Therapeutic Hypothermia and Neuroprotection: An Old Story, a 21st Century Light

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The early recommendations for therapeutic hypothermia can be traced back to the ancient world.[1] Egyptians, Greeks, and Romans first recommended induced cooling for battle inflicted trauma and a variety of other disturbances. In the fourth and fifth centuries before Christ, total body cooling was used for tetanus treatment. During the 18th century, therapeutic hypothermia was also extensively used to treat mental diseases. Sir William Osler, in 1892, reported a dramatic decline in mortality in patients with typhoid fever who were subject to therapeutic hypothermia. Baron de Larrey, chief surgeon of Napoleon, observed that hypothermic soldiers placed closer to a fire died faster than those who remained hypothermic.[1,2]

Accounts of hypothermic patients seemingly miraculous recovering from typically fatal circumstances have piqued the interest of scientists for centuries, prompting many of them to carry out the early animal and human investigations that laid the foundation of our understanding of how cooling affects the central nervous system. The interest in therapeutic hypothermia, however, started to decline during the second half of the 20th century, mainly because of the difficulty in managing side effects (such as arrhythmias, coagulopathy, and infection), but also because this empiric approach was overtaken by the development of active resuscitation techniques.[3]

It was only in the late 1980 decade that the interest in neurological applications of therapeutic hypothermia made its comeback, following the reports of minor side effects in cases where only a mild degree of cooling was applied.[3]

Modern clinical use of this technique was established in the early 21st century. From 2005 to 2011, six major clinical trials evaluated therapeutic hypothermia for neonatal encephalopathy. Despite using different methodologies, all studies included term and late preterm infants with asphyxia at birth.[4] In 2013, a systematic review including 11 randomized controlled trials highlighted the neuroprotective effect of this intervention. This study was essential to establish therapeutic hypothermia as a standard practice for infants with hypoxic-ischemic encephalopathy.[5]

Hypoxic-ischemic encephalopathy and therapeutic hypothermia

Despite advances in perinatal care, hypoxic-ischemic encephalopathy in late preterm and term infants still affects 0.5-1 per 1000 live births and remains an important cause of mortality and acute neurological injury with subsequent long-term neurodevelopmental disabilities.[5]

Immediately following resuscitation and reperfusion there is a latent period comprising around 1-6 hours where the impairment of cerebral oxidative metabolism can be partially recovered. That is the narrow therapeutic window for neuroprotective intervention, in which the prognostic can effectively change. Mild hypothermia mechanism of protection is multifactorial. For every 1°C decrease in body temperature, cerebral metabolic rate decreases by 6%-7%, reducing cerebral metabolic demands. Additionally, therapeutic hypothermia decreases the release of excitatory amino acid transmitters and the synthesis of nitrous oxide to reduce excitotoxicity, lessens the release of reactive oxygen species triggered by reperfusion, decreases expression of proapoptotic mediators, and reduces cytotoxic edema.[1,4]

All studies support that mild hypothermia is generally safe. Therapeutic hypothermia is associated with thrombocytopenia or other coagulopathies, but no increase in hemorrhagic complications. It is also associated with high blood pressure, sinus bradycardia, sepsis and pneumonia, and transitory mild hyperglycemia.[4]

Outcome of hypoxic-ischemic encephalopathy

Before the routine use of therapeutic hypothermia, mortality or severe morbidity in neonates with hypoxic-ischemic encephalopathy was very high. Outcomes

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varied with severity, being worst in neonates with severe hypoxic-ischemic encephalopathy (94%-100% of deaths or major neurologic disabilities). Mild hypoxic-ischemic encephalopathy outcomes had more variability, but recent meta-analysis found mild-to-moderate neurologic disability in 25% of children with mild hypoxic-ischemic encephalopathy at age of 2 years that increased to 35% at age 5 years.[4-6]

In infants treated with therapeutic hypothermia, there is a reduction in cerebral palsy, at 18-24 months, maintaining advantages around 6-7 years, regarding gross motor and fine motor function scores.[4,7] Despite the variations across studies, in hypoxic-ischemic encephalopathy survivors there is a general trend towards worse cognitive outcomes when therapeutic hypothermia is not used.[4] Recent outcomes data for uncooled infants primarily focus on those with mild hypoxic-ischemic encephalopathy who do not meet the current most accepted criteria for therapeutic hypothermia. Studies have demonstrated that school-aged children with a history of untreated neonatal mild hypoxic-ischemic encephalopathy are more likely to require extra academic support and have a significantly lower full scale, verbal and performance intelligence quotients when compared with aged-matched children who did not have hypoxic-ischemic encephalopathy, even in the absence of cerebral palsy and motor deficits.[8,9]

Executive function deficits, such as inattention and impulsivity are generally reported to be worse in patients with hypoxic-ischemic encephalopathy. It is also suggested that rates of autism spectrum disorder are higher in hypoxic-ischemic encephalopathy survivors, but data is limited. Also, there are limited data published for behavior outcome measures after therapeutic hypothermia for hypoxic-ischemic encephalopathy, and some are conflicting.[4,9]

Other considerations

Accurate prediction of outcomes for an infant with hypoxic-ischemic encephalopathy is crucial for establishing the therapeutic plan. Magnetic resonance imaging and amplitude integrated electroencephalogram are essential tools for prognosis but are not accurate enough when many life-altering decisions are made. A concern remains that hypothermia may be less beneficial for infants with severe encephalopathy and that its use may delay end-of-life decision making for infants with an extremely poor prognosis.[5] On the other hand, there is increasing evidence against the historical assumption that newborns with mild neonatal encephalopathy are at low risk for adverse outcomes and do not benefit from therapeutic hypothermia.[8] The search for an ideal biomarker for neonatal hypoxic-ischemic encephalopathy is a research priority.

Other issues remain in discussion. The application of therapeutic hypothermia to additional populations of infants at risk of neurological sequela, including term infants with a diagnosis of hypoxic-ischemic encephalopathy but that surpassed six hours after the hypoxic event, preterm infants, post-natal cardiovascular collapse, or infants being treated with extracorporeal membrane oxygenation.[5]

The use of adjunctive therapies has also become an increased focus of study. Allopurinol, xenon, melatonin, erythropoietin, neural stem cells, and magnesium sulfate are being the focus of multiple studies, but there is insufficient evidence to recommend their use.[7] Antiepileptic drugs should be used with caution, due to their known toxicity, but experts recommend treating neonatal seizures, which are an independent cause of brain injury. A low infusion of morphine or an equivalent opioid is recommended as the initial approach for easing discomfort.[7]

Final remarks

Mild therapeutic hypothermia initiated as soon as possible within the first six hours of life, in a well-defined population of infants, within strict protocols and in tertiary centers with considerable experience in this area, decreases mortality and severe long-term neurodevelopmental disabilities, without major risks.

Questions remain about the ability to maximize the neuroprotective effects of therapeutic hypothermia and provide this powerful tool to reach even more children.

Keywords: Hypothermia, Induced/history; Hypothermia, Induced/therapeutic use; Hypothermia, Induced/trends; Hypoxia-Ischemia, Brain/therapy; Infant, Newborn

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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