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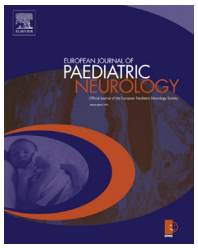

Original article

Cooling in the real world: Therapeutic hypothermia in hypoxic-ischemic encephalopathy

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ABSTRACT

Background and aim: The benefits of therapeutic hypothermia have not been assessed from the perspective of the neurology clinic. We aimed to report the impact of the implementation of a local regional therapeutic hypothermia program on the neurodevelopmental outcomes of surviving hypoxic-ischemic encephalopathy (HIE) infants who were followed in the neonatal neurology clinic.

Methods: Retrospective analysis of term infants referred to the neonatal neurology clinic after having been diagnosed with HIE and meeting eligibility criteria for therapeutic hypothermia between March 1999 and June 2010. Therapeutic hypothermia was implemented in September 2008. Outcome measures were dichotomously defined as: normal or adverse, which included cerebral palsy, global developmental delay, and epilepsy.

Results: Thirty infants were included in the pre-therapeutic hypothermia group. Thirty-one infants received therapeutic hypothermia and 27 were adequately followed and included in the post-therapeutic hypothermia group. The frequency of an adverse outcome was significantly higher in the pre-therapeutic hypothermia infants (19/30 [63%] versus 4/27 [15%]; OR = 0.10; 95% CI, 0.03–0.37; $P < 0.001$). Neonatal clinical seizures were more frequent in the pre-therapeutic hypothermia group ($P = 0.012$). There were no differences regarding frequency of fetal distress, rate of caesarean sections, Apgar scores, need of resuscitation, cord/initial blood gases, and degrees of encephalopathy between the two groups.

Conclusions: The implementation of a regional therapeutic hypothermia program in our institution has vastly reduced the observed neurological morbidity of surviving HIE infants

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followed in our neonatal neurology clinic. A similar change in outcomes of infants with HIE can be anticipated by other centers and other clinics adopting this therapy.

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) is a relatively frequent cause of neurological morbidity and is often accompanied by the occurrence of neonatal seizures.[1,2] It carries a significant risk of long-term neurological sequelae in survivors, which include cerebral palsy, global developmental delay, and epilepsy.[3,4]

Much basic experimental and clinical research, culminating in randomized controlled trials (RCTs) and meta-analyses, has been carried out on therapeutic hypothermia (TH) for infants with moderate or severe HIE.[5–9] Recent meta-analyses reported that the number of HIE newborns needed to treat with TH to prevent one death or eventual neurodevelopmental disability at 18 months was between 7 and 9.[8,9] The results of these studies have led to the widespread establishment of regional cooling centers with the implementation of specific selection and treatment algorithms.[10,11] It is important to note that the extrapolation of experimental therapeutic studies to different settings needs careful evaluation. Also, the RCT results of complex procedures need to be put into the context of the health care delivery system and the actual patients to which they will be applied.[12] In particular, the benefits of TH should be extrapolated to the neurology clinic. Therefore, we aimed to determine and report the "real world" impact of the implementation of a local regional TH program on the neurodevelopmental outcomes of surviving HIE infants who were followed in our neonatal neurology clinic.

2. Materials and methods

2.1. *Population, setting, and inclusion and exclusion criteria*

Our study population was derived from high-risk newborns referred to and followed in a single pediatric neurology university-based practice (MIS), all of whom were discharged from the Montreal Children's Hospital tertiary Level III outborn neonatal intensive care unit (NICU). A comprehensive computerized practice database was initially scanned for all term (37 weeks gestation or greater) neonates who were referred to the neonatal neurology clinic with a diagnosis of perinatal asphyxia, HIE, neonatal encephalopathy, or seizure. Their records were reviewed after approval for a quality assurance project was obtained from the appropriate authorities.

In our institution's NICU, TH was implemented in September 2008. In this study, we evaluated the first 22 months of TH (post-TH group). This group included moderate and severe HIE infants treated with TH in the NICU and referred to the neonatal neurology clinic between September 2008 and June 2010. To evaluate the effect of the program implementation, we reviewed the records of HIE infants born before the program was initiated (pre-TH group). This group included moderate and severe HIE infants who would have met TH eligibility criteria and who were referred to the neonatal neurology clinic. Due to the smaller number of infants in this group, the pre-TH period was extended to March 1999. Infants who had either congenital anomalies affecting the central nervous system or less than one year of follow-up were excluded.

2.2. *Therapeutic hypothermia*

The eligibility criteria for TH were drawn directly from the NICHD Whole Body Hypothermia trial and included gestational age $\geq$36 weeks, BW $\geq$ 1800 g and subsequent fulfillment of specific physiological criteria followed by demonstration of moderate or severe encephalopathy using the modified Sarnat criteria.[6,13] The degree of encephalopathy was assigned on admission by the attending neonatologist.

Whole-body hypothermia was initiated within 6 h of life by positioning the infant on a cooling/heating blanket that was attached to a Blanketrol II or III Hyper-Hypothermia system (Cincinnati Sub-Zero). The infant was maintained at an esophageal temperature of 33.5 °C for 72 h, followed by rewarming at a rate of 0.5 °C per hour up to 36.5 °C. Passive cooling during transport is not performed at our institution.

2.3. *Perinatal and neonatal data*

The following perinatal variables were recorded: maternal report of decreased fetal movements for $\geq$24 h, fetal distress during labor (variable decelerations, late decelerations, fetal bradycardia, fetal tachycardia, or lack of fetal heart rate variability), mode of delivery, and intrapartum sentinel events (placental abruption, placenta previa, vasa previa, fetal–maternal transfusion, uterine rupture, cord prolapse, true cord knot, nuchal cord, shoulder dystocia, and face presentation). Collected neonatal data included sex, gestational age, birth weight, Apgar score (1, 5, and 10 min), pH and base deficit from umbilical cord or blood gas collected within the first hour of life (whichever was worse), a variation of a previously described resuscitation score reflecting the amount of resuscitation required at birth (1 = no intervention; 2 = blow-by oxygen; 3 = endotracheal suctioning; 4 = bag-mask positive pressure ventilation; 5 = endotracheal intubation with positive pressure ventilation; and 6 = endotracheal intubation with chest compressions),[14] clinical seizures, and use of anti-epileptic drugs (AEDs).

Interictal EEG background abnormalities were visually rated by a clinical neurophysiologist with expertise in the interpretation of neonatal EEG as mild, moderate, or severe on