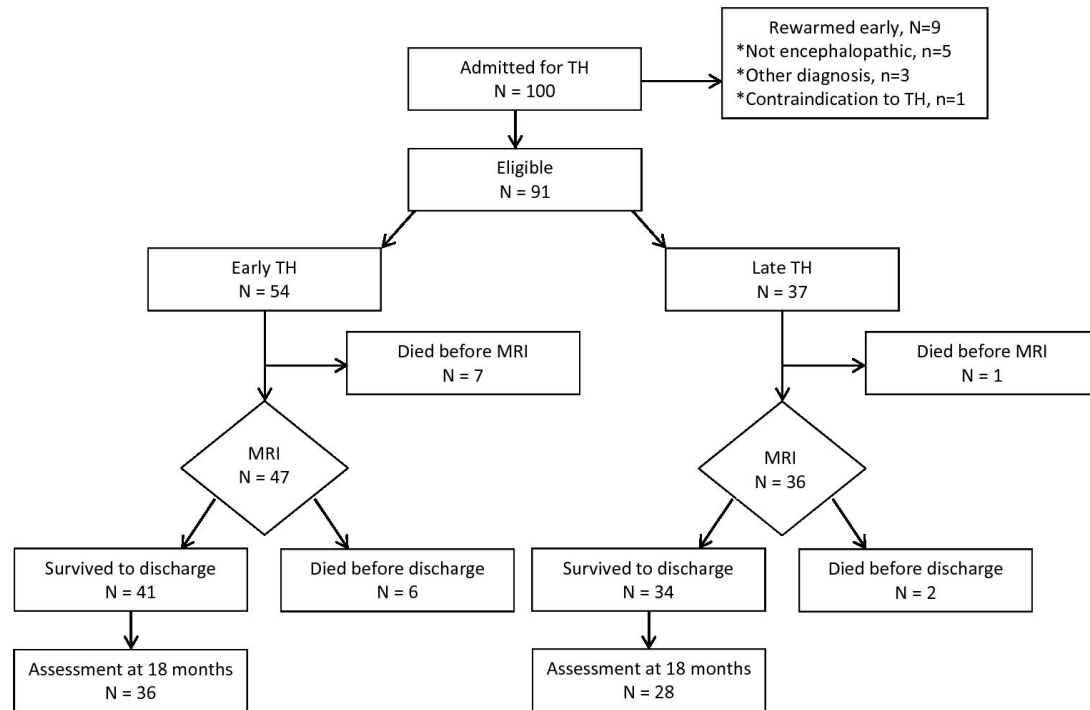
Figure 1. Flow chart for the study population.

outcomes. Analogous analyses using time as a continuous predictor were not significant for moderate to severe impairment.

There was a strong relationship between moderate to severe impairment and severity and pattern of brain injury. More severe brain injury was strongly associated with moderate to severe impairment and a normal brain MRI was associated with no or mild impairment (table 4).

As an alternative approach to correct for confounding, an IV analysis was performed using time of arrival of transport team at referral centre as the IV. Time of arrival of transport team at referral hospital is positively associated with time to TH (r=0.53, p<0.001) but is not believed to directly affect the outcome (death and/or disability) or any confounders. The IV analysis for the outcome of severe disability or death did not reveal a statistically significant association (OR 0.92, 95% CI 0.36 to 2.42, p=0.9) with timing of TH.

DISCUSSION

Our study is the largest reporting on early (≤3 hours of life) versus late (>3 hours of life) initiation of TH and comparing findings on MRI and 18 months of outcomes. In this retrospective observational cohort, timing of initiation of TH, assessed both as a dichotomous and continuous variable, was associated neither with a difference in brain injury on MRI nor better outcomes at 18 months. Given that infants who received TH earlier were sicker at birth and more severely encephalopathic, perhaps this is positive, as one might have expected more brain injury on MRI and/or worse outcomes at 18 months in that

group. The severity of brain injury was strongly associated with neurodevelopmental outcomes at 18 months.

Many preclinical studies support an earlier start of TH to improve neuroprotection. Different neonatal species were studied. In the newborn piglets, the initiation of TH after 3 hours was ineffective.[24] In the neonatal rats with moderate HIE, the effectiveness of TH was maximal immediately after brain injury and decreased linearly with delay in time of initiation.[14] In the near-term fetal sheep, TH was neuroprotective when induced 90 min after injury, it was partially protective when initiated after 5.5 hours and was no longer protective when initiated after 8.5 hours.[25] So far, only one cohort study with 65 surviving newborns demonstrated an improvement in motor outcomes at 18–20 months when TH was started earlier (≤3 hours).[15]

Many factors might have contributed to the non-significant effect of early TH in our cohort. First, unlike what is observed in preclinical models, the timing of injury in neonates with HIE is uncertain and the time of birth might not accurately reflect this timing. Second, the early and late TH groups have some clinical and pathophysiological differences, which can influence their outcomes. Although we minimised the known confounding factors by controlling for encephalopathy severity (regression models and subgroup analysis) and using IV analysis, there are likely residual confounding factors not included in our analysis. Third, our data set is smaller than the cohorts that were needed to establish that cooling was more effective than normothermia; establishing whether early TH has additional benefits may require similarly larger cohorts. Lastly, in comparison with the previous

Table 2 Characteristics of patients with neurodevelopmental assessment at 18 months of age

	Early TH n=36	Late TH n=28	P value
C-section, n (%)	24 (66.6)	12 (42.9)	0.1
Male sex, n (%)	19 (52.8)	19 (67.9)	0.2
Gestational age (weeks), mean (SD)	39 (1.6)	39.2 (1.5)	0.6
Birth weight (kg), mean (SD)	3.4 (0.71)	3.4 (0.43)	0.9
Resuscitation score, median (IQR)	5 (5–5)	4 (4–5)	0.0008
Apgar score at 10 min, median (IQR)	4.5 (3–6)	5 (4–7)	0.3
Arterial cord blood pH, mean (SD)	6.9 (0.1)	6.9 (0.2)	0.2
Who initiated TH?			<0.0001
Centre before advice, n (%)	15 (41.7)	1 (3.6)	
Centre after advice, n (%)	16 (44.4)	8 (28.6)	
Transport team, n (%)	4 (11.1)	14 (50)	
NICU, n (%)	1 (2.8)	5 (17.9)	
Time of referral to CHEO (hours), median (IQR)	1.5 (0.9–2)	2 (1.4–4.1)	0.007
Time of arrival of transport team, median (IQR)	2.4 (1.8–3.3)	4.4 (2.9–5.9)	0.0003
Time of initiation of TH, median (IQR)	1.4 (0.7–2)	4.4 (3.9–6.5)	<0.0001
Time to target temperature, median (IQR)	4.7 (3.4–6.5)	7.9 (6.7–9)	0.05
Degree of encephalopathy before TH			0.07
Normal or Sarnat 1, n (%)	11 (30.5)	10 (35.7)	
Sarnat 2, n (%)	18 (50)	18 (64.3)	
Sarnat 3, n (%)	7 (19.4)	0	
Abnormal cerebral function monitoring*			0.2
Discontinuous	5 (17.2)	4 (16.7)	
Burst suppression	4 (13.8)	6 (25)	
Low amplitude or flat trace	3 (10.3)	0	
Seizures	16 (44.4)	14 (50)	0.7

*Cerebral Function Monitoring performed in 29 patients in early TH with neurodevelopmental assessment at 18 months and 24 patients in late TH with neurodevelopmental assessment at 18 months.
CHEO, Children's Hospital of Eastern Ontario; C-section, caesarean section; NICU, neonatal intensive care unit; TH, therapeutic hypothermia.

Table 3 MRI findings in patients with neurodevelopmental assessment at 18 months of age, stratified by timing of therapeutic hypothermia

	Early TH n=36 (%)	Late TH n=28 (%)	P value
Severity of injury according to NICHD scoring			0.9
0 or 1A or 1B	28 (77.7)	22 (78.6)	
≥2A	8 (22.2)	6 (21.4)	
Barkovich scoring system			
Basal ganglia score			1.0
0, 1	32 (88.8)	25 (89.3)	
2, 3, 4	4 (11.1)	3 (10.7)	
Watershed score			0.3
0, 1, 2	32 (88.8)	22 (78.6)	
3, 4, 5	4 (11.1)	6 (21.4)	
Predominant pattern of injury			0.4
Normal	23 (63.9)	13 (46.4)	
Focal-multifocal	5 (13.9)	4 (14.3)	
Watershed	5 (13.9)	8 (28.6)	
BG/T	3 (8.3)	2 (7.1)	
Total brain injury	0	1 (3.6)	
Moderate to severe brain injury*	5 (13.9)	6 (21.4)	0.4

*Moderate to severe brain injury defined as WS score of ≥3 or BG/T score ≥2.
BG/T, Basal Ganglia/Thalamus; NICHD, National Institute of Child Health and Human Development; TH, therapeutic hypothermia; WS, Watershed.

time difference could have contributed to the absence of differences between our two groups.

Encephalopathy is a medical condition that evolves over time and the early recognition of the signs and symptoms might be challenging. A number of important factors known to influence the recognition of encephalopathy and subsequent timing of initiation of TH include the initial resuscitation and stabilisation requirement of such patients, location and clinical expertise of the treating team. Medical transport, with all logistical ramifications, can be particularly challenging for some patients.[26 27] Our outborn NICU serves a very large geographical region of almost 440 000 km^2. The earliest timing of initiation of TH can be especially challenging in the more remote and distant areas.[28] Despite our study findings, it is important and relevant to initiate TH as early as possible when the therapy is indicated, as early initiation is key to ensure early attainment of target temperatures.[9 26]

As demonstrated in previous studies, we identified useful prognostic factors associated with mortality in patients with HIE. First, non-survivors had significantly lower Apgar score at 10 min. The association of low Apgar score at 10 min and mortality was previously described in the literature.[29] Second, non-surviving newborns were

published cohort showing improved motor outcomes with early TH, TH was initiated earlier in our late TH group (median time of 4.4 hours vs 5.16 hours). This

Table 4 Relationship between MRI findings and neurodevelopmental impairment

	No or mild impairment n=52 (n, %)	Moderate to severe impairment n=12 (n, %)	P value
Severity of injury according to NICHD scoring			0.001
0 or 1A or 1B	45 (86.5)	5 (41.7)	
≥2A	7 (13.5)	7 (58.3)	
Barkovich scoring system			
Basal ganglia			<0.001
0, 1	51 (98.1)	6 (50)	
2, 3, 4	1 (1.9)	6 (50)	
Watershed			0.006
0, 1, 2	47 (90.4)	7 (58.3)	
3, 4, 5	5 (9.6)	5 (41.6)	
Predominant pattern of injury			0.06
Normal	33 (63.5)	3 (25)	
Focal-multifocal	7 (13.5)	2 (16.6)	
Watershed	9 (17.3)	4 (33.3)	
BG/T	3 (5.7)	2 (16.6)	
Total brain injury	0	1 (8.3)	
Moderate to severe brain injury*	5 (9.6)	6 (50)	0.001

*Moderate to severe brain injury defined as WS score of ≥3 or BG/T score ≥2.
†Moderate to severe impairment was defined as confirmed cerebral palsy, deafness, blindness or severe visual impairment and global developmental delay.
BG/T, Basal Ganglia/Thalamus; NICHD, National Institute of Child Health and Human Development; WS, Watershed.

more likely to have an abnormal background on the cerebral function monitoring. It has been previously demonstrated that the type of background pattern in the first 6 hours of life is a strong predictor of neurodevelopmental outcome in normothermic HIE infants.[30] Importantly, in infants treated with TH, the time to normalisation of background activity is a better predictor of outcomes.[31] Lastly, patients with severe encephalopathy (Sarnat 3) were more likely to die. A strong correlation between the Sarnat stage of encephalopathy and neurodevelopmental impairment or death has been previously described.[32]

One of the strengths of our study is the comprehensive MRI assessment, reached by the consensus of two experts in paediatric neuroradiology. The limitations of our study include its retrospective nature, particularly given the topic of encephalopathy which can be challenging to diagnose and can evolve over time. Also, the size of the cohort is relatively small and might have been insufficient to detect a difference between the early and late TH groups. Furthermore, the cohort is limited by the potential for selection of less severe cases due to the redirection of care in a number of patients with the most severe encephalopathy.

In this study, we used the ASQ-3 as our neurodevelopmental assessment tool while Thoresen's study and large RCTs used Bayley scales. Despite reports of concurrent validation of ASQ and Bayley scales,[22 33] comparing our results is more complex when using two different scales. Moreover, the ASQ-3 provides an overall assessment of development, based on five domains—one of which is fine motor skills and one is gross motor skills, without a precise normative value like the PDI (Psychomotor Development Index) or the Motor Composite Score. Also, based on the number of applicable questions, PDI is influenced more by gross motor skills than fine motor skills. Consequently, the ASQ can difficultly be compared with the PDI or Motor Composite Score and might not be precise enough to detect an improvement in one specific area of development, such as motor outcomes. Also, neurodevelopmental assessment at 18 months might miss some infants that may develop impairment later in childhood, particularly cognitive.

Confounding by indication was a significant challenge in analysing data from this study since various factors that influence the timing of TH also affect outcomes. This was addressed using adjustment for potential confounding factors such as HIE severity, as well as an alternative IV analysis.

CONCLUSION

In this retrospective observational cohort, early TH started before 3 hours of life was associated neither with less brain lesions on MRI nor better neurodevelopmental outcomes. In light of the fact that early attainment of target temperatures is closely linked to early initiation of TH, clinicians should aim to initiate TH as soon as possible after birth once the indication is confirmed. Large population studies are needed in the future to better establish the effect of timing of TH.

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