Safety and Short-Term Outcomes of Therapeutic Hypothermia in Preterm Neonates 34-35 Weeks Gestational Age with Hypoxic-Ischemic Encephalopathy

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Objective To evaluate the safety and short-term outcomes of preterm neonates born at 34-35 weeks gestation with hypoxic-ischemic encephalopathy (HIE) treated with therapeutic hypothermia.

Study design Medical records of preterm neonates born at 34-35 weeks gestational age with HIE treated with therapeutic hypothermia were retrospectively reviewed. Short-term safety outcomes and the presence, severity (mild, moderate, severe), and patterns of brain injury on magnetic resonance imaging were reviewed using a standard scoring system, and compared with a cohort of term neonates with HIE treated with therapeutic hypothermia.

Results Thirty-one preterm and 32 term neonates were identified. Therapeutic hypothermia-associated complications were seen in 90% of preterm infants and 81.3% of term infants ($P = .30$). In the preterm infants, hyperglycemia (58.1% vs31.3%, $P = .03$) and rewarming before completion of therapeutic hypothermia (19.4% vs 0.0%, $P = .009$) were more likely compared with term infants. All deaths occurred in the preterm group (12.9% vs 0%, $P = .04$). Neuroimaging showed the presence of injury in 80.6% of preterm infants and 59.4% of term infants ($P = .07$), with no differences in injury severity. Injury to the white matter was more prevalent in preterm infants compared with term infants (66.7% vs 25.0%, $P = .001$).

Conclusions Therapeutic hypothermia in infants born at 34-35 weeks gestational age appears feasible. Risks of mortality and side effects warrant caution with use of therapeutic hypothermia in preterm infants. *(J Pediatr 2017;183:37-42).*

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Hypoxic-ischemic encephalopathy (HIE) affects 0.5-1.0/1000 live births, with associated high mortality (10%-60%) and significant neurologic morbidity (25%) in survivors.[1] Trials of moderate to severely encephalopathic neonates born at ≥36 weeks gestation have shown both safety and efficacy of therapeutic hypothermia in ameliorating the severity of neurologic injury and improving survival without increasing the burden of adverse neurodevelopmental outcomes.[1-5]

The success of therapeutic hypothermia in neonates ≥36 weeks gestational age has led to speculation about the benefits of extending therapeutic hypothermia to more premature neonates.[6] Experimental data suggest that hypothermia could offer neuroprotection in preterm animal models[7] and preterm infants with necrotizing enterocolitis.[8] Further, although epidemiologic data suggest that neurologic and metabolic screening criteria for term neonates with HIE could be applied to identify preterm neonates with HIE,[9,10] a trial of hypothermia in preterm neonates 33-35 weeks gestational age recommended against cooling outside of clinical trials because of high morbidity and mortality (ClinicalTrials.gov: NCT 00620711).[11] However, an ongoing trial by the same group is recruiting preterm neonates 33-35 weeks gestational age (ClinicalTrials.gov: NCT 01793129).[12]

Recent reports suggest a drift in clinical practice as therapeutic hypothermia is offered increasingly to neonates who would not have met eligibility in the original clinical trials.[13,14] Here, we describe the short-term outcomes (as defined by brain injury on magnetic resonance imaging [MRI] scans in the first 10 days of life) and

DNGM	Deep nuclear gray matter
EEG	Electroencephalography
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
PLIC	Posterior limb of internal capsule
WM	White matter

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safety profile of therapeutic hypothermia in preterm neonates born at 34-35 weeks gestational age in comparison with a cohort of term newborn infants with HIE at our institution.

Methods

Our institution participated in the Infant Cooling Evaluation trial[15] that included neonates >35 weeks gestational age. After the trial, intramural guidelines were developed for the evaluation of neonates ≥35 weeks gestational age with HIE and subsequent treatment with therapeutic hypothermia. For neonates <35 weeks, individualized risk and benefits were discussed with the family, and consent was obtained before the initiation of therapeutic hypothermia.

Medical records were reviewed retrospectively from preterm neonates born at 34-35 weeks gestational age with HIE who were treated with therapeutic hypothermia from 2007 through 2015. The comparison group of term neonates born at ≥37 weeks gestation with HIE treated with therapeutic hypothermia during a similar time period has been reported in a previous study.[16] The study was approved by the Washington University Human Research Protection Office.

The administration and monitoring of therapeutic hypothermia has been described previously.[3] Pertinent maternal and neonatal demographic factors, clinical factors, delivery and admission characteristics, and the severity of encephalopathy were recorded from the medical records.[13] Short-term safety data and adverse outcomes associated with therapeutic hypothermia were collected for the period from the initiation of therapeutic hypothermia through 7 days after discontinuation of active cooling. These included coagulopathy requiring treatment (thrombocytopenia or disseminated intravascular coagulation), bradycardia (heart rate <80/minute), hyperglycemia (glucose ≥200 mg/dL), hypothermia (temperature greater than 0.5 degrees below target temperature from start of cooling), and skin necrosis. Metabolic complications included hypokalemia (potassium <3.5 mEq/L), hyponatremia (sodium <135 mEq/L), hypocalcemia (total calcium <8.6 mg/dL or ionized calcium <3.9 mmol/L), hypoglycemia (glucose <45 mg/dL), leukopenia (total white cells <5000/mm^3), and neutropenia (absolute neutrophil count <1000/mm^3). We also recorded reasons for interruptions of therapeutic hypothermia, if any, during the period of active cooling.

Electroencephalography (EEG) data were reviewed from the clinical reports for the presence of seizures and predominant background patterns.[17] Patients receiving therapeutic hypothermia had EEG monitoring for a minimum of 24 hours beginning at the onset of active cooling, with longer durations when seizures occurred or at the discretion of the medical team. Neuroimaging data was collected from MRI scan(s) performed during hospitalization. A single experienced reader in neonatal neuroimaging blinded to the infant's clinical course scored the MRI injury as described previously.[18] Briefly, T1-, T2-, and diffusion-weighted MRI scans were assessed for injury in the following areas: (1) subcortical region; (2) white matter (WM); (3) cortex; (4) cerebellum; and (5) brainstem. The subcortical region included the deep nuclear gray matter (DNGM) and posterior limb of internal capsule (PLIC). DNGM included the following components: (1) caudate nucleus; (2) globus pallidus and putamen; and (3) thalamus. Each region was independently assessed for injury, and an MRI injury score was generated by adding up the 5 regional subscores. The overall severity of MRI injury was graded as none, mild, moderate, or severe. If the neonate underwent 2 MRIs, the scan with the higher injury score was used. To account for the physiological absence of myelination of the PLIC at ≤37 weeks postmenstrual age, the scoring system was modified to exclude assessments of myelination in the PLIC on T1- and T2-weighted images in the preterm infants only. For the purpose of this scoring, absent PLIC on T1 and T2 sequences were scored as "0" (normal) because this finding is normal for postmenstrual age. However, diffusion abnormalities in the PLIC remained in the scoring system if they were consistent with injury even in the absence of myelination. The severity score range remained unchanged with this modification.

In addition to the severity of injury, MRI scans were evaluated for regional patterns of injury. Patterns were classified by the predominant area of involvement into DNGM, watershed (WM and cortex), global (DNGM + WM + cortex + brainstem), isolated WM, or cerebellar injury.

Data analysis was performed with SPSS software v 21.0 (SPSS Inc, Chicago, Illinois) and results reported as the mean (SD) or median (IQR) and percentage (%). Student t tests and χ^2 tests were used for continuous and categorical data, respectively. Pearson and Spearman correlation coefficients were used to determine the relationship between neurologic injury and severity of encephalopathy. A P value of <.05 was considered significant.

Results

The study cohort included 31 neonates born at 34-35 weeks gestation and 32 term-born neonates with HIE. One preterm neonate treated with therapeutic hypothermia at an outside institution and transferred to our institution was included as complete data for this subject were available.

Maternal clinical and demographic factors in the 2 groups are shown in **Table I**. Meconium-stained amniotic fluid occurred more often in term infants than preterm infants. Although abruption was more common in preterm infants, there were no differences in the number of sentinel events between preterm and term neonates (**Table I**). Maternal medical illnesses necessitating delivery were more likely in preterm infants. The severity of clinical encephalopathy at cooling was similar between the preterm and term neonates (**Table I**).

Admission characteristics, infant morbidities, and mortality are shown in **Table II**. Compared with term neonates, preterm neonates were more likely to receive postnatal steroids, were ventilated for a longer duration, and had a longer length of stay. The risk of meconium aspiration syndrome was higher in term neonates. Mortality occurred only in the preterm group and was secondary to the redirection of care following multiorgan failure and severe neurologic injury in all cases. All deaths occurred in neonates with severe encephalopathy.

Table I. Risk factors and severity of encephalopathy

Variables	Preterm N = 31 (n, %)	Term N = 32 (n, %)	*P*-value
Maternal age, y (mean, (SD))	29.6 (5.5)	28.1 (6.2)	.29
Hypertension/preeclampsia	13 (42.0)	7 (21.9)	.09
Maternal diabetes	5 (16.1)	6 (18.7)	.78
Chorioamnionitis	6 (19.0)	9 (28.1)	.41
Smoking	6 (19.0)	4 (12.5)	.46
Meconium-stained amniotic fluid	2 (6.5)	13 (40.6)	**.001**
Premature rupture of membranes	4 (13.0)	1 (3.1)	.15
Mode of delivery			.12
Cesarean	26 (84.0)	21 (65.6)	
Vaginal (includes instrumentation)	5 (16.0)	11 (34.4)	
Apgar 1 min, median (IQ range)	1 (0-2)	2 (1-3)	.59
Apgar 5 min, median (IQ range)	3 (1-6)	4 (2-5)	.24
Lowest cord pH, mean (SD)	7.02 (0.21)	7.01 (0.18)	.81
Cord base deficit, mean (SD)	14.5 (8.8)	13.5 (7.1)	.61
Sentinel events*			.26
Abruption	13 (41.9)	5 (15.6)	**.02**
Nuchal cord	4 (12.9)	7 (21.9)	.35
Cord prolapse	3 (9.6)	0 (0.0)	.07
Uterine rupture	0 (0.0)	2 (6.3)	.15
Maternal indications†	5 (16.1)	0 (0.0)	**.02**
Severity of encephalopathy			.18
Mild	2 (6.5)	0 (0.0)	
Moderate	21 (67.7)	27 (84.3)	
Severe	8 (25.8)	5 (15.7)	

Bold values indicate they were statistically different.
*In the preterm group, 2 neonates had abruption and nuchal cord.
†Maternal medical illness for delivery included cystic fibrosis, lung transplant, ulcerative colitis, and seizures.

Table II. Neonatal admission characteristics and clinical morbidities

Variables	Preterm N = 31 (n, %)	Term N = 32 (n, %)	*P* value
Birth weight (g)*	2518 (501)	3342 (638)	**<.001**
Gestational age (wk)*	34.7 (0.5)	39.3 (0.8)	**<.001**
Sex			.35
Female	10 (32.2)	14 (43.7)	
Male	21 (67.7)	18 (56.3)	
Race			.91
Black	10 (32.2)	10 (31.2)	
White	19 (61.3)	19 (59.4)	
Other	2 (6.5)	3 (9.4)	
Inborn	14 (45.2)	19 (59.4)	.26
INR at admission	2.3 (1.3)	1.8 (0.5)	**.05**
Lactate at admission*	9.7 (5.4)	8.2 (4.8)	.25
Admission nuRBC/100 WBC	32.4 (33.3)	11.9 (14.2)	**.002**
Admission glucose*	118.1 (73.8)	134.1 (53.5)	.34
Admission temperature*	35.3 (1.6)	33.9 (1.6)	**.002**
Intubated at admission	25 (80.6)	20 (62.5)	.11
Postnatal steroids	8 (26.7)	1 (3.1)	**.01**
Ventilator period, d (median, IQR)	4.0 (1.0-10.0)	1.0 (0.0-5.0)	**.02**
Pneumothorax	2 (6.5)	3 (9.4)	.67
Nitric oxide	6 (19.4)	2 (6.3)	.11
Inotrope use	11 (35.5)	9 (28.1)	.53
Seizures	11 (35.5)	12 (37.5)	.87
MAS	1 (3.5)	6 (18.8)	**.05**
Length of stay, d (median, IQR)	19 (15-31)	13.0 (9.0-23.0)	**.02**
Death	4 (12.9)	0 (0.0)	**.04**

INR, International normalized ratio; *MAS*, meconium aspiration syndrome; *nuRBC*, nucleated red blood cells; *WBC*, white blood cells.
Bold values indicate they were statistically different.
*Data shown as mean (SD).

Cooling characteristics are shown in **Table III**. For both groups, the mean (SD) temperature at admission of neonates cooled passively was lower than those who were not cooled passively (34.0 ± 1.6°C vs 35.7 ± 1.4°C, $P < .001$). Hypothermia was also more likely in neonates cooled passively on transport (14/41 [34.1%] vs 2/21 [9.5%], $P = .04$).

Preterm neonates who developed hypothermia had lower mean temperatures at admission (34.0 ± 2.2°C vs 35.6 ± 1.4°C, $P = .03$) and were more likely to require nitric oxide (3/6, [50.0%] vs 3/24 [12.5%], $P = .04$) than preterm infants who did not develop hypothermia.

Term neonates who developed hypothermia were of higher gestational age (39.8 ± 0.6 vs 39.0 ± 0.8 weeks, $P = .01$) and were more likely to receive nitric oxide (2/10 [20.0%] vs 0/22 [0.0%], $P = .03$) than term infants who did not develop hypothermia.

Therapeutic hypothermia-associated complications (**Table III**) were seen in 90% of preterm infants and 81.3% of term infants ($P = .30$). Complications of hyperglycemia and leukopenia were more common in preterm infants than in term infants, but other complication rates were similar between the groups (**Table III**). Preterm infants were rewarmed before completion of therapeutic hypothermia more often than term infants.

EEG and Neuroimaging

EEG data showed no differences in seizures, burst suppression pattern, or status epilepticus between the 2 groups. In the 12 term neonates treated for seizures, electrographic seizures were captured in 6 (50.0%, 5 were treated clinically, 1 had seizures on amplitude integrated EEG only).

The median (range) age at MRI was 6.0 (4.7-10.3) days in preterm infants and 5.0 (4.0-8.5) days in the term infants ($P = .02$). Neuroimaging showed the presence of injury in 81.6% of preterm infants and 59.4% of term infants ($P = .07$). In the preterm group, MRI injuries were severe in 6 (20.0%), moderate in 7 (23.3%), mild in 12 (38.7%), and absent in 6 (20.0%) neonates. In the term neonates, MRI injuries were severe in 1 (3.1%), moderate in 4 (12.5%), mild in 14 (43.8%), and absent in 13 (40.6%) infants. There was a nonsignificant trend toward increased severity of injury in the preterm group compared with the term group ($P = .07$).

Table IV shows the MRI sites of injury. In the preterm group, injuries were seen in all regions with WM being the most frequent, followed by DNGM and the cortex. Compared with the term newborns, preterm neonates had significantly more injury to the WM and cerebellum. However, in term neonates, injury to the WM was more frequently isolated and injury to cerebellum was not seen.

In the preterm group, 2 (6.7%) neonates were noted to have parenchymal hemorrhage, 1 (3.3%) neonate had grade II intraventricular hemorrhage, and 3 (10.0%) neonates had incidental subdural bleeds.

In the preterm group, 6/30 (20.0%) predominant MRI injuries were classified as DNGM and 14/30 (46.7%) as watershed (WM + cortex). Five (16.7%) had global injury, with cerebellar involvement in 2 (6.7%) neonates. The neonate who

Table III. Cooling characteristics and complications associated with therapeutic hypothermia

	Preterm N = 31 (n,%)	Term N = 32 (n,%)	*P* value	Reported in literature*
Passive cooling†	15 (48.3)	26 (31.3)	**.009**	
Admission temperature when passively cooled, °C‡	34.5 (1.7)§	33.7 (1.6)	.14	
Admission temperature when not cooled passively, °C‡	35.9 (1.3)§	34.9 (1.6)	.12	
Age at active cooling (min)‡	230 (112)	227 (106)	.9	
Hypothermia during active cooling	6 (19.4)	10 (31.2)	.28	
Rewarming before completion of active cooling¶	6 (19.4)	0 (0.0)	**.009**	
Any complication	28 (90.3)	26 (81.3)	.30	4%-61%
Coagulopathy	20 (64.5)	14 (43.8)	.09	0%-25%
Bradycardia (heart rate <80/min)	8 (25.8)	13 (40.6)	.21	12%
Hyperglycemia (glucose >200 mg/dL)	18 (58.1)	10 (31.3)	.03	43%
Hypothermia (<33°C)	6 (19.4)	10 (31.3)	.28	1%
Skin necrosis	1 (3.5)	0 (0.0)	.31	7%-27%
Hypoglycemia (<45 mg/dL)	7 (22.5)	2 (6.3)	.07	10%-63%
Hypokalemia (<3.5 mEq/L)	17 (54.8)	22 (68.7)	.15	
Hypocalcemia				28%
Total calcium (<8.6 mg/dL)	22 (70.9)	20 (62.5)	.59	
Ionized calcium (<3.9 mmol/L)	3 (9.6)	6 (18.8)	.23	
Hyponatremia (<135 mEq/L)	28 (90.3)	27 (84.3)	.48	1%-6%
Leukopenia (<5000/mm^3)	4 (12.9)	0 (0.0)	**.04**	
Neutropenia (<1000/mm^3)	1 (3.2)	0 (0.0)	.31	
Liver function tests				11%-38%
Elevated AST	10 (32.2)	16 (50.0)	.12	
Elevated ALT	9 (29.0)	12 (37.5)	.42	

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase.
Bold values indicate they were statistically different.
*Data from references 1-5, 19, 25.
†1 missing data in preterm group.
‡Data shown as mean (SD).
§In the preterm group, temperature in babies cooled passively compared with those not cooled passively was statistically significantly different ($P = .01$) but was not significant in the term group ($P = .11$).
¶Reasons for rewarming included coagulopathy (n = 2), pulmonary hypertension (n = 1), severe encephalopathy (n = 2), and intolerance to cooling (n = 1).

Table IV. Site(s) of injury on MRI

Site(s) of injury	Preterm* N = 30 (%)	Term Infants N = 32 (%)	*P* value	Reported in literature†
DNGM (any)	13 (43.3)	12 (37.5)	.64	**30%-59%**
DNGM, isolated	0 (0.0)	4 (33.3)		
+ cortex	10 (76.9)	3 (25.0)		
+ WM	8 (61.5)	3 (25.0)		
+ WM +cortex	6 (46.2)	1 (8.3)		
+ brainstem	4 (30.7)	0 (0.0)		
+ cerebellum	1 (7.6)	0 (0.0)		
WM (any)	20 (66.7)	8 (25.0)	**.001**	**8%-64%**
WM, isolated	7 (35.0)	6 (75.0)		
+ cortex	8 (40.0)	2 (25.0)		
+ DNGM	10 (50.0)	2 (25.0)		
Cortex (any)	11 (36.7)	6 (18.8)	.11	**15%-47%**
Cortex, isolated	1 (9.1)	2 (33.3)		
+ WM	8 (72.7)	2 (33.3)		
+ DNGM	2 (18.2)	3 (50.0)		
Brainstem (any)	4 (13.3)	1 (3.1)	.14	
+ DNGM	4 (100.0)	0 (0.0)		
+ cortex	4 (100.0)	1 (100.0)		
+ WM	3 (75.0)	0 (0.0)		
+ cerebellum	2 (50.0)	0 (0.0)		
Cerebellum (any)	4 (13.3)	0 (0.0)	**.03**	
+ DNGM	3 (75.0)	0 (0.0)		
+ brainstem	2 (50.0)	0 (0.0)		
+ cortex	2 (50.0)	0 (0.0)		

Bold values indicate they were statistically different.
*One neonate died of severe encephalopathy before MRI could be performed (and was considered to have severe injury on MRI).
†Data from references 4, 19, 25, 22.

died without an MRI had severe encephalopathy and was considered to have a severe global injury. In the term neonates, DNGM predominant injury was seen in 9/32 (28.1%), watershed in 7/32 (21.8%), and global injury in 3 (9.3%).

In preterm infants, the severity of encephalopathy correlated with injury to the DNGM (r = 0.36, $P = .047$), cortex (r = 0.42, $P = .02$), and brainstem (r = 0.44, $P = .015$), but not with injury to the WM (r = 0.23, $P = .23$) or cerebellum (r = 0.25, $P = .18$). In term infants, the severity of encephalopathy did not correlate with injury to the WM (r = 0.35, $P = .05$), with injury to cortex (r = 0.01, $P = .94$), DNGM (r = 0.20, $P = .27$), or the brainstem (r=-0.07, $P = .67$).

Discussion

In this study of preterm neonates born at 34-35 weeks gestation age with HIE, therapeutic hypothermia was feasible and can be considered as a management strategy for these infants. Although there were no statistical differences in the severity of brain injury on MRI, preterm neonates had an increased incidence of brain injury in the WM and increased mortality secondary to redirection of care related to the severity of encephalopathy.

In randomized trials of therapeutic hypothermia in neonates born at ≥36 weeks gestation, short-term adverse outcomes were transient and recovered without significant long-term sequelae. The complications noted in our study were similar to that reported in the literature. Coagulopathy was a frequent complication in both groups.[1,3,15] Significant thrombosis or hemorrhage is reported in less than 3% of neonates treated with whole body hypothermia but was not seen on neuroimaging in our cohort of preterm neonates.

Hyperglycemia, a factor that may impact long-term neurodevelopment, occurred in a higher proportion of preterm infants. A recent study noted 100% mortality or moderate to severe disability (n = 9) in term neonates treated with therapeutic hypothermia who had a blood glucose >200 mg/dL during the first 24 hours of life compared with controls.[19] We noted hyperglycemia in over one-half of our cohort but mortality was not increased in these patients.

Hypothermia during cooling has been noted both with passive[20] as well as with active phases of cooling, with transient overshooting from the target temperature even on servo-controlled cooling units.[21] Transient core temperature <32°C has been noted in lower birth weight infants without increased risks of mortality.[21] In our current cohort, preterm, but not term, neonates who became hypothermic had lower temperatures at admission. Importantly, in both the preterm and term neonates, a higher proportion of neonates who developed

hypothermia needed nitric oxide therapy suggesting a higher risk for pulmonary hypertension, as also noted by others.[22]

The overall mortality of 12.9% in our preterm cohort is lower than mortality reported in the meta-analyses of trials of therapeutic hypothermia of neonates ≥36 weeks gestation[1] (approximately 25%) and may reflect the higher number of mild-moderate (74%) compared with severely (26%) encephalopathic neonates in the preterm group. All mortality occurred in preterm infants and those with severe encephalopathy, with death occurring in 50% of preterm infants with severe encephalopathy in our cohort. This is similar to prior reports which have identified that 88%-94% of all mortality occurs in neonates with severe HIE.[13,14]

Seizures were noted in over one-third of both preterm and term neonates, consistent with rates reported in near-term and term neonates[3,5,15] MRI scans performed within a few days after birth in infants with HIE are considered excellent biomarkers, as they accurately identify the site and timing of injury reflecting the underlying etiology and are highly predictive of neurodevelopmental outcomes.[23] Even though the therapeutic hypothermia trials noted that the severity of injury may be ameliorated by cooling and that patterns of injury may have been influenced by the timing of the MRI scans, the predictive value of MRI in HIE is not altered by therapeutic hypothermia.[24] Two major patterns of injury have been identified in term neonates that predict outcomes as well as identify underlying etiology[25]; basal ganglia and thalamus predominant, also involving the brainstem and hippocampus; and watershed predominant involving the WM and the overlying cortex (our scoring system includes the basal ganglia and thalamus regions in the DNGM score). A third pattern involving focal WM injury without involvement of the basal ganglia and thalamus has also been associated with poor prognosis and is similar to the WM injury seen in preterm infants.[26]

In our study, watershed (cortex and WM) predominant injury was the prevalent pattern in preterm neonates, whereas the term cohort had more neonates with DNGM prominent injury. These differences may be reflective of the underlying etiology. For example, the watershed injury pattern is suggestive of chronic intermittent hypoxia, an etiology also supported by the elevated nucleated red blood cell counts noted in the preterm neonates.[27] The DNGM pattern is more often associated with acute hypoxia and is seen in 30%-59% of near-term and term neonates with HIE treated with therapeutic hypothermia.[24]

In our study, rates of brain injury on MRI in preterm infants were higher (80.6%) than term neonates (59.4%) and also higher than the 40%-46% reported in neonates ≥36 weeks enrolled in the therapeutic hypothermia trials.[3,4,15] The MRI abnormalities in our study noted primarily in the WM may be reflective of the lower gestational age and the selective vulnerability of the WM and the cerebellum during this period. However, the higher incidence of MRI injury in our preterm group is comparable to rates in preterm infants with HIE not treated with therapeutic hypothermia; Logitharajah et al[28] reported neuroimaging findings from 55 preterm infants born at 26-36 weeks gestation. In that study, the median gestational age of the infants was 35 weeks (5 infants were <32 weeks gestation), and the median age of the first scan was 7 days. They noted injury in the WM in nearly 89% neonates, in the basal ganglia and thalamus in 72%, in the cortex in 47%, and brainstem in 43% of infants. Therapeutic hypothermia trials that enrolled infants at 35 weeks gestation[15] did not report MRI results by gestational age.

Our study is limited by the retrospective nature and small cohort size. The lack of a control group of preterm neonates at this gestational age not treated with therapeutic hypothermia is a limitation that cannot be overcome without clinical trials (currently ongoing). In the absence of a preterm control group, we have compared the safety outcomes and neurologic injury on MRI to a cohort of term neonates from our unit, as well as with published data in neonates born at ≥36 weeks gestational age treated with therapeutic hypothermia. The absence of mortality in our term cohort may also be a source of bias. Moreover, we included neonates with mild encephalopathy in our analyses as there has been drift in clinical practice, and these neonates are more commonly being treated with therapeutic hypothermia. Further, we have performed only a limited analysis of the EEG characteristics. We do not have complete neurodevelopmental follow-up on our survivors in the preterm cohort currently, and this precludes further analyses at this time. However, our data as well as isolated case reports[29] of cooling in late preterm neonates suggest that therapeutic hypothermia can be extended to neonates ≥34 weeks gestation. Our date suggests that rates of most adverse events associated with the active cooling process are similar to those seen in term neonates. The high proportion of preterm infants with injury, particularly to the WM, noted on MRI scans may reflect the selective vulnerability of WM to injury at this gestational age but also warrants caution. Although further randomized controlled trials are needed to establish the safety and efficacy of therapeutic hypothermia in the preterm neonates, these data can be used to provide parents with important information regarding therapeutic hypothermia in this population. ■

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