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Commentary

Hypothermic neuroprotection following neonatal hypoxic-ischemic encephalopathy: medico-legal implications

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Hypoxic- Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) continues to be an important cause of long-term neurologic disability among newborn infants. The estimated incidence ranges from 2-3/1000 live births in developed countries, to as high as 10-20/1000 in developing countries [1]. Affected infants who survive are at a 25% risk for cerebral palsy, epilepsy, and cognitive deficits and may require lifelong medical care.

The pathogenesis of HIE stems from diminished oxygen delivery to the brain brought about by a reduction in blood flow, oxygen content of the blood, or both. Deficits may arise from the mother (such as severe hypotension and diminished uterine blood flow), placenta (such as abruptio placentae), or fetus (such as umbilical cord accidents). Two patterns of injury have been identified. Prolonged partial asphyxia leads to a redistribution of blood flow to preserve oxygen delivery to the brain, heart, and adrenal glands (at the expense of virtually every other organ), and it results primarily in injury to the parasagittal cortical gray matter. Total or near-total asphyxia results from a sudden and catastrophic condition in which there is no time to compensate and results in damage to the deep subcortical white matter, basal ganglia, and thalamus.

The resultant cerebral hypoxia initiates what has been referred to as the "neurotoxic cascade", a series of events which leads to primary energy failure followed by reperfusion, which may cause additional injury by exposure to oxygen free radicals. Secondary energy failure may occur 6-48 hours later and results in irreversible neuronal injury. Events during secondary energy failure include failing oxidative metabolism, seizures, cytotoxic edema, excitatory neurotransmitter release, and cell death. The severity of secondary energy failure is correlated with both survival and neurodevelopmental outcome [2].

Previous attempts to ameliorate neurologic injury following HIE have included the use of calcium channel antagonists, magnesium sulfate, phenobarbital, corticosteroids, and xanthine oxidase inhibitors, but none of these proved to be effective, likely because they act on only a single aspect of the neurotoxic cascade. On the other hand, therapeutic hypothermia has shown promise in improving the outcomes of affected infants under certain circumstances. Neuroprotective hypothermia applied during the latent phase of injury within 6 hours of the initial injury and continued for 72 hours is the first treatment shown to be beneficial in this population [3]. The exact mechanisms of neuroprotection are not fully understood. Cooling the brain may better maintain the cerebral energy state, attenuate the release of excitatory neurotransmitters, decrease caspase-3 activation and morphologic evidence of apoptosis, reduce free radical generation, and modulate microglial activation and cytokine production. Thus, hypothermia may attack the neurotoxic cascade at multiple levels.

A systematic review of several randomized controlled trials of hypothermia following HIE showed a statistically significant reduction (26%) in the primary outcome of death or moderate-to-severe neurodevelopmental disability and the number needed to treat (NNT) was only 6, meaning that six infants need to be cooled to achieve the desired outcome in one [4]. Neuroprotective hypothermia (NPH) has become standard care in the treatment of infants with HIE believed to be the result of an intrapartum asphyxial insult. Criteria for administering NPH to infants with HIE are based on the clinical trials and generally require that it be initiated within 6 hours of the insult to infants who

are acutely encephalopathic and have evidence of having sustained a severe intrapartum insult, such as persistently low Apgar scores, need for resuscitation, and early metabolic acidosis.

The United States Tort System

In the United States, as well as most of the developed world, a patient who may have been injured as a consequence of medical negligence has the right to seek compensatory damages through litigation. Medical malpractice litigation falls under the category of civil law, which concerns wrongs committed by one party versus another. Physicians, nurses, and other health care professionals are expected to provide a certain level of care, which if deemed substandard are used as grounds for the injured party (plaintiff) to sue. The plaintiff must show that the defendant physician(s) and/or health care entity had a duty to the defendant, was negligent in the performance of that duty, and that the negligent care led to the injury. The legal standard in most circumstances is not the medical or scientific probability ($p<0.05$ or 95%) but is "more likely than not" or greater than a 50% likelihood, or $p<0.5$. It is important to note that most medical malpractice is regulated at the state level, and so varies from state to state.

Physicians are expected to provide "reasonable" care and standards are now national. The "standard of care" in most states is defined as the degree of care which a reasonably prudent physician would exercise in the same or similar circumstances [5]. The issues of standard of care, causation of injury, and damages are addressed by expert medical witnesses retained by each side. Should a case proceed to trial, in most instances a lay jury will determine the outcome.

NPH and HIE

As noted above, HIE continues to be a significant cause of long-term neurologic sequelae. NPH has shown promising benefit in improving the outcomes of some infants with HIE and has become a standard care in most developed nations. Not surprisingly, NPH has become an important element in medico-legal litigation related to HIE.

A decision to offer NPH may engender subsequent litigation by pre-supposing that acute intrapartum asphyxia caused the HIE, or NPH would not have been offered, and it is often used by plaintiff attorneys to establish a causal link. Conversely, a failure to offer NPH to an encephalopathic newborn may result in an allegation that the standard of care was violated.

In each situation, it may be helpful to educate providers and implement protocols to timely identify neonatal encephalopathy. Carefully document the nature and degree of the encephalopathy and other neurologic findings, including the head circumference. The decision to utilize NPH is time sensitive, and not all relevant information may be available by the six-hour limit. Later facts might indicate an earlier or chronic injury unresponsive to NPH. Most affected infants are born at other hospitals and require transport to a cooling center and may not have been thoroughly evaluated by a neonatologist at the time a decision to treat needs to be made. These are practical decisions made at the cribside but do not "prove" that the injury was acute HIE any more so than starting antibiotics proves sepsis. In addition, because NPH has very few complications, once it became assimilated into clinical practice, the rigorous criteria applied in the clinical trials were relaxed. Many infants are cooled who would not have qualified for inclusion even though the American Academy of Pediatrics recommends that "infants offered hypothermia should meet inclusion criteria outlined in published clinical trials." [6].

If a decision is made to not offer NPH to an encephalopathic newborn, providers should clearly document that NPH was considered, along with the reasons for exclusion. As examples, polyhydramnios and decreased fetal movement suggest an earlier timing of injury. Perhaps the Apgar scores or umbilical cord blood gases were non-qualifying, or the neonate did not have moderate or severe encephalopathy on examination. Intrauterine growth restriction with congenital microcephaly is not the result of an acute injury. Ultimately, determining the etiology of neonatal encephalopathy requires consideration of multiple factors including a thorough prenatal history, placental pathology, and neuroimaging.

Conclusion

Good risk management dictates the performance and documentation of a thorough neurologic examination, which includes elements of encephalopathy- neuromuscular tone, level of consciousness, primitive and deep tendon reflexes, and seizures, if present. Provide a clear-cut explanation of medical decision-making. If a decision is made to offer NPH, explain why and document the inclusionary criteria. If you decide to withhold NPH, discuss the rationale and document the exclusionary criteria utilized in reaching that decision.

Keep current on evolving standards of care regarding neonatal HIE and its treatment. Unfortunately, even with NPH there is an 40% incidence of death and disability, and consequently research is continuing to evaluate additional therapies that hopefully will improve outcomes for this population of newborns.

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