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Outcomes of Infants with Hypoxic Ischemic Encephalopathy and Persistent Pulmonary Hypertension of the Newborn: Results from Three NICHD Studies

Prashant Agarwal, MD[1], **Seetha Shankaran, MD**[1], **Abbot R. Laptook, MD**[2], **Dhuly Chowdhury, MS**[3], **Satyan Lakshminrusimha, MD**[4,5], **Sonia Lomeli Bonifacio, MD**[6], **Girija Natarajan, MD**[1], **Sanjay Chawla, MD**[1], **Martin Keszler, MD**[2], **Roy J. Heyne, MD**[7], **Namasivayam Ambalavanan, MD**[8], **Michele C. Walsh, MD, MS**[9], **Abhik Das, PhD**[10], **Krisa P. Van Meurs, MD**[6], ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development (NICHD) Neonatal Research Network***

[1]Department of Pediatrics, Wayne State University, Detroit, MI

[2]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

[3]Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC

[4]Department of Pediatrics, University of Buffalo Women's and Children's Hospital of Buffalo, Buffalo, NY

[5]University of California at Davis, Sacramento, CA

[6]Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

[7]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

[8]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

[9]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

[10]Social, Statistical and Environmental Sciences Unit, RTI International, Rockville, MD

Abstract

Corresponding author: Prashant Agarwal, MD, 3901 Beaubien Street, Detroit, MI 48201, Phone: 313-745-5638, pagarwal@med.wayne.edu.

*A complete list of group members appears in the Appendix

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Conflict of Interest

The authors declare no conflicts of interest.

Objective: To determine the association of persistent pulmonary hypertension of the newborn (PPHN) with death or disability among infants with moderate or severe hypoxic ischemic encephalopathy (HIE) treated with therapeutic hypothermia.

Methods: We compared infants with and without PPHN enrolled in the hypothermia arm from three randomized controlled trials (RCTs): Induced Hypothermia trial, "usual-care" arm of Optimizing Cooling trial, and Late Hypothermia trial. Primary outcome was death or disability at 18–22 months adjusted for severity of HIE, center, and RCT.

Results: Among 280 infants, 67 (24%) were diagnosed with PPHN. Among infants with and without PPHN, death or disability was 47% vs. 29% (adjusted OR 1.65, 0.86–3.14) and death was 26% vs. 12% (adjusted OR 2.04, 0.92–4.53), respectively.

Conclusions: PPHN in infants with moderate or severe HIE was not associated with a statistically significant increase in primary outcome. These results should be interpreted with caution given the limited sample size.

Keywords

cooling; pulmonary hypertension; neurodevelopmental impairment

Neonatal hypoxic ischemic encephalopathy (HIE) is an important clinical problem and is associated with substantial mortality and long-term neurologic morbidities. Therapeutic hypothermia significantly decreases death or childhood disability and has become the standard of care for term neonates with moderate or severe HIE(1–5). Currently, approximately 29% of infants with moderate or severe HIE die or have significant neurodevelopmental disability despite therapeutic hypothermia(6).

The incidence of PPHN ranges from 15 to 29% among infants with HIE(3, 6, 7). Animal studies have shown an increase in pulmonary vascular resistance with hypothermia to 30°C −34°C(8, 9) and in human neonates, hypothermia to 32°C is associated with an increased need for iNO and ECMO therapy(6). There are also reports of development of pulmonary hypertensive crisis and need for ECMO during rewarming(10). However, the NICHD NRN trials have not shown a difference in prevalence of PPHN with hypothermia to 33.5°C compared to the normothermic control group(11). In addition, the meta-analysis of 4 trials involving 614 infants showed a risk ratio of 1.36 (95% CI .94–1.97) for pulmonary hypertension among infants receiving hypothermia at 33°C −34°C and 3 trials found no significant difference in the use of iNO when compared to normothermic controls(3).

There are multiple potential causes of hypoxemic respiratory failure and PPHN in infants with HIE including perinatal hypoxia and acidosis, meconium aspiration syndrome, ventricular dysfunction, and pulmonary hemorrhage(11–14). Hypoxemia and acidosis, especially when sustained, can persistently elevate pulmonary vascular resistance, leading to cardiac dysfunction and shunting of deoxygenated blood to the systemic circulation through the foramen ovale or ductus arteriosus, thus resulting in systemic hypoxemia(15).

Persistent pulmonary hypertension (PPHN) is characterized by elevated pulmonary arterial pressure and resultant right to left shunting of blood thus causing systemic hypoxemia.

Therapies for PPHN include positive pressure ventilation with optimal lung recruitment, maintenance of optimal intravascular volume and cardiac function, pulmonary vasodilators such as inhaled nitric oxide (iNO), and extra-corporeal membrane oxygenation (ECMO)(16–18). Infants with HIE may have decreased cerebral perfusion due to cerebral edema, impaired cerebral autoregulation, ventricular dysfunction, systemic hypotension, and hypocarbia, while PPHN may decrease cerebral oxygenation, and cause additional brain injury(19–21). Although survival among infants with PPHN has improved in recent decades, 15%−30% of survivors continue to have neurodevelopmental impairment likely due to the primary disease process, oxidant stress from hyperoxia, and complications associated with other therapies such as hyperventilation or ECMO(22–25). Neurodevelopmental follow up at 18–24 months of infants enrolled in the iNO treated arm of Neonatal Inhaled Nitric Oxide Study (NINOS) trial showed 35% infants had one or more neurodevelopmental disabilities, including Bayley Scales of Infant Development (BSID) II Mental Developmental Index (MDI) <70 in 27% and Psychomotor Developmental Index (PDI) <70 in 22%, cerebral palsy in 12%, sensorineural hearing loss in 13%, hearing aid in 8%, and blindness in 2%(25).

Currently there are no data available on neurodevelopmental outcomes of infants with moderate or severe HIE and PPHN. We hypothesized that among infants with moderate or severe HIE treated with therapeutic hypothermia, those with PPHN will have an increased risk of death or disability compared to infants who do not develop PPHN.

Methods

This was a retrospective analysis of prospectively collected data on infants enrolled in the hypothermia arm of one of three trials- the Induced Hypothermia (IH) trial (1), “usual-care” arm (33.5°C for 72h) of Optimizing Cooling Strategies (OC) trial (26), and Late Hypothermia (LH) trial (27) performed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN). For all three trials, infants were screened if they had gestational age ≥ 36 weeks and were admitted to the neonatal intensive care unit with a diagnosis of acute perinatal asphyxia, neurological depression, encephalopathy, and/or fetal acidemia. Postnatal age for eligibility was <6 hours for IH and OC trial and 6 to 24 hours for the LH trial. Moderate or severe HIE in all these trials was defined using the NICHD screening biochemical criteria along with neurologic examination (modified Sarnat staging) consistent with moderate or severe encephalopathy or seizures (1). For IH and the “usual care” arm of OC trial, eligible infants received whole body therapeutic hypothermia to 33.5°C for 72 hours, initiated within 6 hours of age. For the LH trial, eligible infants received whole body therapeutic hypothermia to 33.5°C for 96 hours, initiated between 6 to 24 hours of age. Infants with major congenital anomalies were excluded from all three trials.

In these trials, PPHN was diagnosed on the basis of clinical signs consistent with this diagnosis and echocardiographic evidence of pulmonary hypertension (i.e., no structural heart disease; positive indication of elevated pulmonary arterial pressure; and/or flattened ventricular septum). We also included infants who were not diagnosed with PPHN (by clinical or echocardiographic criteria) but who received iNO with the PPHN cohort. The

interpretation of echocardiograms and management of PPHN, including use of iNO and ECMO were according to individual center practices.

The follow up data from the three trials were used to evaluate the neurodevelopmental outcomes at 18–22 months. The primary outcome for this study was death or moderate or severe disability as defined in the trials(1, 26, 27). Moderate disability was defined as BSID III cognitive score 70–84 in the OC and LH trials and BSID II MDI 70–84 in the IH trial, **and** either GMFCS level 2, active seizures or hearing impairment (hearing impairment with no amplification for IH trial and hearing with amplification for OC and LH trial). Severe disability was defined as any of the following: BSID III cognitive score <70 in the OC and LH trials and MDI <70 in the IH trial, GMFCS level 3–5, blindness or severe hearing impairment (hearing impairment requiring amplification for IH trial and hearing impairment despite amplification for OC and LH trial). Secondary outcomes included components of the primary outcome: death, moderate or severe disability in survivors, and cerebral palsy, composite cognitive score or MDI score, composite motor score or PDI score, blindness, and severe hearing impairment.

Statistical analysis

Descriptive statistics included mean (SD) or median (IQR) for continuous variables and frequency and percentage for categorical variables. Unadjusted comparisons of baseline maternal and infant characteristics and neonatal morbidities were performed between the infants with or without PPHN using chi squared test, t-test, or Wilcoxon test, as appropriate. Generalized linear mixed models were used to compare neurodevelopmental outcomes between the infants with and without PPHN after adjusting for severity of HIE, center and study (IH, OC or LH), as possible. Center of birth was included as a random effect and other covariates were included as fixed effects. For some of the outcomes (Bayley III Motor score or Bayley II PDI, moderate cerebral palsy, and blindness), the adjusted model did not include center and/or study due to small sample size. No adjustments were made for multiple comparisons. A two-sided p-value of <0.05 was considered significant. Statistical analyses were performed using SAS 9.4, Cary, NC.

Results

A total of 280 infants (IH trial n=102, OC n=95, LH n=83) were included in this study. Sixty-seven infants (24%) were diagnosed with PPHN (n=64; IH trial n=25, OC n=19, LH n=20) or received iNO (n=3, all in OC trial) and 213 (76%) did not have PPHN (Figure 1).

Maternal and intrapartum neonatal characteristics are shown in Table 1. Maternal chronic hypertension and uterine rupture were more common among infants in the no- PPHN group. Infants in the PPHN group had a higher incidence of severe encephalopathy (39% vs. 17%, P <0.0001) and continued need for resuscitation at 10 minutes (94% vs. 82%, P=0.02).

Hospital outcomes are shown in Table 2. Pulmonary diagnoses (meconium aspiration syndrome and pulmonary hemorrhage) were more commonly observed among infants in PPHN group. Cardiac dysfunction (defined as any of the following: cardiomegaly, cardiac failure, dysfunction on ECHO, or elevated cardiac enzymes) and vasopressor use for

hypotension were also higher among infants in the PPHN group. Forty-seven infants (70%) in the PPHN group received iNO and 9 (13%) received ECMO. Infants in the PPHN group had higher rates of other in-hospital morbidities including disseminated intravascular coagulation, need for blood and platelet transfusion, hypoglycemia, hypocalcemia and sepsis with positive blood culture. Infants in PPHN group had a longer length of hospital stay, more days of ventilation, and days of supplemental oxygen. Mortality before discharge was also higher among infants in the PPHN group. Among survivors, there was no difference in receipt of oxygen, gavage/gastrostomy tube feeds, or seizures requiring anticonvulsant therapy at hospital discharge.

At 18–22 months follow-up, the primary outcome of death or moderate/severe disability was available for 66 (98.5%) infants in PPHN group and 206 (96.7%) infants in the no-PPHN group (Table 3). While the PPHN group had a significant increase in the primary outcome in the unadjusted analysis [47% vs. 29%, OR (95% CI) 2.12 (1.18–3.81), P=0.01], there was no significant difference after adjustment for severity of encephalopathy, center, and specific RCT [adjusted OR (95% CI) 1.65 (0.86–3.14), P=0.13]. Death was also higher in the PPHN group in unadjusted analysis [26% vs. 12%, OR (95% CI) 2.54 (1.24–5.19), P=0.01], but was not statistically different between the groups after adjusted analysis [adjusted OR (95% CI) 2.04 (0.92–4.53, P=0.08]. There was no difference in the incidence of moderate or severe disability, cerebral palsy, or blindness between the groups. Severe hearing impairment was higher among infants in the PPHN group. In subgroup analysis, among infants with moderate encephalopathy at trial enrollment, death or moderate/severe disability was higher among infants in the PPHN group compared to those in the no-PPHN group [39% vs. 20%, adjusted OR (95%CI) 2.58 (1.20–5.53), P=0.02]. Among infants with severe encephalopathy at trial enrollment, there was no difference in death or moderate or severe disability between the groups [60% vs. 70%, OR (95% CI) 0.67 (0.22–2.02), P=0.47]. Among the 9 infants (moderate HIE, n= 7; severe HIE, n= 2) who received ECMO, all survived to follow up and 3 (33%) had moderate or severe disability at 18–22 months.

Discussion

We performed a secondary analysis evaluating the outcome of infants with and without PPHN, who were enrolled in the hypothermia arm of one of the three NICHD NRN RCTs of hypothermia for HIE. In this study, PPHN was present in 24% of infants with moderate or severe HIE. This study did not find a statistically significant difference in the primary outcome of death or moderate/severe disability among infants with HIE and PPHN when compared to those without PPHN, following statistical adjustment for severity of HIE, center, and specific RCT. Infants with moderate or severe HIE are at risk of development of PPHN, which may potentially increase their risk of brain injury by exposing them to hypoxemia directly, or hyperoxemia and hypocarbia due to PPHN management. We speculate that the lack of a significant association between PPHN and death or disability at 2 years of age in infants with HIE may be related to our sample size, the varying severity and timing of PPHN, and the confounding effects of HIE severity on outcome. Currently there are conflicting results regarding the early predictive markers of developmental disability among newborns with HIE and PPHN. More et al. reported increased incidence of PPHN among infants with HIE who had evidence of brain injury on magnetic resonance imaging

(MRI)(28); however, another study did not find association of PPHN with neurologic examination at discharge or MRI abnormalities(11). Longer term neurodevelopment outcomes were not reported in these studies. In this study, PPHN was not associated with increased incidence of moderate or severe disability at 18–22 months.

The NICHD NRN reported morbidity following PPHN in the Induced Hypothermia trial (n=208, 106 normothermia, 102 hypothermia) and usual care arm of the Optimizing Cooling Strategies trial (n=95)(11). In-hospital mortality (27% vs. 16%) was not different after adjustment for severity of HIE [adjusted OR (95% CI) 1.52 (0.76–3.02) *P*=0.24]. Mortality among infants with moderate HIE was higher [OR (95% CI) 2.73 (1.01–7.39), *P*=0.048] among the PPHN group (18%) compared to no PPHN group (8%). Mortality among infants with severe HIE was not associated with the presence of PPHN (38% mortality in both groups, OR 0.98, 0.40–2.41, P=0.96). Similarly, in the current analysis of infants with moderate encephalopathy at study entry, PPHN was associated with significantly higher death or moderate/severe disability. Among those with severe encephalopathy at study entry, PPHN was not associated with death or moderate/severe disability. Whether early identification and management of PPHN among infants with moderate encephalopathy during therapeutic hypothermia could potentially improve the mortality or disability rate in this subgroup is unknown. It has recently been noted that signs of right ventricular dysfunction on early echocardiography performed at or within 24 hours of age, may identify infants with HIE at risk for progression to receipt of iNO or ECMO for PPHN(29). Another study noted that right ventricular dysfunction identified on early echocardiography at 24 hours of age is associated with abnormal MRI or death among infants with HIE(30).

The use of ECMO among infants receiving therapeutic hypothermia for HIE is increasing(31). About 4–9% of infants with HIE and PPHN receive ECMO therapy(1, 6). The Extracorporeal Life Support Organization (ELSO) registry, from 2006–2012, reported that the use of ECMO among infants receiving therapeutic hypothermia for HIE has increased from 0 to 37 annually(32). These infants are at high risk for intracranial hemorrhage during anticoagulation with ECMO since they often have coagulopathy and multiorgan injury(3). In a study from the ELSO registry, among 78 neonates with HIE receiving therapeutic hypothermia and ECMO, 17 (22%) developed neurological complications and 12 (15%) died before hospital discharge(32). Another single center study of 20 neonates with HIE receiving therapeutic hypothermia and ECMO noted a 30% incidence of intracranial hemorrhage during ECMO and 20% in-hospital mortality; with 44% normal MRI before discharge among survivors(33). None of these studies reported neurodevelopmental outcomes. In the present study, among the 9 infants receiving ECMO, all survived to discharge and 6 (66%) had no or mild disability at follow up. However, no definite conclusions can be made from this very small sample size, and follow up data of larger number of infants with HIE and ECMO are needed to determine the neurodevelopmental outcomes of these high risk infants. Also, there is a potential for selection bias, with some infants not being considered a candidate of ECMO due to the high risk of intracranial hemorrhage or poor neurodevelopmental outcomes.

Approximately 5% survivors of moderate to severe HIE have sensorineural hearing loss, with no difference among hypothermia or normothermia infants(3). Follow up data of

randomized controlled multicenter trials of iNO for PPHN showed that about 7% −14% of surviving infants had sensorineural hearing loss with 2–8% requiring amplification; there was no difference among infants who received iNO compared to those who did not (23–25). In our cohort of infants with HIE and PPHN, 13% required amplification for hearing loss.

There are several limitations to our study. PPHN in these trials was diagnosed on the basis of clinical signs and echocardiographic evidence of pulmonary hypertension which may have both intra-center and inter-center variation. The timing of diagnosis, severity or duration of PPHN, and indication and time of initiation of iNO and ECMO were not recorded. There is a 20 year time span between the trial data sets and clinical care may have changed during this period(34). However, despite the 20 year time span between these data sets, the incidence of PPHN has remained stable at 20–25% among the hypothermia group of IH, usual-care arm of OC, and the hypothermia group of LH. Mortality was much lower in the OC and LH trials compared to the IH trial (9% and 11.5% in OC and LH trial respectively, 24% in IH trial). The lower mortality in the Optimizing Cooling Strategies trial is probably related to lower number of severe HIE infants enrolled (~ 23% compared to 35% in Induced Hypothermia), while in the Late Hypothermia trial, more moderate HIE infants were enrolled (~90%). The differing editions of standardized development assessment tool (BSID II in IH trial and BSID III in OC and LH trial) could limit the ability to compare outcomes between these trials. Also, analysis was not adjusted for multiple comparisons, since only the primary outcome analysis is considered as definitive. The strengths of this study are the inclusion of the largest number of infants with HIE and PPHN treated with hypothermia; however, it must be noted that the absolute number of infants with PPHN was small.

In summary, among RCT participants treated with hypothermia for HIE, PPHN was associated with an increased risk of death or moderate or severe disability at 18–22 months when compared to those without PPHN; however the difference was no longer statistically significant after adjustment for the severity of HIE, center, and specific RCT. Among infants with moderate encephalopathy at study entry, PPHN was associated with significantly higher death or moderate or severe disability. These results should be interpreted with caution as the limited sample size may preclude the possibility of detecting statistically significant group differences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) - William Oh, MD; Betty R. Vohr, MD; Angelita M. Hensman, PhD RNC-NIC; Barbara Alksninis, RNC PNP; Joseph Bliss, MD PhD; Carmena Bishop; Robert T. Burke, MD MPH; William Cashore, MD; Melinda Caskey, MD; Nicholas Guerina, MD PhD; Hussnain Mirza, MD; Katharine Johnson, MD; Mary Lenore Keszler, MD; Andrea M. Knoll; Theresa M. Leach, MEd CAES; Martha R. Leonard, BA BS; Emilee Little, RN BSN; Elizabeth C. McGowan, MD; Ross Sommers, MD; Birju A. Shah, MD MPH; Bonnie E. Stephens, MD; Suzy Ventura; Elisa Vieira, RN BSN; Victoria E. Watson, MS CAS.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) - Anna Maria Hibbs, MD; Avroy A. Fanaroff, MD; Deanne E. Wilson-Costello, MD; Nancy S. Newman, RN; Beau Batton, MD; Monika Bhola, MD; Juliann M. Di Fiore, BSEE; Harriet G. Friedman, MA; Bonnie S. Siner, RN; Elizabeth Smart, MS; Eileen K. Stork, MD; Gulgun Yalcinkaya, MD; Arlene Zadell, RN.

Children's Mercy Hospital, University of Missouri Kansas City School of Medicine (U10 HD68284) - William E. Truog, MD; Eugenia K. Pallotto, MD MSCE; Howard W. Kilbride MD; Cheri Gauldin, RN BS CCRC; Anne Holmes RN MSN MBA-HCM CCRC; Kathy Johnson RN, CCRC; Allison Knutson, BSN RNC-NIC.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Medical Center, and Good Samaritan Hospital (U10 HD27853, M01 RR8084, UL1 TR77) - Brenda B. Poindexter, MD MS; Kurt Schibler, MD; Edward F. Donovan, MD; Suhas G. Kallapur, MD; Kimberly Yolton, PhD; Cathy Grisby, BSN CCRC; Barbara Alexander, RN; Estelle E. Fischer, MHSA MBA; Teresa L. Gratton, PA; Jody Hessling, MSN RN; Lenora Jackson, CRC; Jennifer Jennings, RN BSN; Kristin Kirker, CRC; Stephanie Merhar, MD MS; Holly L. Mincey, MS RN BSN; Greg Muthig, BA; Jean J. Steichen, MD; Sandra Wuertz, RN BSN CLC.

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Nationwide Children's Hospital and The Ohio State University Wexner Medical Center (U10 HD68278) - Pablo J. Sánchez, MD; Leif D. Nelin, MD; Nehal A. Parihk, DO MS; Sudarshan R. Jadcherla, MD; Patricia Luzader, RN; Roopali Bapat, MD; Thomas Bartman, MD; Elizabeth Bonachea, MD; Louis G. Chicoine, MD; Bronte Clifford; Erin Ferns; Christine A. Fortney, PhD RN; Jennifer Fuller, MS RNC; Ish Gulati, MD; Julie Gutentag, BSN; Krista Haines, MD; Brandon Hart, MD; Michael Hokenson, MD; Marissa E. Jones, RN MBA; Sarah McGregor, BSN RNC; Marliese Dion Nist, BSN; Elizabeth Ann Rodgers, BSN; Ruth Seabrook, MD; Tiffany Sharp; Edward G. Shepherd, MD; Jonathan Slaughter, MD, MPH; Jodi A. Ulloa, MSN APRN NNP-BC; Jon Wispe, MD; Tara Wolfe, BSN; L. Yossef, MD; Nahla Zaghoul, MD.

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University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) - Waldemar A. Carlo, MD; Myriam Peralta-Carcelen, MD MPH; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN; Vivien A. Phillips, RN BSN; Richard V. Rector, PhD; Sally Whitley, MA OTR-L FAOTA.

University of California - Los Angeles, Mattel Children's Hospital, Santa Monica Hospital, Los Robles Hospital and Medical Center, and Olive View Medical Center (U10 HD68270) - Uday Devaskar, MD; Meena Garg, MD; Isabell B. Purdy, PhD CPNP; Teresa Chanlaw, MPH; Rachel Geller, RN BSN.

University of California - San Diego Medical Center and Sharp Mary Birch Hospital for Women & Newborns (U10 HD40461) - Neil D. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Wade Rich, BSHS RRT; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Christopher Henderson, AS CRTT; David Kaegi, MD.

University of Iowa and Mercy Medical Center (U10 HD53109, UL1 TR442) - Edward F. Bell, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA; Michael J. Acarregui, MD MBA; Jane E. Brumbaugh, MD; Jacky R. Walker, RN; Claire A. Goeke, RN; Jonathan M. Klein, MD; Nancy J. Krutzfield, RN MA; Jeffrey L. Segar, MD; John M. Dagle, MD PhD; Julie B. Lindower, MD MPH; Steven J. McElroy, MD; Glenda K. Rabe, MD MME; Robert D. Roghair, MD; Lauritz R. Meyer, MD; Dan L. Ellsbury, MD; Donia B. Bass, RNC-NIC; Cary R. Murphy, MD; Vipinchandra Bhavsar, MB BS.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) - Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (U10 HD53089, UL1 TR41) - Kristi L. Watterberg, MD; Robin K. Ohls, MD; Conra Backstrom Lacy, RN; Sandra Sundquist Beauman, MSN RNC; Sandra Brown, BSN; Erika Fernandez, MD; Andrea Freeman Duncan, MD; Janell Fuller, MD; Jean R. Lowe, PhD.

University of Pennsylvania, Hospital of the University of Pennsylvania, Pennsylvania Hospital, and Children's Hospital of Philadelphia (U10 HD68244) - Barbara Schmidt, MD MSc; Haresh Kirpalani, MB MSc; Sara B. DeMauro, MD MSCE; Kevin C. Dysart, MD; Soraya Abbasi, MD; Aasma S. Chaudhary, BS RRT; Toni Mancini, RN BSN CCRC; Dara M. Cucinotta, RN; Judy C. Bernbaum, MD; Marsha Gerdes, PhD; Hallam Hurt, MD.

University of Rochester Medical Center, Golisano Children's Hospital, and the University of Buffalo Women's and Children's Hospital of Buffalo (U10 HD68263, UL1 TR42) - Carl D'Angio, MD; Ronnie Guillet, MD PhD; Dale L. Phelps, MD; Nirupama Laroia, MD; Gary J. Myers, MD; Osman Farooq, MD; Stephanie Guilford, BS; Rosemary L. Jensen; Diane Hust, MS RN CS; Linda J. Reubens, RN CCRC; Ann Marie Scorsone, MS CCRC; Karen Wynn, NNP RN; Kelley Yost, PhD; Anne Marie Reynolds, MD MPH; Michelle E. Hartley-McAndrew, MD; Michael G. Sacilowski, MAT; Holly I.M. Wadkins, MA; Ashley Williams, MS Ed; Joan Merzbach, LMSW; Patrick Conway,

MS; Melissa Bowman, MSN; William Zorn, PhD; Julie Babish Johnson, MSW; Emily Kushner, MA; Cait Fallone, MA; Kyle Binion, BS; Constance Orme; Satyan Lakshminrusimha, MD.

University of Texas Southwestern Medical Center, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) - Myra H. Wyckoff, MD; Luc P. Brion, MD; Merle Ipson, MD; Walid A. Salhab, MD; Pablo J. Sánchez, MD; Sue Broyles, MD; P. Jeannette Burchfield, RN BSN; Lina F. Chalak, MD MSCS; Lijun Chen, PhD RN; Janet S. Morgan, RN; Diana M. Vasil, MSN BSN RNC-NIC; Sally S. Adams, MS RN CPNP; Catherine Twell Boatman, MS CIMI; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, MS MA PA-C PsyD; Jackie F. Hickman, RN; Lizette E. Lee, RN; Melissa H. Leps, RN; Linda A. Madden, BSN RN CPNP; Susie Madison, RN; Nancy A. Miller, RN; Emma Ramon, RNC-NIC RN BSN.

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124) - Bradley A. Yoder, MD; Roger G. Faix, MD; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; R. Edison Steele, RN; Mike Steffen, PhD; Karena Strong, RN BSN; Kimberlee Weaver-Lewis, RN BSN; Shawna Baker, RN; Sarah Winter, MD; Karie Bird, RN BSN; Jill Burnett, RNC BSN.

Wake Forest Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) - T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP.

Wayne State University, University of Michigan, Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) - Athina Pappas, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Monika Bajaj, MD; Kirsten Childs, RN BSN; Lilia C. De Jesus, MD; Laura A. Goldston, MA; Mary E. Johnson, RN BSN; Yvette R. Johnson, MD MPH; Deborah Kennedy, RN BSN; Geraldine Muran, RN BSN; Bogdan Panaitescu, MD; Jeannette E. Prentice, MD; Laura Sumner, RN BSN; Kathleen Weingarden, RN BSN; Eunice Hinz Woldt, RN MSN; Melissa February, MD; John Barks, MD; Mary Christensen, RT; Stephanie A. Wiggins, MS; Martha Carlson, MD; Diane F. White, RRT CCRP.

Yale-New Haven Children's Hospital (U10 HD27871, UL1 TR142) - Richard A. Ehrenkranz, MD (deceased); Matthew Bizzarro, MD; Monica Konstantino, RN BSN; Nancy Close, PhD; Patricia Gettner, RN; JoAnn Poulsen, RN; Elaine Romano, MSN; Janet Taft, RN BSN.

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Abbreviations:

BSID	Bayley Scales of Infant Development
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
GMFCS	Gross Motor Function Classification System
HIE	Hypoxic ischemic encephalopathy
IH	Induced hypothermia
iNO	Inhaled nitric oxide
LH	Late Hypothermia
MAS	Meconium aspiration syndrome

MDI	Mental Developmental Index
MRI	Magnetic Resonance Imaging
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NRN	Neonatal Research Network
OC	Optimizing cooling
PDI	Psychomotor Developmental Index
PPHN	Persistent pulmonary hypertension of the newborn
RCT	Randomized controlled trial

References:

1. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. The New England journal of medicine. 2005;353(15):1574–84. [PubMed: 16221780]
2. Higgins RD, Raju T, Edwards AD, Azzopardi DV, Bose CL, Clark RH, et al. Hypothermia and other treatment options for neonatal encephalopathy: an executive summary of the Eunice Kennedy Shriver NICHD workshop. The Journal of pediatrics. 2011;159(5):851–8 e1. [PubMed: 21875719]
3. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. The Cochrane database of systematic reviews. 2013(1):CD003311. [PubMed: 23440789]
4. Committee on F, Newborn, Papile LA, Baley JE, Benitz W, Cummings J, et al. Hypothermia and neonatal encephalopathy. Pediatrics. 2014;133(6):1146–50. [PubMed: 24864176]
5. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, et al. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2010;122(16 Suppl 2):S516–38. [PubMed: 20956259]
6. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. Jama. 2014;312(24):2629–39. [PubMed: 25536254]
7. Shankaran S, Pappas A, Laptook AR, McDonald SA, Ehrenkranz RA, Tyson JE, et al. Outcomes of safety and effectiveness in a multicenter randomized, controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy. Pediatrics. 2008;122(4):e791–8. [PubMed: 18829776]
8. Benumof JL, Wahrenbrock EA. Dependency of hypoxic pulmonary vasoconstriction on temperature. Journal of applied physiology: respiratory, environmental and exercise physiology. 1977;42(1):56–8.
9. Toubas PL, Hof RP, Heymann MA, Rudolph AM. Effects of hypothermia and rewarming on the neonatal circulation. Archives francaises de pediatrie. 1978;35(10 Suppl):84–92. [PubMed: 749756]
10. Shah SK, Khan AM, Cox CS Jr. Pulmonary hypertensive crisis requiring ECMO associated with re-warming from whole body hypothermia for hypoxic ischemic encephalopathy: clinical observations from a case series. European journal of pediatric surgery. 2010;20(3):205–6. [PubMed: 19866416]
11. Lakshminrusimha S, Shankaran S, Laptook A, McDonald S, Keszler M, Van Meurs K, et al. Pulmonary Hypertension Associated with Hypoxic-Ischemic Encephalopathy-Antecedent Characteristics and Comorbidities. The Journal of pediatrics. 2018;196:45–51 e3. [PubMed: 29502880]

12. Lakshminrusimha S The pulmonary circulation in neonatal respiratory failure. Clinics in perinatology. 2012;39(3):655–83. [PubMed: 22954275]
13. Lapointe A, Barrington KJ. Pulmonary hypertension and the asphyxiated newborn. The Journal of pediatrics. 2011;158(2 Suppl):e19–24. [PubMed: 21238701]
14. Aggarwal S, Natarajan G. Biventricular function on early echocardiograms in neonatal hypoxic-ischaemic encephalopathy. Acta paediatrica. 2017;106(7):1085–90. [PubMed: 28374415]
15. Murphy JD, Rabinovitch M, Goldstein JD, Reid LM. The structural basis of persistent pulmonary hypertension of the newborn infant. The Journal of pediatrics. 1981;98(6):962–7. [PubMed: 7229803]
16. Davidson D, Barefield ES, Kattwinkel J, Dudell G, Damask M, Straube R, et al. Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study. The I-NO/PPHN Study Group. Pediatrics. 1998;101(3 Pt 1):325–34. [PubMed: 9480993]
17. Roberts JD Jr., Fineman JR, Morin FC 3rd, Shaul PW, Rimar S, Schreiber MD, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. The New England journal of medicine. 1997;336(9):605–10. [PubMed: 9032045]
18. Lazar DA, Cass DL, Olutoye OO, Welty SE, Fernandes CJ, Rycus PT, et al. The use of ECMO for persistent pulmonary hypertension of the newborn: a decade of experience. The Journal of surgical research. 2012;177(2):263–7. [PubMed: 22901797]
19. Pryds O, Greisen G, Lou H, Friis-Hansen B. Vasoparalysis associated with brain damage in asphyxiated term infants. The Journal of pediatrics. 1990;117(1 Pt 1):119–25. [PubMed: 2115079]
20. Gagnon MH, Wintermark P. Effect of persistent pulmonary hypertension on brain oxygenation in asphyxiated term newborns treated with hypothermia. The journal of maternal-fetal & neonatal medicine. 2016;29(13):2049–55. [PubMed: 27480206]
21. Pappas A, Shankaran S, Laptook AR, Langer JC, Bara R, Ehrenkranz RA, et al. Hypocarbia and adverse outcome in neonatal hypoxic-ischemic encephalopathy. The Journal of pediatrics. 2011;158(5):752–8 e1. [PubMed: 21146184]
22. Rosenberg AA, Lee NR, Vaver KN, Werner D, Fashaw L, Hale K, et al. School-age outcomes of newborns treated for persistent pulmonary hypertension. Journal of perinatology : official journal of the California Perinatal Association. 2010;30(2):127–34. [PubMed: 19798045]
23. Konduri GG, Vohr B, Robertson C, Sokol GM, Solimano A, Singer J, et al. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. The Journal of pediatrics. 2007;150(3):235–40, 40 e1. [PubMed: 17307536]
24. Lipkin PH, Davidson D, Spivak L, Straube R, Rhines J, Chang CT. Neurodevelopmental and medical outcomes of persistent pulmonary hypertension in term newborns treated with nitric oxide. The Journal of pediatrics. 2002;140(3):306–10. [PubMed: 11953727]
25. Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the neonatal inhaled nitric oxide study group (NINOS). The Journal of pediatrics. 2000;136(5):611–7. [PubMed: 10802492]
26. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, et al. Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. Jama. 2017;318(1):57–67. [PubMed: 28672318]
27. Laptook AR, Shankaran S, Tyson JE, Munoz B, Bell EF, Goldberg RN, et al. Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. Jama. 2017;318(16):1550–60. [PubMed: 29067428]
28. More KS, Sakhuja P, Giesinger RE, Ting JY, Keyzers M, Sheth JN, et al. Cardiovascular Associations with Abnormal Brain Magnetic Resonance Imaging in Neonates with Hypoxic Ischemic Encephalopathy Undergoing Therapeutic Hypothermia and Rewarming. American journal of perinatology. 2018;35(10):979–89. [PubMed: 29475200]
29. Aggarwal S, Agarwal P, Natarajan G. Echocardiographic prediction of severe pulmonary hypertension in neonates undergoing therapeutic hypothermia for hypoxic-ischemic

encephalopathy. Journal of perinatology : official journal of the California Perinatal Association. 2019.

30. Giesinger RE, El Shahed AI, Castaldo MP, Breatnach CR, Chau V, Whyte HE, et al. Impaired Right Ventricular Performance Is Associated with Adverse Outcome after Hypoxic Ischemic Encephalopathy. American journal of respiratory and critical care medicine. 2019;200(10):1294–305. [PubMed: 31251076]
31. Weems MF, Upadhyay K, Sandhu HS. Survey of ECMO practices for infants with hypoxic ischemic encephalopathy. Journal of perinatology : official journal of the California Perinatal Association. 2018;38(9):1197–204. [PubMed: 30046182]
32. Cuevas Guaman M, Lucke AM, Hagan JL, Kaiser JR. Bleeding Complications and Mortality in Neonates Receiving Therapeutic Hypothermia and Extracorporeal Membrane Oxygenation. American journal of perinatology. 2018;35(3):271–6. [PubMed: 28946160]
33. Agarwal P, Altinok D, Desai J, Shanti C, Natarajan G. In-hospital outcomes of neonates with hypoxic-ischemic encephalopathy receiving extracorporeal membrane oxygenation. Journal of perinatology : official journal of the California Perinatal Association. 2019;39(5):661–5. [PubMed: 30842551]
34. Bonifacio SL, McDonald SA, Chock VY, Wusthoff CJ, Hintz SR, Laptook AR, et al. Differences in patient characteristics and care practices between two trials of therapeutic hypothermia. Pediatric research. 2019;85(7):1008–15. [PubMed: 30862961]

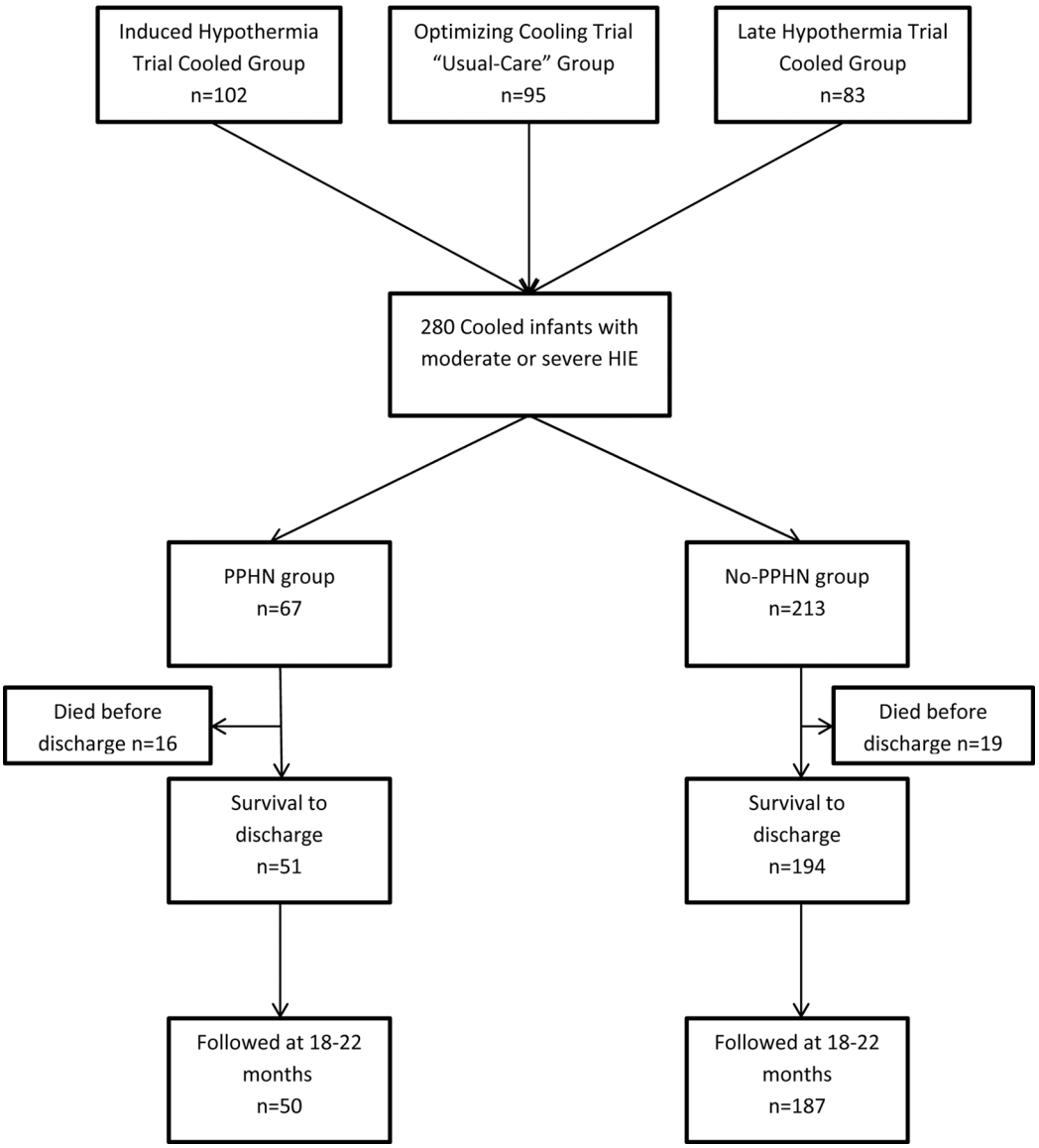

Figure 1.
Flowchart showing the source of subjects and grouping based on presence of PPHN.

Table 1:

Maternal and Neonatal Characteristics of Cooled Infants with Hypoxic Ischemic Encephalopathy with and without PPHN.

Characteristics	PPHN [n= 67] n (%)	No PPHN [n= 213] n (%)	P-value
Maternal			
Race			
Black	23 (34%)	52 (24%)	
White	37 (55%)	149 (70%)	0.07
Other	7 (10%)	12 (6%)	
Maternal age, yr	27 ± 5.6	28 ± 6.1	0.58
Complications of pregnancy			
Chronic hypertension *	4 (6%)	37 (17%)	0.02
Antepartum hemorrhage	6 (9%)	19/212 (9%)	1.00
Diabetes	7 (10%)	17 (8%)	0.53
Intrapartum complications			
Fetal heart rate decelerations	55 (82%)	176/212 (83%)	0.86
Cord prolapse	9 (13%)	39 (18%)	0.36
Uterine rupture *	1 (1%)	20 (9%)	0.03
Maternal pyrexia	8 (12%)	23 (11%)	0.80
Shoulder dystocia	5/66 (8%)	20 (9%)	0.65
Maternal hemorrhage	6 (9%)	16 (8%)	0.70
Emergency cesarean delivery	47 (70%)	133 (62%)	0.25
Infant			
Birth weight, g	3266 ± 649	3351 ± 536	0.29
Gestational age	38.9 ± 1.7	38.8 ± 1.5	0.67
Male sex	38 (57%)	112(53%)	0.55
Apgar score ≤5			
At 5 min	55 (82%)	174/212 (82%)	1.00
At 10 min	38/62 (61%)	119/194(61%)	0.99
Intubation in delivery room	54 (81%)	165 (77%)	0.59
Continued resuscitation at 10 min *	63 (94%)	175 (82%)	0.02
Cord blood			
pH	6.9 ± 0.2 (n=52)	6.9 ±0.2(n=160)	0.69
Base deficit — mmol/liter	16 ± 6.6 (n=46)	17 ± 7.3(n=124)	0.78
Clinical Seizures before randomization	25 (37%)	108 (51%)	0.06
Severe encephalopathy ¶	26 (39%)	37/212 (17%)	0.0003

Data shown as n (%) or mean ± SD

* Significant at P<.05.

¶ Severity of encephalopathy data missing on one infant.

Table 2:

Hospital Course and Status at Discharge among cooled infants with Hypoxic ischemic encephalopathy with and without PPHN

Characteristics Median (IQR) or n (%)	PPHN [n= 67] n (%)	No PPHN [n= 213] n (%)	P-value
During hospital course			
Pulmonary pathology			
Meconium aspiration syndrome	33 (49.3)	17 (8.0)	<0.0001
Pulmonary hemorrhage	7 (10.4)	6 (2.8)	0.02
Inhaled Nitric Oxide	47 (70.1)	~	~
ECMO	9 (13.4)	~	~
Days of Mechanical ventilation	9 (4–14)	2 (1–5)	<0.0001
Days of supplemental oxygen	13.0 (5–18)	3 (1–6)	<0.0001
Hypotension treated with Vasopressors	43/66 (65.2)	51 (23.9)	<0.0001
Cardiac arrhythmia	4/66 (6.1)	5(2.3)	0.22
Cardiac dysfunction *	24/66 (36.4)	13/211 (6.2)	<0.0001
Bloodstream infection	7 (10.4)	3 (1.4)	0.002
Blood transfusion	31 (46.3)	41 (19.2)	<0.0001
Platelet transfusion	29 (43.3)	37 (17.4)	<0.0001
Disseminated intravascular Coagulopathy	16/66 (24.2)	25 (11.7)	0.02
Oliguria	20/66 (30.3)	41 (19.2)	0.06
Anuria	2/66 (3.0)	7 (3.3)	1.00
Hepatic dysfunction	19/66 (28.8)	37 (17.4)	0.053
Hypoglycemia	15/66 (22.7)	24 (11.3)	0.023
Hypocalcemia	28/66 (42.4)	49 (23.0)	0.003
Seizures	27/54 (50.0)	88/192 (45.8)	0.64
Death	16 (23.9)	19 (8.9)	0.003
Length of stay — days	23 (11.7–36)	12 (9–18.8)	<0.0001
Discharge status			
Gavage feeding	5/46 (10.9)	16/187 (8.6)	0.575
Gastrostomy tube feeding	6/46 (13.0)	12/187 (6.4)	0.214
Anticonvulsant therapy	13/46 (28.3)	69/187 (36.9)	0.305
Supplemental Oxygen	2/46 (4.3)	5/187 (2.7)	0.630

* Cardiac dysfunction as defined by the status form (any of the following: cardiomegaly, cardiac failure, dysfunction on ECHO, elevated enzymes).

Table 3:

Outcome at 18 to 22 Months of Age among Cooled Infants with Hypoxic Ischemic Encephalopathy with and without PPHN

			Adjusted		Unadjusted	
	PPHN [n= 66] n (%)	**No PPHN [n= 206] n (%)**	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**
Death or moderate/severe disability *	31/66 (47)	60/206 (29)	1.65 (0.86, 3.14)	0.13	2.12 (1.18, 3.81)	0.01
Moderate disability *	2/49 (4)	2/182 (1)	4.08 (0.52, 32.2)	0.18	3.78 (0.51, 28.39)	0.19
Severe disability *	12/49 (25)	34/182 (19)	1.11 (0.48, 2.53)	0.81	1.44 (0.67, 3.10)	0.35
Death *	17/66 (26)	24/206 (12)	2.04 (0.92, 4.53)	0.08	2.54 (1.24, 5.19)	0.01
Cause of death						
Asphyxial brain injury	9/17 (53)	12/24 (50)				
Multiorgan failure	1/17 (6)	3/24 (13)				
PPHN	3/17 (18)	0/24 (0)				
Other	3/17 (18) ¶	8/24 (33) §				
Missing data	1/17 (6)	1/24 (4)				
Among survivors						
Bayley III Cognitive score or Bayley II MDI						
≥85 *	27/46 (59)	116/175(66)	0.84 (0.40, 1.76)	0.651	0.79 (0.39, 1.58)	0.49
70–84 *	10/46 (22)	30/175 (17)	1.47 (0.63, 3.46)	0.369	1.29 (0.57, 2.93)	0.54
<70 *	9/46 (20)	29/175 (17)	0.94 (0.38, 2.33)	0.892	1.21 (0.52, 2.82)	0.65
Bayley III Motor score or Bayley II PDI						
≥85 **	26/44 (59)	122/175(70)	0.86 (0.41, 1.82)	0.70	0.63 (0.32, 1.25)	0.18
70–84 **	7/44 (16)	20/175 (11)	1.28 (0.48, 3.40)	0.61	1.47 (0.57, 3.75)	0.42
<70 *	11/44 (25)	33/175 (19)	1.01 (0.43, 2.40)	0.98	1.43 (0.65, 3.14)	0.37
Cerebral palsy	10/48 (21)	37/182 (20)	0.68 (0.28, 1.65)	0.394	1.03 (0.47, 2.27)	0.94
Mild *	2/10 (20)	8/37 (22)	1.07 (0.13, 8.71)	0.952	0.91 (0.15, 5.40)	0.91
Moderate ***	4/10 (40)	3/37 (8)	8.41 (1.29, 54.76)	0.027	7.55 (1.28, 44.72)	0.03
Severe *	4/10 (40)	26/37 (70)	0.17 (0.02, 1.30)	0.086	0.25 (0.04, 1.54)	0.13
Blindness **	1/48 (2)	13/180 (7)	0.14 (0.02, 1.21)	0.074	0.27 (0.03, 2.17)	0.22
Severe hearing impairment *	6/48 (13)	5/182 (3)	4.25 (1.08, 16.7)	0.04	5.06 (1.46, 17.48)	0.01

* OR Adjusted for study, severity of HIE, and center as random effect.

¶ One infant- intracranial hemorrhage; one infant- respiratory failure; one infant- sudden infant death syndrome.

§ One infant- one infant- pneumonia and asphyxial brain injury; one infant- viral pneumonia; 6 infants- other cause of death not specified.

** OR Adjusted for study, severity of HIE.

*** OR Adjusted for severity of HIE.