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.