



Questions about the HELIX trial

In the HELIX study,¹ Sudhin Thayyil and colleagues suggested that all low-income and middle-income countries (LMICs) should immediately suspend use of cooling in neonates.¹ The reported absence of benefit and increased mortality in neonates who were cooled are in contrast to our experience and the findings in meta-analyses in LMICs.^{2,3}

We represent academic hospitals in South Africa who use therapeutic hypothermia to treat neonatal encephalopathy with suspected hypoxic ischaemic encephalopathy. We also study the role of genetic and environmental influences in the national Neonatal Encephalopathy with Suspected Hypoxic Ischaemic Encephalopathy (NESHIE) study.

Several differences in the HELIX study preclude the generalisation of their findings to all LMICs. First, the HELIX cohort showed increased illness severity compared with a South African cohort; more infants required ventilation (60% vs 34%), inotropes (80% vs 17%), and treatment for coagulopathy (39% vs 14%) in the HELIX trial than in the South African cohort.²

Second, intrapartum hypoxia was not adequately defined: 11% of neonates had cord pH measurements; 67% of neonates had 5 min Apgar scores; and fetal heart rate decelerations were documented in 6% of neonates. The low proportion of neonates with prolonged second stage (3%) and obstructed labour (1%) further calls into question the contribution of intrapartum hypoxia.

Third, encephalopathy and seizures were not robustly defined. Seizure onset before cooling is associated with reduced treatment effect; 73% of infants in the HELIX study had seizures before recruitment. Seizures are underdiagnosed in the absence of amplitude integrated electroencephalography (aEEG).

Although clinical scores can be used to define encephalopathy, they lack specificity compared with aEEG.⁴ Fourth, the inclusion of infants with anthropometry 2 SD below the mean and the use of low temperature targets in the control group (36.0°C vs 36.5°C) might have mitigated the benefits of cooling. However, anthropometric data are difficult to interpret because WHO growth charts are not gestation-specific.

Lastly, sepsis limits the benefit of cooling and might have had a role in increased mortality.⁵ Increasing antibiotic usage from 88% at 24 h to 95% at 96 h suggests that acquired infection was under-reported. Although data for chorioamnionitis were absent, funisitis in 16% of neonates implies antenatal infection (which is common in LMICs) that could explain the predominant white-matter damage that was detected by MRI.

Despite these limitations, the HELIX study found an important benefit of decreased disabling cerebral palsy in cooled infants (11% vs 21%; risk ratio 0.53 [95% CI 0.28–0.98]), which is particularly relevant in resource-constrained settings. For the reasons we outline, the HELIX study therefore does not provide sufficient evidence to recommend cessation of cooling in all LMICs. Their study highlights the need to review outcomes in relation to selection criteria before changing cooling practice.

ARH reports a patent issued to himself and to the University of Cape Town, in 2008, for a fan-cooling system for inducing neuroprotective hypothermia in neonates (patent number, WO 2008 142650 A1). All other authors declare no competing interests. NESHIE study leaders include Gugu T J Kali, Shakti Pillay, Michael S Pepper, Alan R Horn, Daynia Ballot, Melantha Coetzee, Khomotso Masemola, Firdose Nakwa, Nicola Robertson, Cally Tann, Jeanne Van Rensburg, and Sithembiso Velaphi.

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- 1 Thayyil S, Pant S, Montaldo P, et al. Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): a randomised controlled trial in India, Sri Lanka, and Bangladesh. *Lancet Glob Health* 2021; **9**: e1273–85.
- 2 Kali GTJ, Martinez-Biarge M, Van Zyl J, Smith J, Rutherford M. Therapeutic hypothermia for neonatal hypoxic-ischaemic encephalopathy had favourable outcomes at a referral hospital in a middle-income country. *Acta Paediatr Int J Paediatr* 2016; **105**: 806–15.
- 3 Abate BB, Bimerew M, Gebremichae B, et al. Effects of therapeutic hypothermia on death among asphyxiated neonates with hypoxic ischemic encephalopathy: a systematic review and meta-analysis of randomized control trials. *PLoS One* 2021; published online Feb 25. <https://doi.org/10.1371/journal.pone.0247229>.
- 4 Horn AR, Swingler GH, Myer L, et al. Early clinical signs in neonates with hypoxic ischemic encephalopathy predict an abnormal amplitude-integrated electroencephalogram at age 6 hours. *BMC Pediatr* 2013; **13**: 1–11.
- 5 Martinello KA, Meehan C, Avdic-Belltheus A, et al. Hypothermia is not therapeutic in a neonatal piglet model of inflammation-sensitized hypoxia-ischemia. *Pediatr Res* 2021; published online May 10. <https://doi.org/10.1038/s41390-021-01584-6>.