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Outcomes of preterm infants treated with hypothermia for hypoxic-ischemic encephalopathy

Tamara I. Herrera[a], Laura Edwards[b], William F. Malcolm[b], P. Brian Smith[b,d], Kimberley A. Fisher[b], Carolyn Pizoli[c], Kathryn E. Gustafson[b], Ricki F. Goldstein[b], C. Michael Cotten[b], Ronald N. Goldberg[b], Margarita Bidegain[b,*]

[a] Servicio de Recién Nacidos del Centro Hospitalario Pereira Rossell, Montevideo, Uruguay
[b] Division of Neonatology, Duke University School of Medicine, Durham, NC, United States of America
[c] Division of Pediatric Neurology, Department of Pediatrics, Duke University School of Medicine, Durham, NC, United States of America
[d] Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, United States of America

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ABSTRACT

Background: Therapeutic hypothermia reduces the risk of death, or moderate to severe neurodevelopmental impairment (NDI) in term infants with hypoxic-ischemic encephalopathy (HIE). Reports of its safety and efficacy in preterm infants are scarce.

Objective: Report short and long-term outcomes of preterm infants with HIE who received therapeutic hypothermia.

Methods: A retrospective cohort analysis of all preterm infants < 36 weeks' gestation with HIE who received whole body hypothermia in a single center from January 2007 to April 2015. The primary outcome was death or moderate to severe NDI defined by moderate or severe cerebral palsy, severe hearing or visual impairment, or cognitive score < 85 on the Bayley Scales of Infant Development III (BSID III) at 18–24 months' adjusted age.

Results: 30 infants with a median gestational age and birthweight of 35 weeks' (range; 33–35) and 2575 g (1850–4840) and a median first postnatal blood pH of 6.81 (6.58–7.14). Complications included coagulopathy (50%), early clinical seizures (43.3%), arterial hypotension (40%), persistent metabolic acidosis (37%) and thrombocytopenia (20%). Four infants died before or soon after discharge (18.2%). Eighteen surviving infants (69.2%) had follow up data; 7 of them had moderate to severe NDI (38.9%). Cognitive, motor and language mean composite BSID III scores were 84 (54–110), 83 (46–118), and 78 (46–112). Death or moderate to severe NDI occurred in 11/22 (50%) infants with known outcomes.

Conclusion: Large randomized trials on efficacy and safety are needed in this highly vulnerable population as the incidence of complications and the combined outcome of death and NDI is concerning.

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) occurs in 1–2/1000 live term births in developed countries [1] and remains an important cause of death and brain injury with neurodevelopmental deficits in childhood among survivors [2,3]. Selective head or whole-body cooling initiated within 6 h of birth and continued for 72 h is well tolerated and reduces the risk of death or neurodevelopmental impairment (NDI) in term infants at 2 years of age with outcome improvements persisting into childhood [4–12]. Therapeutic hypothermia is currently the standard of care for term infants with moderate to severe HIE in developed countries [13–15]. However, though the American Academy of Pediatrics (AAP) has included infants 35 weeks' and higher in its guidelines for therapeutic hypothermia, little is known about the clinical safety and effects of therapeutic hypothermia among infants < 36 weeks' at birth [3,16–19]. Three of the pivotal whole-body hypothermia trials included only infants ≥ 36 weeks' at birth [4,6,8]. Two randomized clinical trials (RCT) of whole body cooling included infants

Abbreviations: NDI, Neurodevelopmental impairment; HIE, Hypoxic-ischemic encephalopathy; BSID, Bayley Scales of Infant and Toddler Development; ECMO, Extracorporeal membrane oxygenation; RDS, Respiratory distress syndrome; PDA, Persistent patent ductus arteriosus; NEC, Necrotizing enterocolitis; IVH, Intraventricular hemorrhage

* Corresponding author at: Division of Neonatology, Duke University School of Medicine, 2424 Erwin Rd, Box 2739, Durham, NC, United States of America.
E-mail address: margarita.bidegain@dm.duke.edu (M. Bidegain).

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of 35 $^{0/7}$–35 $^{6/7}$ weeks' gestation, but the authors did not report subgroup analysis of these infants [5,20]. The TOBY registry [21] and the Vermont Oxford Neonatal Encephalopathy Registry (VON) [22] also recorded data of preterm infants < 36 weeks' gestation who underwent therapeutic hypothermia, but specific subgroup analyses and outcomes are not available.

Standard therapeutic hypothermia has been used in infants > 36 weeks' gestation at Duke University Hospital since December 2005. However, unit guidelines allowed for consideration and implementation of rescue therapeutic hypothermia in infants between 33 and 35 weeks' gestation based on perinatal history, blood gas analyses and neurologic assessments. The Academic Medical Center Patient Safety Organization (AMC PSO), a component patient safety organization within The Risk Management Foundation of the Harvard Medical Institutions Incorporated, has published guidelines inclusive of consideration of cooling of infants > or equal to 34 weeks' gestational age [23].

Our goal is to report short and long-term outcomes of a group of preterm infants < 36 weeks' gestational age who underwent therapeutic hypothermia for HIE.

2. Methods

We reviewed the electronic medical records of infants < 36 weeks' gestational age who were admitted to the Neonatal Intensive Care Unit (NICU) at Duke University Hospital and underwent therapeutic hypothermia for moderate to severe HIE between January 2007 and April 2015. Data collected included: demographics variables, perinatal events, mode of delivery, place of birth, neonatal characteristics, resuscitation at birth and Apgar scores at 1, 5 and 10 min, blood gases within the first postnatal hour, severity of encephalopathy on admission, early clinical seizures and treatment with anticonvulsants, electroencephalography (EEG) reports, brain imaging, survival to discharge and neurodevelopmental outcomes. This retrospective cohort study was approved by the Institutional Review Board at Duke University.

2.1. Selection criteria and whole-body hypothermia method

Infants received whole body hypothermia treatment according to unit guidelines based on the NICHD hypothermia trial [4]. Eligibility criteria included a pH of 7.0 or less, or a base deficit of 16 mmol/l or more in a sample of umbilical-cord blood or any blood during the first postnatal hour. If pH was between 7.01 and 7.15, the base deficit was between 10 and 15.9 mmol/l, or a blood gas was not available, additional criteria were required: an acute perinatal event (e.g., late or variable decelerations, cord prolapse) and either a 10-min Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 min. Initial neurological assessments were performed by an attending physician or neonatology fellow, assessing level of consciousness, spontaneous activity, posture, tone, primitive reflexes, and autonomic nervous responses, and staged according to the modified Sarnat neurologic examination criteria utilized in the NICHD trial [4].

Infants were cooled using the system described in the NICHD NRN's Hypothermia trials (Blanketrol II, CSZ, Cincinnati, OH) [4]. Servo control mode was used to maintain esophageal temperature at 33.5 °C and blanket, axillary, and esophageal temperature were monitored. As per unit guidelines, vital signs including blood pressure, blood gases and serum electrolytes were monitored daily during treatment. Prothrombin time activated partial thromboplastin time, and fibrinogen were measured at baseline and at 24 h. If clinically indicated, more labs were done according to clinical needs. Re-warming occurred after completing 72 h of hypothermia, by increasing the temperature at a rate of 0.5 °C per hour. When a temperature of 36.5 °C was reached, the infant's temperature was maintained between 36.5 and 37.2 °C for 24 additional hours.

2.2. Short-term outcomes

2.2.1. Complications during hypothermia

We collected previously reported complications occurring during hypothermia, including: 1) coagulopathy, defined as abnormal clotting test result and treatment with fresh frozen plasma, cryoprecipitate or factor VII; 2) thrombocytopenia, defined as platelet count < 100,000 per μl and platelet transfusion; 3) hypotension, defined as treatment with dopamine, epinephrine or vasopressin; 4) pulmonary hypertension, defined by use of inhaled nitric oxide, sildenafil or extracorporeal membrane oxygenation (ECMO); 5) persistent metabolic acidosis defined as lactate of 5 mg/dl or higher after 24 postnatal hours; 6) hyperkalemia, defined as high potassium and treatment with insulin or Kayexalate; 7) hypocalcemia defined as clinicians' use of calcium boluses; 8) anuria defined as absence of urinary output; and 9) intracranial, pulmonary or gastrointestinal acute bleeding.

2.2.2. Complications during hospital course

Other reported in-hospital complications collected included: 1) respiratory distress syndrome (RDS) requiring at least one dose of surfactant; 2) persistent patent ductus arteriosus (PDA) requiring treatment with indomethacin or surgical ligation; 3) necrotizing enterocolitis (NEC) of modified Bell's criteria II or higher [24]; 4) isolated bowel perforation without NEC; 5) unconjugated hyperbilirubinemia defined as clinicians' use of phototherapy or exchange transfusion; 6) conjugated hyperbilirubinemia, defined by clinicians' use of phenobarbital without concurrent documented or suspected seizures, or use of ursodeoxycholic acid; and 7) early-onset sepsis (EOS), defined as positive blood culture in the first 48 postnatal hours.

2.2.3. Electroencephalography (EEG) data

Infants receiving therapeutic hypothermia undergo regular EEG monitoring throughout cooling and the rewarming period. All EEG reports were reviewed for the presence of seizures and classified based on the predominant background patterns.

2.2.4. Brain imaging findings in preterm infants with HIE

Brain imaging data was collected from magnetic resonance imaging (MRI) and/or cranial tomography (CT) scans. MRI was obtained after cooling was completed and before hospital discharge. MRI studies were analyzed and scored for injury pattern and severity by a pediatric neurologist (Author) using the qualitative scoring system of regional injury described by Bednarek et al. [25] which was modified to a 0–3 scale instead of 1–4 for ease of use. Diffusion-weighted imaging (DWI), T1 and T2-weighted images were analyzed for abnormalities in the caudate, putamen, thalamus, posterior limb of the internal capsule (PLIC), cortex, white matter, brain stem (BS) and cerebellum. Injury scores, on a scale of 0–3 (except for the BS scaled 0–2, due to its small size) with 0 = normal, 1 = mild focal abnormality affecting < 25% of the region, 2 = moderate abnormality affecting 25–50% of the region, or 3 = severe, diffuse abnormality affecting > 50% of the region, were generated for each location and separately for the right and left hemispheres. Regional scores were summed and ranged between 0 and 18 for the cortex, white matter and cerebellum, and between 0 and 12 for the BS. The component scores of the caudate, putamen, thalamus and PLIC were summed together for a single basal ganglia (BG) score, ranging from 0 to 72. The BG score was intentionally weighted due to the severity of neurodevelopmental deficits associated with injuries to this region. The global injury score is the total sum of component scores (range 0–138) with mild injury between 1 and 11, moderate between 12 and 32, and severe if > 33. Additionally, the incidence of intraventricular hemorrhage (IVH) was categorized as germinal matrix hemorrhage (grade I), IVH without ventricular dilatation (grade II), IVH with acute ventricular dilatation > 50% (grade III), grade IV IVH or intraparenchymal hemorrhage [26].