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Hypothermia: An Evolving Treatment for Neonatal Hypoxic Ischemic Encephalopathy

Alistair J. Gunn, Thomas Hoehn, Georg Hansmann, Christoph Bührer, Georg Simbruner, Jerome Yager, Malcolm Levene, Shannon E. G. Hamrick, Seetha Shankaran and Marianne Thoresen

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To the Editor.—

It has always been challenging to know when new therapies should be considered ready for use in practice. History has provided many contrasting examples of simple and effective treatments (such as phototherapy and antenatal steroids) that languished for decades before being adopted and treatments that were and often continue to be used well after they proved to be either useless or less effective than simpler alternatives. However, it is extremely difficult to understand why Kirpalani and colleagues[1] are so concerned that some neonatologists are now choosing to offer therapeutic hypothermia on a compassionate basis. Neither these practitioners nor any official body have, to our knowledge, declared that hypothermia should be the standard of care. They, and several of the undersigned, helped develop the consensus of the 2005 National Institute of Child Health and Human Development workshop that hypothermia is an evolving (not unproven or experimental) therapy, with many questions around its optimal use.[2] Thus, the underlying premise of their commentary is shaky.

Three independent systematic reviews published this year have concluded that (1) therapeutic hypothermia can significantly reduce both death and medium-term disability after perinatal encephalopathy, (2) is safe, and (3) its outcomes are homogenous both within and between trials.[3–5] Overall, although analysis strategies varied, reliable published information is available on ~638 randomly assigned infants for mortality and 506 for death or disability.[5] Kirplani and colleagues seemed to suggest, somewhat arbitrarily, that perhaps 692 infants would be enough for reasonable certainty.[1] If we may note the further outcome data from 157 randomly assigned infants that have been publically presented but not yet published (and are concordant with the current meta-analysis[6]) this target seems to have been broadly achieved.

Although new randomized trials are both highly unlikely and arguably inappropriate, we anticipate that information on nearly as many more infants again will become available over the next 3 years from existing completed trials.[5] How likely is it that these trials will change the current consensus? If, at 1 extreme, there was no apparent effect in the next 600 children (bringing the total to a conservative 1106[1]), with a 60% adverse control event rate, the relative risk (95% confidence interval) would go from 0.76 (0.65–0.89); $P = .006$)[5] to 0.89 (0.8–0.98); $P = .017$). This estimate does not include unpublished data[6]; the estimates would be correspondingly more favorable if they were included. Thus, the current finding of benefit is already strikingly robust.[3–5]

The remaining issues raised by Kirpalani et al are of dubious relevance. The consistent a priori concern for these trials was that inappropriate prolongation of care in treated patients would lead to increased survival rates of disabled infants. Reassuringly, in the event, there was a reduction in disability rates in survivors.[3] In addition, several of the authors can personally attest that all acute deaths in the CoolCap and National Institute of Child Health and Human Development trials were attributable to either overwhelming systemic complications or withdrawal of invasive care with compelling evidence of profound, unrecoverable neurologic injury. First, the few deaths in later infancy were related to complications of profound disability such as aspiration and tended to be fewer in treated infants.[7,8] Next, the meta-analyses were based entirely on prospective, intention-to-treat recruitment of all patients without subgroup selection. Finally, all control infants in the major trials received the best available, optimal conventional care. Pyrexia occurs in a significant subset of control infants.[9] Although the relationship of pyrexia with outcome may be partly noncausal, it is likely from experimental data that pyrexia is as deleterious as hypothermia is beneficial.[10] However, there is no known strategy that is likely to successfully prevent all increases in infant temperature, although, speculatively, active cooling to the lower half of the reference range might achieve this. Realistically then, Kirpalani and colleagues[1] are merely proposing that clinicians should cool, but to a lesser degree.

On this background is it now timely for practicing clinicians to ask whether they may, in consultation with

and with consent from affected families, cautiously use this first treatment for neonatal encephalopathy while they wait for the many questions around its optimal use to be answered? It is our personal view that, given the robust evidence for benefit from current meta-analyses, the remarkable safety profile, the strong foundation in basic science,[10] and supporting evidence from related disease states such as encephalopathy after cardiac arrest,[11,12] the answer is now yes.

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In Reply.—

We thank Gunn et al for their thoughtful comments. They state that we are "concerned" about therapeutic hypothermia being offered on a "compassionate basis." On the contrary, we agree that clinicians who are persuaded of the robustness of the data can reasonably and cautiously offer the therapy to individual parents. Indeed, one of us (Dr Barks) participated in the Cool Cap continued access protocol, in which more infants were cooled on a compassionate-use basis (300) than in all 3 large randomized trials published thus far, and in which all safety data continued to be reported to the US Food and Drug Administration.

Gunn et al seem to agree with our stated position in the commentary that cooling should not be currently considered a standard of care. Nevertheless, despite the absence of new published randomized trials since official statements[1–4] cautioned against acceptance of cooling as "standard of care," there may have been a change of climate. This is suggested because an informal survey has suggested that procedure-specific consent is not being universally obtained from affected families (N. Cook MD, and J. Evans MD, Children's Hospital of Philadelphia, personal communication, 2007); and 1 trial Infant Cooling Evaluation was recently halted due to "lack of equipoise." Cautious clinicians in the larger neonatal community are still left to ask whether the evidence is

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