Pulmonary Hypertension Associated with Hypoxic-Ischemic Encephalopathy—Antecedent Characteristics and Comorbidities

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Objective To determine the characteristics of term infants with persistent pulmonary hypertension of the newborn (PPHN) associated with moderate or severe hypoxic ischemic encephalopathy (HIE).

Methods We compared infants with and without PPHN enrolled in 2 randomized trials of therapeutic hypothermia: the induced hypothermia trial of cooling to 33.5°C for 72 hours vs normothermia, and the "usual-care" arm (33.5°C for 72 hours) of the optimizing cooling trial.

Results Among 303 infants with HIE from these 2 studies, 67 (22%) had PPHN and 236 (78%) did not. We compared infants with PPHN with those without PPHN. The proportion of patients treated with therapeutic hypothermia was similar in PPHN and no-PPHN groups (66% vs 65%). Medication use during resuscitation (58% vs 44%), acidosis after birth (pH: 7.0 ± 0.2 vs 7.1 ± 0.2), severe HIE (43% vs 28%), meconium aspiration syndrome (39% vs 7%), pulmonary hemorrhage (12% vs 3%), culture-positive sepsis (12% vs 3%), systemic hypotension (65% vs 28%), inhaled nitric oxide therapy (64% vs 3%), and extracorporeal membrane oxygenation (12% vs 0%) were more common in the PPHN group. Length of stay (26 ± 21 vs 16 ± 14 days) and mortality (27% vs 16%) were higher in the PPHN group.

Conclusions PPHN is common among infants with moderate/severe HIE and is associated with severe encephalopathy, lung disease, sepsis, systemic hypotension, and increased mortality. The prevalence of PPHN was not different between those infants receiving therapeutic hypothermia at 33.5°C in these 2 trials (44/197 = 22%) compared with infants receiving normothermia in the induced hypothermia trial (23/106 = 22%). *(J Pediatr 2017;■■:■■-■■).*

Moderate hypothermia (33.5°C) is neuroprotective in infants who suffer from perinatal hypoxic-ischemic encephalopathy (HIE). The American Academy of Pediatrics[1] and Neonatal Resuscitation Program[2] support whole-body or selective head cooling for neonates with moderate to severe HIE. Persistent pulmonary hypertension of the newborn was reported in 6%-25% neonates with HIE enrolled in the clinical trials of head and whole body cooling[3-5] and is higher than the incidence of PPHN in the general population (1.9 per 1000 live births).[6] The definition of PPHN in these trials was variable and based on clinical features, presence of hypoxemic respiratory failure, echocardiography, or use of inhaled nitric oxide (iNO).

There are several potential mechanisms causing hypoxemic respiratory failure and PPHN in asphyxiated newborn infants.[7] Fetal hypoxemia, meconium aspiration syndrome (MAS), sepsis, ventricular dysfunction, and acidosis can increase pulmonary vascular resistance (PVR) and result in PPHN. Among fatal cases of PPHN secondary to MAS, 10 of 11 infants had evidence of remodeling of intra-acinar pulmonary arteries at autopsy contributing to increased PVR.[8,9]

In the first *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Rockville, Maryland—Neonatal Research Network trial (induced hypothermia [IH]), moderate hypothermia to 33.5°C was not associated with an increase in the incidence of PPHN or the need for iNO and extracorporeal membrane oxygenation (ECMO) compared with the normothermia group (25% vs 22%). In the optimizing cooling (OC) strategies trial, the incidence of PPHN among infants cooled to 33.5°C was 20%. However, in the OC trial where neonates were randomly assigned to 4 combinations of duration and depth of cooling, whole body

ECMO	Extracorporeal membrane oxygenation
HIE	Hypoxic ischemic encephalopathy
IH	Induced hypothermia
iNO	Inhaled nitric oxide
MAS	Meconium aspiration syndrome
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
OC	Optimizing cooling
PPHN	Persistent pulmonary hypertension of the newborn
PVR	Pulmonary vascular resistance

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hypothermia to 32°C for duration of 72 or 120 hours was associated with an increased use of iNO and ECMO, compared with infants randomized to the 33.5°C cooling for either 72 or 120 hours.[10] Currently, moderate hypothermia with a core temperature of 33.5°C for 72 hours initiated within 6 hours of birth is recommended for newborns with moderate or severe HIE.[1,2,11]

Our primary objective was to determine the clinical characteristics and comorbidities before delivery, intrapartum, and during the hospital course prior to discharge that were associated with PPHN in term neonates with moderate to severe HIE. We hypothesized that lung disease (eg, MAS, pulmonary hemorrhage), sepsis, and cardiac dysfunction would be more common in neonates with HIE who also had PPHN, and that infants with PPHN would have a lower PaO_2 at baseline, higher rate of severe encephalopathy, and higher mortality. We also evaluated the use of iNO and ECMO in infants with PPHN and compared the mortality between infants with and without PPHN. We used prespecified data collected from 2 randomized controlled trials, IH and OC. Because prolonged (120 hours) and deeper cooling (32°C) are not standard of care, we excluded infants enrolled in these arms from the OC trial.

Methods

This study was a secondary analysis of data from the NICHD IH Trial (IH- NCT00005772, 2000-2003) and the "usual care" arm (33°C for 72 hours) of the optimizing cooling strategies trial (OC-NCT01192776, 2010-2013). For both trials, infants were screened if they were of gestational age ≥36 weeks and were admitted to the neonatal intensive care unit at <6 hours of age, with an admitting diagnosis of acute perinatal asphyxia, neonatal depression, encephalopathy, and/or fetal acidemia. Infants were evaluated according to physiologic criteria and a neurologic examination. Eligibility criteria included pH of ≤7.0 or base deficit of ≥16 mmol/L in cord blood or during the first 1 hour after birth. If, during this interval, the pH was between 7.01 and 7.15, the base deficit was between 10 and 15.9 mmol/L, or an arterial blood gas value was not available, then additional criteria were required (an acute perinatal event and either a 10-minute Apgar score of ≤5 or assisted ventilation for ≥10 minutes from birth). Once these criteria were met, all infants underwent a standardized neurologic examination, performed by a certified physician. Encephalopathy was defined as ≥1 moderate or severe signs in at least 3 of the 6 categories. The number of moderate or severe signs determined the degree of encephalopathy; if signs were distributed equally, then the designation was based on the level of consciousness. Moderate or severe encephalopathy or seizures qualified infants for the trials.

The diagnosis of PPHN was based on clinical signs consistent with this diagnosis and echocardiographic evidence of pulmonary hypertension (ie, no structural heart disease; positive indication of elevated pulmonary arterial pressure; and/or flattened ventricular septum).[12] The centers were instructed to obtain and report blood gases at patient's actual temperature. The interpretation of echocardiograms, ventilator management, use of iNO, and ECMO was as per individual center practices. The distribution of patients in various arms of these trials is shown in **Figure 1**.

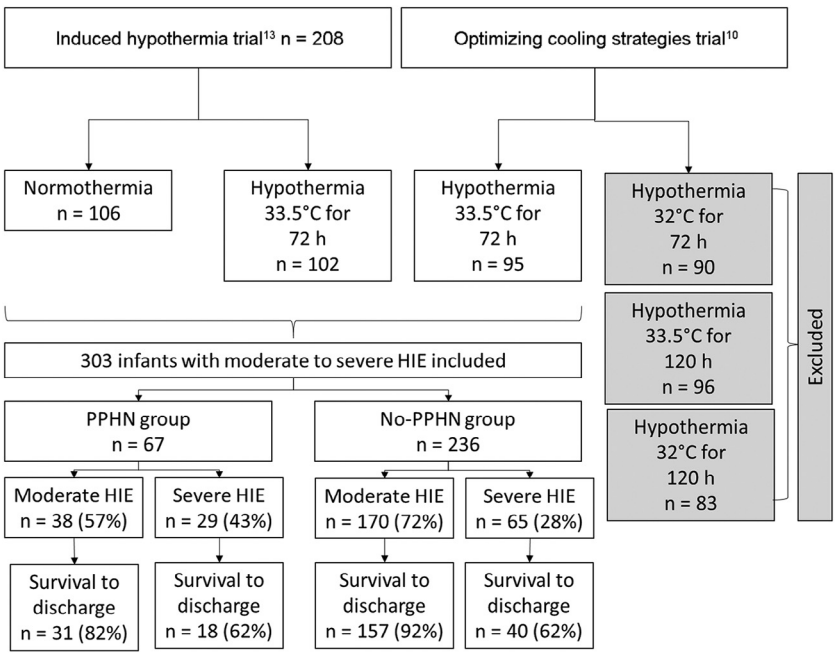

Figure 1. Flow chart depicting the source of subjects and classification based the presence of PPHN (clinical and echocardiographic) and severity of HIE. *One patient in the no-PPHN group did not have the severity of HIE documented and is missing from the reminder of the flow-chart.

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