Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy

Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews 2007; 4: CD003311. This version first published online: 17 October 2007.

INTRODUCTION

Neuronal injury following perinatal hypoxic ischemic insult involves two distinct phases: an immediate primary neuronal death related to cellular hypoxia and depletion of energy stores, and a secondary phase of delayed (about 6 hours) neuronal death related to reperfusion injury. Therapeutic hypothermia during this window period has the propensity of reducing the delayed neuronal death by reducing the cellular energy expenditure in asphyxiated newborns. This reduction in cellular injury should manifest clinically in terms of reduction in mortality and neurological sequel. This systematic review was conducted to determine the effect of therapeutic hypothermia in encephalopathic asphyxiated newborn infants in terms of mortality, long-term neurodevelopmental disability and clinically important adverse effects.

SUMMARY

Eight randomized controlled trials were included in this review, comprising 638 (319 intervention vs. 319 standard care) term infants with moderate/ severe encephalopathy and evidence of intrapartum asphyxia. Five trials were multicentric whereas one each was from single centers in China, New Zealand and Turkey. Four studies used head cooling devices in conjunction with mild systemic hypothermia while the other four used whole body cooling alone. The range of core temperature in various studies varied between 32.5ºC and 35.0ºC. Whole body cooling was achieved with servo-controlled cooling blankets and the head cooling was done by using cooling cap devices. The intervention was started within 6 hours in all the trials and continued for 72 hours except in one study where it was continued for 48 hours. The outcome of mortality was reported in all eight studies whereas the long term (12-22 months) neurological outcomes in survivors were available from only four studies.

Therapeutic hypothermia resulted in a significant reduction in the combined outcome of mortality or major neurodevelopmental disability [RR 0.76 (95% CI 0.65, 0.89); 506 participants, 4 trials]. Cooling also resulted in statistically significant reductions in mortality [RR 0.74 (95% CI 0.58, 0.94); 638 participants, 8 trials] and in neurodevelopmental disability in survivors [RR 0.68 (95% CI 0.51, 0.92); 336 subjects, 4 trials]. A statistically significant benefit was seen only with studies which used whole body cooling and in infants with severe HIE. The results did not reach statistical significance if only studies using selective head cooling were included or when moderate HIE alone was evaluated. A significant benefit in term of neurodevelopmental disability in survivors was also reported. The adverse effects of hypothermia included an increase in the need for inotrope support of borderline significance [RR 1.17 (95% CI 1.00, 1.38); 505 subjects, 5 trials] and a significant increase in thrombocytopenia [RR 1.55 (95% CI 1.14, 2.11); 531 infants, 4 trials]. The authors concluded that therapeutic cooling reduces mortality without increasing major disability in survivors and the benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects.

COMMENTARY

Are the results valid?

The research question addressed in this review is important as HIE is a very common problem and the associated morbidity and mortality is high especially in developing countries. However, this review comprises an analysis based on less than half of all infants currently known to be randomized into eligible trials of cooling. Incorporation of data from ongoing and completed (but yet unpublished) randomized

KEY MESSAGES

- Whole body cooling decreases the mortality and long-term neurodevelopmental disability in term neonates with hypoxic ischemic encephalopathy.
- The quantum of benefit of this intervention is modest and the cost efficacy is uncertain.

trials will be important to further clarify the effectiveness and safety of cooling(1). The quality of the randomization in most studies was acceptable but the blinding of caregivers and outcome assessors was not possible because of the nature of the intervention. The heterogeneity was not an issue with outcomes of mortality but there was mild heterogeneity in the outcome of long-term neurodevelopmental disability.

How precise and clinically significant is the treatment effect?

The pooled results from the review reported a 15% absolute risk reduction in the combined outcome of mortality or neurodevelopmental disability. This means, we need to treat 7 infants to prevent one adverse outcome (Number needed to treat 'NNT'=7; 95% CI 4-14). When only the outcome of mortality is evaluated, NNT is 11 (95% CI 6-50) meaning one death is preventing by treating 11 infants and the number may vary from 6 to 50. These figures appear clinically important especially when the reduction in mortality is not associated with a corresponding increase in neurological disability, but the benefit can only be described as modest. If only severe encephalopathy is included, there is greater benefit in term of reduction of mortality (NNT=6; 95% CI 3-20). As far as the adverse effects of intervention are concerned, the only significant one was thrombocytopenia with a number needed to harm (NNH) being 11 (95% CI 7-33). This means that for every 11 treated neonates, one would benefit in term of survival whereas one would be harmed because of thrombocytopenia. However, the outcome of thrombocytopenia is functionally not very important especially when it does not result in any risk of clinical bleeding.

IMPLICATIONS FOR PRACTICE AND POLICY

Evidence provided in this review support the use of therapeutic hypothermia in term neonates with hypoxic ischemic encephalopathy. However, it is to be noted that most of these trials were conducted in advanced neonatal centers in industrialized countries with considerable experience in therapeutic hypothermia and the results might not be replicable to other settings. The extremely high cost of the equipment and the need to rigorously monitor and control the temperatures further limits the use of this modality for most settings. Procedural difficulties requiring repeated revisions in the cooling techniques have earlier been reported(2). Also, the quantum of benefit of this intervention is modest and a direct cost-benefit analysis is not available. After results of some of the ongoing/completed trials are available, this systematic review needs to be updated for any new finding before giving any final recommendations.

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