Whole Body Hypothermia, Using Low Cost technique, is Safe and Effective in Term and Near-Term babies with Moderate and Severe Hypoxic Ischemic Encephalopathy

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STUDY DESIGN
Multicenter, international, randomized controlled trial.

Study setting
Neonatal intensive care units (N=28) in Australia, New Zealand, Canada, and the United States, from February 2001 through July 2007.

Study question
Is moderate whole-body hypothermia, provided by refrigerated gel packs, safe and effective in neonatal hypoxic-ischemic encephalopathy?

Participants
Term and near-term infants (≥35 weeks’ gestation) with moderate to severe hypoxic ischemic encephalopathy diagnosed clinically using modified Sarnat Criteria (lethargy, stupor, coma, abnormal tone, and/or seizures).

Exclusion
Major congenital anomalies, birth weight <2.0 kg, postnatal age more than 6 hours, overt bleeding, ventilator support requiring >80% FiO₂.

Randomization
Performed by an independent statistician using sequentially numbered sealed envelopes containing computer-generated random numbers in a 1:1 ratio with variable block sizes.

Intervention
Arm A: Whole-body hypothermia to 33.5°C for 72 hours (n=110) started within 6 hours of birth.

Method: Infants were treated at ambient environmental temperature by turning off the radiant warmer and then applying two refrigerated gel packs, across the chest and/or under the head and shoulders to maintain rectal temperature at 33.5°C (range 33–34°C) for 72 hours followed by slow rewarming over 8–12 hours at a rate of 0.5°C every 2 hours.

Arm B: Standard neonatal care at normal body temperature 37°C (N=111).
Primary outcome measure and neurodevelopmental follow-up

The primary outcome measure was death or major sensorineural disability at 2 years of age. The median age of assessment at neurodevelopmental follow-up was 24.6 months (interquartile range, 24.1–26.1 months).

RESULTS

The RR of primary composite outcome (death or major sensorineural disability), death alone, and survival free of any disability are shown in [Table 1]. The absolute risk reduction of primary outcome measure was 15% (95% CI 2%–28%). Treating seven newborns (95% CI, 4–59) with hypothermia prevented one infant from dying or surviving with a major disability. There was a significant association between severity of encephalopathy at assessment for eligibility and primary outcome (P<0.01). The survival rate free of any sensorineural disability increased (risk difference 17%, 95% CI 4%–29%, P=0.08). Adverse effects of hypothermia were minimal.

CONCLUSIONS

Whole-body hypothermia, provided by refrigerated gel packs, is safe and effective. There was a significant reduction in the composite outcome of death or major sensorineural disability at 2 years of age. This simple method of hypothermia could be used, within strict protocols, with appropriate training on correct diagnosis and application of hypothermia, in nontertiary neonatal settings and while awaiting retrieval and transport to the regional neonatal intensive care unit.

COMMENTARY

Prenatal asphyxia, which alone is responsible for 0.8 million neonatal deaths every year worldwide, contributes to 9% of global under 5 mortality and 22% of global neonatal mortality. A significant number survive with major sensorineural disability. The recent multicenter randomized controlled trials and meta analyses have shown that moderate therapeutic hypothermia (33–34°C) started within first 6 hours of birth, maintained for 72 hours and then followed by 8 hours of slow rewarming and is neuroprotective in term babies with moderate to severe hypoxic ischemic encephalopathy secondary to perinatal asphyxia. Hence, therapeutic hypothermia, using either head cooling or total body cooling, has now become a standard of care in the NICUs worldwide. Unfortunately, the majority of neonatal deaths due to perinatal asphyxia occur in developing countries which have limited resources and are unable to buy expensive head cooling/total body cooling machines and provide intensive neonatal care. The current publication by ICE Trial Group is a landmark contribution toward saving millions of newborn babies with HIE who are born in disadvantaged situations. By providing evidence that therapeutic hypothermia, using low-cost refrigerated gel packs, is safe and effective, the ICE trial has facilitated the global use of this technique, not only in low-income countries but also in nontertiary neonatal units in high-income countries and during neonatal transport to tertiary care units. The ICE Trial is also the first trial to provide evidence that therapeutic hypothermia is safe and effective in near-term (≥35 weeks gestation) babies with hypoxic ischemic encephalopathy, hence widening the spectrum of therapy of lower gestation ages. This can further be extended in future trials of hypothermia.

Abstracted from

Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy. Arch Pediatr Adolesc Med 2011; 165:692-700.

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