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Does late therapeutic hypothermia reduce risk of death or disability?

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COMMENTARY

Hypoxic-ischemic encephalopathy (HIE), also known as neonatal encephalopathy, affects an estimated 1-3 term infants per 1000 live births and leads to significant long-term morbidity and mortality(1). Several clinical trials evaluating the use of therapeutic hypothermia (TH), cooling the core body temperature to 33-34°C for 72 hours, initiated within 6 hours of birth, have demonstrated benefit with decreased moderate-severe disability or death at 18-22 months(2). As such, TH for infants with HIE has become standard of care. While animal studies have demonstrated superior treatment effect with early cooling initiated prior to 6 hours of age(3), not all eligible infants undergo initiation of TH within this ideal timeframe.

This randomized clinical trial by Laptook and colleagues enrolled infants who met clinical or laboratory criteria for TH, but who were between 6 and 24 hours of age at time of randomization(4). Infants underwent whole body cooling to a goal core temperature of 33.5°C (range 33-34°C) for 96 hours. This longer cooling time, compared to the standard 72 hours, was chosen due to previous data suggesting that longer hypothermia was necessary for neuroprotection, although this has been recently refuted(5). The results of this study suggest that the benefit of beginning hypothermia >6 hours of age is much less than starting it earlier which is supported by preclinical data. However, despite most of the patients being >12 hours of age at randomization, there was still a small benefit to TH, indicated by Bayesian analysis, despite an increased seizure burden in the TH group at randomization. Combined with the lack of increased serious in-hospital adverse effects in the treatment

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group (no difference in hypotension, coagulopathy or seizures, though possible increase in hypoglycemia in TH group), and the significant risk for moderate-severe neurodevelopmental disability after HIE, the small potential benefit purported by this trial should prompt NICUs to consider initiation of TH beyond 6 hours of age. It is important to note that reasons for lack of initiation of early TH are many and while not specifically stated in this population, may include prolonged transport distance from referring hospital to a tertiary care center capable of cooling and under recognition of clinical encephalopathy after birth, among others(6).

The difficulty in translating preclinical pharmacologic interventions for neonatal ischemia has prompted a discussion to expand the inclusion criteria for hypothermia after HIE. Among these groups are infants initiated beyond 6 hours of life, mild encephalopathy, preemies, and neonatal stroke(7). While others have evaluated non-standard therapeutic hypothermia(7), this is the only randomized clinical trial to date to evaluate the effectiveness of this practice. While trials such as that reviewed here may be difficult to design and fund, it is certainly the better course of action to let randomly controlled clinical trials guide clinical care than to practice medicine by anecdote or trial and error. Much hope remains though that new therapeutic options to augment TH are on the horizon(8). Hence, the concerted efforts of researchers and funding agencies to discover novel strategies to treat acquired neonatal brain injury must continue in earnest.

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