INVITED COMMENTARY

From Therapeutic Hypothermia to Targeted Temperature Management in Low-Resource Settings

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In high-income countries, therapeutic hypothermia reduces death or survival with moderate or severe disability at 18 months in infants with moderate and severe encephalopathy [1], and has been the standard of care for over a decade. Use of cooling therapy in low- and middle-income countries (LMICs), where the highest burden of encephalopathy occurs, has been more controversial. HELIX, the largest cooling trial in the world, recruiting 408 infants with moderate or severe encephalopathy from India, Sri Lanka and Bangladesh, recently reported that therapeutic hypothermia does not reduce death or disability at 18 months after moderate or severe encephalopathy [2].

Although non-randomized trials cannot inform the safety or efficacy of an intervention, retrospective data from Indian Neonatal Collaborative including 352 infants (211 cooled) from 17 neonatal units is consistent with the HELIX trial data – on regression analysis therapeutic hypothermia was not associated with reduced neonatal mortality [3]. The authors found that severe encephalo-pathy, persistent pulmonary hypertension and adminis-tration of Epinephrine during resuscitation were associated with decreased odds of survival to hospital discharge. The report does not include data on neurodevelopmental outcomes of children – the current standard of effectiveness of any neonatal neuroprotective intervention.

While the data on several important variables including perinatal sentinel events, seizure onset, bleeding tendencies, inotropic support, nurse:infant ratio, hyperthermia in non-cooled infants, and outcome of infants transferred to other hospitals (all presumed as survivors) were not reported, these data do raise further questions: Firstly, the median umbilical cord pH was 7.18 (IQR 7 to 7.28) and only 48 (14%) of the 352 infants had a cord pH less than 7. Hence most infants would not have met the high-income country cooling criteria. Secondly, only 62 (17%) received mechanical ventilation, with the majority ventilated for less than 24 hours unlike the HELIX trial and high-income country cooling trials. Thus, most cooled infants were less sick than those enrolled in the trials in high-income countries. Unless a standardized neurological examination using certified examiners or amplitude-integrated electroence-phalography is used, infants with mild encephalopathy can be misclassified as moderate, not just in LMICs, but in high income countries as well and many such infants may receive cooling therapy [4]. Despite the lower severity of encephalo-pathy, 62 (17%) infants died or were discharged against medical advice, and further 16 transferred to another hospital [3]. The clinical status of the infants discharged against medical advice or transferred to other hospitals is not presented. Infants of 34 and 35 weeks gestation were included in the report, although the numbers and severity of encephalopathy is not documented; it should be noted that neither the safety nor the efficacy of hypothermia for moderate or severe encephalopathy among late preterm infants has yet been demonstrated.

Where do these data leave clinicians in low-resource settings? The pooled data from all randomized trials in LMICs, including the HELIX trial, now provide definitive evidence that therapeutic hypothermia does not reduce death or disability after moderate or severe encephalo-pathy, and hence continued cooling in these settings cannot be justified [5]. It is possible that the better outcomes seen in the control arm of the HELIX trial might have been due to better targeted temperature manage-ment at 36.5°C unlike the original high-income cooling trials [1] that had hyperthermia in 14% to 39% of the control arm infants. In pediatric [6] and adult [7] trials of hypothermia for cardiac arrest, targeted temperature management (normothermia) had similar outcomes to hypothermia therapy [6,7].

However, not everyone is convinced that hypothermia is not safe or effective in moderate or severe encephalopathy in LMICs. Some argue that the population in LMICs is very diverse and that there is a subgroup of infants who have access to high quality antenatal, intrapartum and neonatal care as in high income countries, who might benefit from therapeutic hypothermia [8].

While all these arguments are valid, several issues need to be considered. Firstly, all the cooling trials reported from India including the THIN trial from a private sector hospital had nurse to infant ratios of 1:3-4 or greaterdespite using low-cost manual cooling devices [9]. Secondly, the population characteristics of infants in these trials are very similar to the HELIX trial, with low incidence of acute perinatal sentinel events (<10%) and high (>80%) incidence of seizures at randomization (baseline) [10]. This may indicate acute on chronic hypoxic-ischemic injury. Finally, there are very limited published data on burden of neonatal encephalopathy amongst inborn babies from private sector hospitals in India, and this situation is very complex due to very high rates of caesarean sections. In the present study, seven hospitals did not have a single infant with encephalo-pathy, although details of these hospitals and caesarean rates are not provided.

Clinicians in low-resource settings need to decide if it is appropriate to continue an expensive and possibly ineffective cooling therapy, or shift to a less resource-intensive and evidence-based targeted temperature management at 36.5°C.

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