Authors response: Rise and Fall of Therapeutic Hypothermia in Low-Resource Settings; Lessons from the HELIX Trial

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We thank the authors for critically evaluating our review article[1] and for commenting on the results of the Hypothermia for encephalopathy in low and middle-income countries (HELIX) trial[2]. We have responded to the comments by grouping those comments that were similar.

In the letters to the editor of this journal it has been suggested that we were critical of research performed in India and other low and middle-income countries (LMICs), individuals performing the research, trial design, obtaining informed consent, reliability of data and research governance[3-10]. Our comments were not meant to be critical, and we apologize if our comments were offensive. Many well-conducted studies have been performed in LMICs. We are aware that the continued use of hypothermia for encephalopathy will depend on clinicians view of the HELIX trial. Some of the letters commented that we were critical of cooling devices being used currently; we understand the importance of low-cost cooling devices.

There are comments that the HELIX trial data were not available at the time of the publication of the articles in the Indian Journal of Pediatrics. The full text of the HELIX trial manuscript was publicly available from May 2021 soon after it was accepted for publication in Lancet Global Health; approximately one and half months before the publication of our review article in Indian Journal of Pediatrics.

Our response to the comments by Amboiram and Balakrishnan[3] are given below:

- Tecotherm-Neo used in the HELIX trial, is a highly accurate and fully automated servo-controlled cooling system that requires minimal additional nursing input for maintaining hypothermia, unlike manual cooling devices. Hence, many infants cooled in the UK using servo-controlled devices do not require 1:1 nursing care. Furthermore, one HELIX site (Bangabandhu Sheikh Mujib Medical University Hospital, Dhaka) did have 1:1 nursing care; nevertheless, therapeutic hypothermia was still ineffective and increased mortality at this site.

- The Tecotherm-Neo system stored the temperature data continuously in the hard drive, which were then downloaded to crosscheck the accuracy of manual temperature data entry. Transient temperature fluctuations due to a machine failure did occur in one case, but otherwise the core temperature was closely within the target range in all cooled infants.

- In the HELIX feasibility study, we used a low-cost servo-controlled device (Tecotherm-HELIX) that we had specifically developed for use in LMIC, and not Tecotherm Neo. However, Tecotherm-HELIX did not have a re-warming mode to ensure controlled re-warming, nor had facilities for downloading the temperature data for quality assurance. The HELIX feasibility study was a non-randomised observational study, and hence the lower mortality may reflect a selection bias.

- The mortality and disability rates in the control arm of the HELIX trial was similar to the high-income country cooling trials. We are unable to explain why previous studies using low-cost manual cooling devices in Indian hospitals with 1:3–4 ratio of nursing care has reported far lower mortality than in high income country cooling trials and the HELIX trial.

- The minimisation method was used to control for recruiting centres, and the number of inborn and outborn were equally distributed between the control and usual care arms in the HELIX trial.

- One centre in Chennai that admitted only inborn babies had the lowest neonatal mortality amongst all sites (risk ratio 1.04 (0.55, 1.97); but this centre also had the highest neurodisability rates (risk ratio 1.78 (0.51, 6.2).

- In our cooling survey conducted prior to the HELIX trial, we found that most private hospitals in India had low delivery rates, high caesarean section rates, were offering cooling predominantly to out-born infants using protocols that varied widely from established practices in high income country cooling trials, and did not have 3 Tesla Magnetic resonance imaging and spectroscopy. Hence private hospitals were not included in the HELIX trial.

Our responses to the comments by Serane and Toshniwal[9] are given below:

- All HELIX centres were designated as tertiary neonatal intensive care centres in their country, had facilities for invasive ventilation, in-house blood gas analysis facilities, inotropic support and continuous non-invasive cardiorespiratory monitoring. During the trial regular face to face and online training was provided, and additional staff were appointed at the sites, as per the local requirements.

- We used multiple layers of data checks and validation including data checks by local research nurses or fellows, site principal investigators, trial monitors and research nurses at Imperial College including source file verification, automated quality checks using bespoke algorithms in an International Conference on Harmonisation Good Clinical Practices Complaint research database, and a final check of all case report forms by the chief investigator of the trial and the trials manager.

- Hypothermia protocols were standardised across sites, and clinical protocols were similar. Some variation in clinical practices is invariable in multi-country studies. This increases the generalisability of the HELIX trial as cooling was uniformly ineffective across all trial sites in South Asia.

- Pre-exiting conditions were identified only in three infants; one in the hypothermia arm, and two in the control arm; these cannot explain the lack of hypothermic neuroprotection.

- We acknowledge we did not have data on the number of infants with mild encephalopathy in the prior cooling studies from India, but we are aware that differentiating babies with mild from moderate encephalopathy is challenging, not just in India, but in high income countries as well.

Our responses to the comments by Chirla and Panigrahy[4] are given below:

The conclusions of the HELIX trial are based on the primary outcome, and not secondary outcomes[2]. When interpreting 95% confidence intervals, any value over 0 should be considered as significant if one is calculating relative risk as a proportion (and not 10%), and any value over 1 would be significant if it is a risk ratio.

Our responses to the comments by Thomas and colleagues[11] are given below:

- Although the THIN study[12] had 25 infants per arm, primary outcome data were available only in 11 infants (Figure 1[12]) in each arm which is what we were referring to. The mortality during the intervention period was 2/25 (8%) in the cooling arm and 1/25 (4%) in the usual care arm (Table 3[12]) in the THIN study. In our review paper, we had explicitly mentioned that we were discussing the mortality during the intervention period as this was the time most mortality occurred in the HELIX trial as well.

- Magnetic resonance (MR) biomarkers in neonatal encephalopathy are useful in early phase trials to see which treatments should proceed to further evaluation in a phase III trial, and not as confirmative tests for efficacy. Neurodevelopmental outcomes at 18 months or more are the only definitive proof for efficacy for any neuroprotective intervention. Using quantitative MR biomarkers for measuring treatment effects is complex and requires very careful protocols, particularly on how poor-quality MR data are excluded to avoid selection bias. We consider the sample size of the THIN study too small to make comparisons with high income countries, as the confidence intervals are likely to be wide.

Our responses to the comments by *Kaoushal and colleagues[7] are given below:*

We agree differences in the infants enrolled in the HELIX trial compared to high income country trials is the key factor for lack of hypothermic neuroprotection, rather than inadequate cooling device or sub-optimal supportive care. The HELIX data suggest that the brain injury may be occurring earlier, and secondary energy failure had possibly occurred before the infant is born. Such infants are unlikely to respond to therapeutic hypothermia. We appreciate the HELIX trial results creates a dilemma for those private health care settings where infants with encephalopathy currently receive cooling for moderate or severe encephalopathy due to hypoxia-ischemia. We cannot comment on the safety and efficacy of cooling for infants in these settings, but we strongly encourage the publication of data on mortality and outcomes from these centres.

References

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