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Therapeutic Hypothermia: A Hot Legal Topic

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"The neurological exam at 1 hour of life revealed jitteriness, intermittent decreased spontaneous activity, mild hypotonia, poor suck, incomplete Moro reflex, and stable vital signs. The infant appeared stable; however, at 12 hours of life, the parents noted cyanosis and periods of apnea. A neonatologist is consulted, and the diagnosis of clinical seizures is made."

A term AGA newborn male was delivered by emergency cesarean section in a community level 2 hospital for persistent Category 2 tracings. The infant was born depressed, requiring positive pressure ventilation for 4 minutes. By 10 minutes of age, the infant had decreased tone but good respiratory effort on room air. Apgar scores were 2, 5, and 7 at 1, 5, and 10 minutes, respectively. A cord arterial blood gas revealed a pH of 7.14, pO_2 12, pCO_2 65, and a base excess of -10. The neurological exam at 1 hour of life revealed jitteriness, intermittent decreased spontaneous activity, mild hypotonia, poor suck, incomplete Moro reflex, and stable vital signs. The infant appeared stable; however, at 12 hours of life, the parents noted cyanosis and periods of apnea. A neonatologist is consulted, and the diagnosis of clinical seizures is made. The newborn is transferred to the regional center for more extensive neurological evaluation. The workup with MRI reveals extensive partial prolonged hypoxic ischemia with a possible acute grey matter injury. At two years of age, the child has spastic quadriplegia and is neurologically devastated. Approximately three years after the delivery, you receive a summons. The allegation is that if the standard of care (SOC) were followed, this infant would have been transferred within 6 hours of life for Therapeutic Hypothermia (TH). The plaintiffs also allege that a normal neurologic outcome would have resulted if cooling had been initiated.

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Neonatal encephalopathy is a clinical syndrome of disordered neonatal brain functioning occurring in the first days after birth in infants born at 35 weeks gestation or greater. It is a clinically defined syndrome with multiple etiologies characterized by abnormal levels of consciousness and/or seizures. It is often accompanied by difficulty in initiating respirations at birth and depression of tone and reflexes. Hypoxic ischemic encephalopathy (HIE) affects 2 million infants annually worldwide. The incidence of HIE in developed countries is approximately 1.5/1000 live births. The pathophysiology of HIE is characterized at the cellular level by a biphasic process of primary and secondary energy failure. The initial phase consists of the triggering hypoxic-ischemic insult that leads to primary energy failure and can be severe enough to cause permanent brain damage. Approximately 6 to 24 hours later, secondary energy failure occurs, characterized by the activation of the neurotoxic cascade, leading to apoptosis and neuronal necrosis. Recognition and early initiation of TH for all eligible infants is important to attempt to ameliorate the secondary energy failure accompanying acute HIE and improve outcomes. However, only one of every 7-8 infants treated with TH will avoid death or moderate to severe disability compared to those who do not receive TH. This modest level of the number needed to treat (NNT) to benefit is because treatment was probably started too late (i.e., the injury did not occur intrapartum), the injury was too severe (i.e., Sarnat 3), or the etiology of the encephalopathy was not HIE (1, 2, 3).

"Any infant with perinatal depression or an acute perinatal event history should receive a prompt evaluation for TH. This evaluation begins in the delivery room with the assignment of Apgar scores. Evaluation should include a detailed birth history, cord or early newborn blood gas sampling within 1 hour of birth and physical examination with particular attention paid to elements of a modified Sarnat examination."

Any infant with perinatal depression or an acute perinatal event history should receive a prompt evaluation for TH. This evaluation begins in the delivery room with the assignment of Apgar scores. Evaluation should include a detailed birth history, cord or early newborn blood gas sampling within 1 hour of birth and physical examination with particular attention paid to elements of a modified Sarnat examination. History should be examined for clues of an acute perinatal event capable of causing hypoxic ischemia or a history of potential pregnancy complications that might cause neonatal encephalopathy. Critical features of the physical exam include alteration in the degree of consciousness, activity, tone, posture, reflexes, and cardiorespiratory hemodynamics. The Sarnat stages include stage I encephalopathy, described as mild and often associated with sympathetic overdrive and hyper-alertness, resulting in an excellent neurologic prognosis. Moderate

encephalopathy, or stage 2, is marked by lethargy and hypotonia, and stage 3 encephalopathy essentially describes an obtunded, flaccid, comatose infant. The presence of seizures is always considered moderate or severe encephalopathy (i.e., Sarnat stage 2 or 3) (4).

The optimal timing to initiate TH is within 6 hours of birth. Studies on the use of TH after 6 hours have not shown statistical improvement in outcomes. The optimal timing of the neurologic examination is around 1 hour of age after initial resuscitation is completed, but it should be repeated in the first 6 hours of life to determine if the baby meets encephalopathic criteria. The consensus is that an infant with moderate to severe encephalopathy who meets historical, neurologic, and biochemical criteria should receive TH. Initial management would also focus on avoiding hypocapnia, hyperoxia, hyperthermia, or hypothermia with passive cooling (5, 6). If TH is going to be initiated, the failure to start passive cooling at the birth hospital can be viewed as a deviation from the standard of care. However, there are no studies that indicate that passive TH is effective in improving the outcome of transported babies. Several hospitals now initiate TH on transport. The clinician should be vigilant for seizures; however, most seizures secondary to hypoxic-ischemic insult occur beyond 6 hours of life and are often subtle and can go undetected. Transferring to a higher level of care with continuous EEG monitoring is recommended.

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Threshold blood gas criteria reported in trials to institute TH include the following:

1. pH less than or equal to 7.0 or a base deficit of 16 mmol/L or more in umbilical cord blood or any blood sample within the first hour of life.
2. pH between 7.01 and 7.15, base deficit 10 to 15.9 mmol/L within the first hour with any of the following:
   - An acute perinatal event AND
   - 10-minute Apgar score of 5 or less OR
   - Assisted ventilation was initiated at birth and continued for at least 10 minutes
   - Neurologic exam findings, including seizures or evidence of moderate-severe neonatal encephalopathy or other signs of central nervous system dysfunction, such as jitteriness, clonus, apnea, abnormal posturing and movement

The majority of clinical trials have focused on moderately and severely affected infants. In a meta-analysis, TH has been shown to decrease death and disability at two years from 45% to 29%. Both from a clinical and medico-legal perspective, there is an ambiguity to either support or refute TH with mild hypoxic-ischemic encephalopathy. The PRIME study (Prospective Research in Mild HIE) provided the first empirically validated definition of mild hypoxic-ischemic encephalopathy within 6 hours of birth using two steps as in prior cooling trials. The first step is screening for fetal acidosis and acute perinatal events per established criteria. The second step is performing the modified Sarnat scoring by a competent examiner. The study expanded the criteria for TH to include mild in addition to moderate and severe abnormalities. Results showed that most infants with this definition of mild hypoxic-ischemic encephalopathy had abnormal outcomes when not treated with hypothermia (7). However, more robust data on the effectiveness of TH in this population are lacking. Analogous to resuscitation of 22-week gestational age preterm newborns, neonatologists have significant variation in managing newborns with mild hypoxic-ischemic encephalopathy. In both instances, the standard of care essentially has become blurred.

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Some points to consider to decrease professional liability:

1. Plaintiff experts often minimize the side effects of TH. TH is not benign and can adversely affect almost every infant organ system. The more common side effects include thrombocytopenia, coagulopathy, increased risk of bleeding, and persistent pulmonary hypertension in the newborn (8).
2. A newborn who is born depressed should prompt the resuscitation team to request cord blood gases, usually drawn by the obstetrical team.
3. After the birth of a depressed newborn with a potential adverse outcome, it is recommended that the placenta be sent for analysis. The placenta can make a great witness.
4. Sometimes arterial or venous access is impossible in the first hour of life. In that case, one can obtain a capillary blood gas when the first glucose is drawn. However, it should be recognized that a capillary blood gas may give a falsely low pH and/or falsely elevated base deficit if drawn from a poorly perfused foot or hand. An early lactate level may also help decide whether the baby should receive TH.
5. Therapeutic hypothermia criteria should be posted in labor and delivery, neonatal intensive care unit, special care, and newborn nursery.
6. Yearly training for all newborn caregivers to assess eligibility for TH should be implemented.
7. If you do not cool a depressed newborn, document your thought process; if you are not in a center capable of cooling, document your conversation with the perinatal center.
8. A very small percentage of cerebral palsy is directly related to the last 2 hours of a normal 7000-hour pregnancy. More

often than not, the etiology of cerebral palsy is remote or post-delivery, in which TH would not significantly affect the outcome. Other etiologies, such as perinatal infection, genetic abnormalities, placental abnormalities, metabolic disorders, maternal risk factors, and neonatal vascular stroke, need to be ruled out.

9. Any off-protocol use of TH should be documented.
10. Most Sarnat stage 3 encephalopathy infants will not benefit from TH.

"The American Academy of Pediatrics Committee of The Fetus and Newborn promulgated the current guidelines on TH in 2014 (9). These guidelines are currently being reviewed to establish new criteria to address TH in infants with mild encephalopathy and reevaluate the existing strict criteria for initiating TH. From a clinical and medico-legal perspective, one should err on the side of treatment and initiate TH in equivocal scenarios where no major contradiction exists. "

The American Academy of Pediatrics Committee of The Fetus and Newborn promulgated the current guidelines on TH in 2014 (9). These guidelines are currently being reviewed to establish new criteria to address TH in infants with mild encephalopathy and reevaluate the existing strict criteria for initiating TH. From a clinical and medico-legal perspective, one should err on the side of treatment and initiate TH in equivocal scenarios where no major contradiction exists. There is not enough evidence-based data to initiate TH routinely in mild encephalopathy as the standard of care.

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Disclaimer:

This column does not give specific legal advice, but rather is intended to provide general information on medicolegal issues. As always, it is important to recognize that laws vary state-to-state and legal decisions are dependent on the particular facts at hand. It is important to consult a qualified attorney for legal issues affecting your practice.