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Response to a different view concerning the NICHD neonatal research network late hypothermia trial

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We read with interest A Different View entitled, ‘Major concerns about late hypothermia study’ by Walløe, Hjort and Thoresen (1) which raised questions about a randomised clinical trial of initiating therapeutic hypothermia between 6 and 24 hours after birth (2). The Late Hypothermia trial (LH) was designed for infants whom hypothermia could not be initiated within 6 hours. Clinicians need a full appreciation of the points discussed.

Walløe, et al. state ‘...any outcome difference between hypothermia and normothermia must be small, and not significant ($p \approx 0.75$)’. This appears to be a frequentist analysis. As emphasised by the American Statistical Association, clinically important differences may not be close to statistical significance ($p < 0.05$) when sample size is limited; other approaches are advocated (3). A limited sample size and statistical power for LH were unavoidable and anticipated even though the trial lasted eight years and involved 21 centres. For this reason, frequentist analysis provides little help to clinicians confronted with an encephalopathic infant who meets hypothermia criteria but is beyond six hours. A Bayesian analysis was prespecified since it is recommended for trials of rare diseases (4). Bayesian analysis, unlike conventional frequentist analysis, provides a direct assessment of the probability of treatment benefit based on the trial results and a prior probability distribution within a plausible range.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

Walløe, et al. contend that a noninformative prior probability should be used, that is, a flat prior in which extreme and highly implausible values (e.g. a risk ratio of <0.01 or >1000) would be as likely as values >0.5 or <2.0 as more typically identified in multicentre trials. For this reason, we strongly disagree with Walløe, et al. and used a 95% credible interval for the risk ratio of 0.5–2.0. This is *a more conservative approach* that shrinks the posterior probability and 95% credible interval towards the null (no effect). Walløe, et al. asserts that relevant prior information was available from head cooling studies in foetal sheep compared to sham controls (5). A close reading suggests less neuronal loss in selected brain regions when cooling was initiated at eight and half hours. Animal studies are of value to establish biologic plausibility for specific treatments. However, direct extrapolation from foetal sheep (5) or rat pups (6) to newborns may be limited given multiple variables in the clinical setting (e.g. duration, repetitiveness, severity of hypoxia-ischaemia and acute superimposed on chronic insults). Furthermore, LH results were also analysed using a sceptical prior (assuming that late cooling increases the primary outcome by 10% compared to noncooling). There was little difference in the posterior probabilities compared to the neutral prior (73% probability of benefit vs 76%, Table 3, (2)).

The LH results indicated an adjusted relative risk of 0.86 for death or disability and a 76% probability of some reduction in this outcome. A true reduction of 14% in the risk for such an important outcome would not be considered a small difference. Unfortunately, treatment decisions must often be made despite uncertainty about the treatment effect due to limitations of the best available evidence. The 168 infants enrolled in LH were randomly allocated, comparable at baseline, and assessed at 18 months by certified personnel masked to treatment intervention, and the follow-up rate was 93.5%. Some centres may choose not to provide hypothermia beyond six hours given the uncertainty of the results. Others may view LH as the best clinical evidence available on the potential benefits of cooling beyond 6 hours and provide the treatment given the probability of some reduction in death or disability, absence of obvious harm and the seriousness of the potential outcome.

An important point of agreement with Walløe, et al. is that the results of LH should not alter current cooling regimens. We purposefully included the following statement in our JAMA publication (2): ‘The results of this trial should not change the priority of early identification of infants with HIE and initiation of hypothermia at less than six hours.’

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