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Original Article

Subacute Hypoxia-Ischemia and the Timing of Injury in Treatment With Therapeutic Hypothermia

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ABSTRACT

OBJECTIVE: This study aims to categorize infants treated with therapeutic hypothermia who presented with suspected subacute hypoxia-ischemia—that is, injury that likely occurred well before delivery and thus beyond the 6-hour window for therapeutic hypothermia—and to contrast the clinical characteristics with infants who suffered a known acute hypoxia-ischemia event. **DESIGN:** A retrospective chart review was undertaken of infants treated with therapeutic hypothermia at our center during a 6-year period. Suspected subacute injury is defined as decreased fetal movement greater than 6 hours before delivery or severe depression at birth without need for cardiopulmonary resuscitation. Acute injury is defined as an acute perinatal event including placental abruption, ruptured uterus, or umbilical cord abnormalities. Abnormal outcome is defined as death, cognitive delay, or spastic quadriplegia at follow-up. **RESULTS:** Infants with subacute (n = 7) versus acute injury (n = 26) were less likely to require cardiopulmonary resuscitation, were less acidotic at birth on cord gases with no significant difference in initial postnatal pH or base deficit, were more severely encephalopathic with severe amplitude electroencephalogram suppression, and demonstrated universal adverse outcome. **CONCLUSIONS:** These data demonstrate greater benefit of therapeutic hypothermia for those infants with acute versus subacute injury. Early initiation of therapeutic hypothermia relative to the presumed onset of hypoxia-ischemia is critical. Early severe encephalopathy in the absence of a known acute perinatal event should raise concern in some cases for a subacute insult where the effect of therapeutic hypothermia is unlikely to be of benefit.

Keywords: cerebral hypoxia-ischemia, hypothermia, induced, infant, newborn

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Introduction

Neonatal encephalopathy secondary to intrapartum hypoxia-ischemia is an uncommon event, occurring in approximately 1 per 1000 deliveries in the developed world, yet represents an important precursor of neonatal neurological sequelae or death.[1] Randomized controlled trials of therapeutic hypothermia in this setting have demonstrated a reduced risk of death and/or neurodevelopmental disability at 18 months to 2 years of age, with long-term neurocognitive benefits also apparent between 6 and 8 years of age.[2-7] Despite treatment, up to 50% of infants still have adverse outcomes including death or long-term neurocognitive deficits.[2-4] This substantial lack of benefit may be related to numerous factors including the timing of the insult. Early animal studies of therapeutic hypothermia have highlighted the importance of initiating cooling early, and within 6 hours of the suspected insult.[8-10] Clinically, it is often difficult to estimate the timing of injury when assessing an infant as a potential candidate for treatment. Timing may be obvious with evidence of an acute perinatal event related to placental abruption, uterine rupture, or umbilical cord abnormalities. Conversely, it may be less clear with a subacute insult, such as with abnormal fetal heart rate

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patterns of uncertain duration or feto-maternal hemorrhage where injury is likely to have occurred more than 6 hours before delivery, in which case therapeutic hypothermia may not confer any benefit. The aim of this study is to elucidate perinatal, obstetric, and neonatal characteristics of infants that may identify subacute versus acute injury in infants meeting criteria for therapeutic hypothermia.

Materials and Methods

Study population

This is a retrospective review of both inborn and referred infants treated with selective head cooling in the neonatal intensive care unit at New York-Presbyterian Hospital/Weill Cornell Medical Center between May 2007 and December 2013. The Weill Cornell Medical College Institutional Review Board approved this retrospective study. The enrollment criteria for head cooling at New York-Presbyterian Hospital are consistent with the primary randomized "cooling studies" and included both amplitude electroencephalograph (aEEG) and clinical assessment of encephalopathy.[2-6] In approximately 20% of cases, the aEEG was difficult to interpret because of artifact, and the clinical examination was used for enrollment. Cases were reviewed where injury was categorized by a single neonatal attending at enrollment as acute, based upon a known acute perinatal event during labor including placental abruption, uterine rupture, or umbilical cord abnormalities (i.e., vasa previa, cord prolapse, velamentous cord insertion), or subacute based on the following characteristics: absence of known acute perinatal event and decreased fetal movement for more than 6 hours immediately before delivery or evidence of early severe encephalopathy following birth without the need for delivery room cardiopulmonary resuscitation (CPR). CPR was defined as the need for chest compressions and/or administration of epinephrine. Infants who did not clearly meet criteria for acute or subacute injury were categorized as "other."

Selective head cooling was initiated within 6 hours of life in all treated infants. Infants were cooled to goal rectal temperature of 34.5°C for 72 hours and were rewarmed over 4 to 6 hours following this period per protocol.

Clinical characteristics

The medical charts were retrospectively reviewed for the following characteristics: injury categorization; gestational age; birthweight; sex, labor complications; fetal heart rate tracing abnormalities; meconium; mode of delivery; need for CPR in the delivery room; 1-, 5-, and 10-minute Apgar scores; arterial cord pH; and base deficit. Postnatal information included initial pH, base deficit, lactate, and bicarbonate levels. The aEEG was recorded with the Olympus CFM 6000 Infant aEEG Cerebral Function Monitor (Natus, San Carlos, CA) and characterized as previously described by al Naqeeb et al, with the exception of cases in which artifact rendered the aEEG uninterpretable. Moderate suppression was defined as background voltage with the upper margin >10 μV and lower margin ≤5 μV; severe suppression was defined with the upper margin <10 μV and lower margin <5 μV.[11] Encephalopathy staging was classified based on clinical examination using modified Sarnat stages as follows: stage 1 (mild)—hyperalert, exaggerated Moro, generalized sympathetic effects, normal tone; stage 2 (moderate) —lethargy or obtundation, hypotonia, strong distal flexion, weak or absent suck, parasympathetic effects including bradycardia and meiosis, seizures; or stage 3 (severe)—stuporous, flaccid, suppression of brainstem and autonomic function.[12] Diffusion-weighted and T1-weighted brain magnetic resonance imaging (MRI) scans were reviewed by a single neonatal attending for signal changes and damage within the basal ganglia and/or thalami, hippocampus, and the supratentorial white matter. MRI scans were obtained on days 5 to 10 (median 7) of life. Autopsies were reviewed when available.

Follow-up data

Infants treated with head cooling are followed in a neurodevelopmental clinic at 3, 6, 12, and 18 months and 3 and 6 years. A Bayley Scale of Infant and Toddler Development is performed at 18 months with report of a cognitive score, and a Wechsler Preschool and Primary Scale of Intelligence at 3 and 6 years with report of a full-scale intelligence quotient. A normal cognitive score and full-scale intelligence quotient is regarded as a score of 100 ± 15, moderate delay 70 to 84, and severe delay <70. Combined primary outcome was abnormal neurodevelopment, defined as motor deficits (specifically spastic quadriplegia), and/or cognitive delay at most recent follow-up, or death.

Statistical analysis

Data were analyzed by SPSS 20 (IBM Statistics 20). Clinical characteristics between groups were compared by *t* test, chi-squared test, and Fisher's exact test when appropriate. Two-sided *P*-values ≤ 0.05 were considered significant.

Results

General

A total of 107 infants were treated with head cooling over the 6-year period, 12 (11%) were inborn and 95 (89%) were transferred from outside hospitals. Infants were categorized as having suffered acute (n = 26), subacute (n = 7), and "other" injury (injury that from the clinical history was deemed to around the time of delivery) (n = 74). Labor complications for all three groups are listed in Table 1. Umbilical cord abnormalities present in the acute group included velamentous cord insertion, cord prolapse, and vasa previa in two infants. Two of the infants with subacute injury had evidence of a significant feto-maternal hemorrhage and presented with decreased fetal movement 12 to 36 hours immediately before delivery. Specific clinical characteristics of infants with subacute injury are listed in Table 2 because this patient population is the focus of this report. The gestational age, birthweight, and number of infants with a 5- or 10-minute Apgar score ≤5 did not differ between the subacute and acute groups (Table 3). Infants with subacute injury were significantly less likely to deliver via emergent cesarean section, required CPR less frequently in the delivery room, and exhibited a higher cord pH and base deficit with no significant difference in initial postnatal pH or base deficit compared with the acute group. Infants with subacute injury were more severely encephalopathic at birth on clinical examination and demonstrated severe aEEG suppression more commonly compared with the other two groups. Of infants with initial severe encephalopathy, six of six (100%) of the subacute versus five of 11 (45%) of the acute group ($P = 0.045$) versus 12 of 25 (48%) of

TABLE 1.
Labor Characteristics of Infants With Subacute, Acute, and "Other" Injury

Acute (n = 26)	Subacute (n = 7)	"Other" (n = 74)
Placental abruption (n = 17)	Nonreassuring FHRT (n = 3)	Nonreassuring FHRT (n = 35)
Uterine rupture (n = 5)	Decreased fetal movement (n = 2)	Chorioamnionitis (n = 15)
Umbilical cord abnormalities (n = 4)	Maternal fever (n = 1)	Meconium (n = 8)
	No known complications (n = 1)	Other (n = 9)
		No known complications (n = 7)

Abbreviation:
FHRT = Fetal heart rate