Randomized Controlled Trial Evaluating Hypothermia for Neonatal Encephalopathy in Low- and Middle-Income Countries

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SUMMARY

In this open-label, randomized controlled trial in seven tertiary neonatal intensive care units in India, Sri Lanka, and Bangladesh, infants born at or after 36 weeks of gestation with moderate or severe neonatal encephalo-pathy and a need for continued resuscitation at 5 min of age or an Apgar score of less than 6 at 5 min of age (for babies born in a hospital), or both, or an absence of crying by 5 min of age (for babies born at home), were recruited. In a web-based randomization system, infants were allocated into a group receiving whole body hypothermia (33·5°C) for 72 h using a servo-controlled cooling device, or to usual care (control group), within 6 h of birth. All recruiting sites had facilities for invasive ventilation, cardiovascular support, and access to 3 Tesla MRI scanners and spectroscopy. The primary outcome was a combined endpoint of death or moderate or severe disability at 18-22 months, assessed by the Bayley Scales of Infant and Toddler Development (third edition) and a detailed neurological examination. Analysis was by intention to treat. After exclusions, 202 eligible infants were assigned to the hypothermia group and 206 to the control group. Primary outcome data were available for 195 (97%) of the 202 infants in the hypothermia group and 199 (97%) of the 206 control group infants. 98 (50%) infants in the hypothermia group and 94 (47%) infants in the control group died or had a moderate or severe disability (risk ratio 1·06; 95% CI 0·87–1·30; *P*=0·55). 84 infants (42%) in the hypothermia group and 63 (31%; *P*=0·022) infants in the control group died, of whom 72 (36%) and 49 (24%; *P*=0·0087) died during neonatal hospitalisation. Five serious adverse events were reported: three in the hypothermia group (one hospital readmission relating to pneumonia, one septic arthritis, and one suspected venous thrombosis), and two in the control group (one related to desaturations during MRI and other because of endotracheal tube displacement during transport for MRI). Therapeutic hypothermia did not reduce the combined outcome of death or disability at 18 months after neonatal encephalopathy in low-income and middle-income countries, but significantly increased death alone. The authors conclude that therapeutic hypothermia should not be offered as treatment for neonatal encephalopathy in low-income and middle-income countries, even when tertiary neonatal intensive care facilities are available.

COMMENTARIES

Evidence-based Medicine Viewpoint

Introduction: Therapeutic hypothermia (TH) is widely practiced in new-born infants with hypoxemic ischemic encephalopathy (HIE). It has been included as a standard of care in many guidelines published in developed as well as developing countries. Its use has become so widespread that the International Liaison Committee on Resuscitation (ILCOR) statement in 2020 cautioned that TH should only be used in neonatal care units with facilities for multidisciplinary care, respiratory support, oxygenation monitoring, etc. [1]. TH appears to be supported by robust evidence. A network meta-analysis of randomized controlled trials (RCT) examining multiple interventions for HIE [2], identified whole-body cooling as the top-ranking intervention that reduced mortality at 18 months of age, closely followed by selective head cooling. Both interventions were also associated with better neuro-developmental outcomes at that age. Even cerebral palsy in later life was found to be decreased with TH [3].

Despite the overall benefit reported with TH, it is not always successful, particularly in severe HIE. Perhaps this is why there is intense search for alternate interventions for neuroprotection and/or improvement of neuro-developmental outcomes following neonatal encephalopathy. Several interventions have been explored with and without TH, including erythropoietin [4,5], melatonin [6,7], and xenon [8]. There are also several pre-clinical studies as well as registered human RCTs exploring stem cell therapy [9,10]. These diverse data suggest that there is room for further evidence despite the reported benefits of TH. Recently, a multi-centric RCT in three developing countries, evaluated TH in moderate-to-severe HIE [11]. **Table I** summarizes the trial details.

Critical appraisal: Overall, the trial [11] had low risk of bias. The random sequence was generated using an online program that controlled for the stage of encephalopathy as well as study site. Random permuted blocks of variable sizes were used, although the range of block sizes was not specified. Allocation was concealed from the on-site investigators, who had to enter participant details after informed consent was obtained, to identify the arm to which the neonate was allocated. Adherence to the assigned arm, was cross-verified by a team based in London. Although the treating physicians/teams were not blinded, the assessors recording the primary outcome, long-term outcomes, and the MRI data were blinded to the allocation of each neonate. A wide range of clinically important outcomes were recorded, without omitting any from reporting. There was very low attrition in this trial, as 97% of the enrolled infants could be followed-up. This RCT [11] was not only registered, but its protocol was also published [12], and there are no significant deviations from either. Even after randomization, there were hardly any protocol deviations.

The trial [11] included several refinements in addition to meticulous planning, execution and analysis. This enabled the investigators to overcome many biases that crept into previous similar trials. For example, neonates who underwent passive cooling prior to randomization were not included. Variability in assessments that could creep into clinical examinations, neuro-developmental evaluation, etc. were diminished, because these were performed by well-experienced physicians, and stringent definitions were used for every subjective evaluation. Even the MRI scanning procedure, protocols, and acquisition time, were standardized across the sites. Raw data from MR scanning were centrally evaluated for quality before processing. Two experienced neonatal neurologists used a prior-validated scoring system to read the images, while blinded to all clinical information.

In addition to the clinical outcomes, the investigators included a large number of MRI-related parameters. The choice of these is supported by a systematic review [13] which confirmed that ratios of NAA/creatine and NAA/choline in the basal ganglia/thalamus, as well as myo-inositol/choline in the cerebral cortex on Proton magnetic resonance spectroscopy, correlated well with adverse effects in neonates undergoing TH. Similarly, MRI findings of injury to the internal capsule posterior limb (on diffusion weighted imaging), and increased lactate/N-acetylaspartate peak on MR spectroscopy, had high predictive value for adverse neurodevelopmental outcomes [14]. All these were analyzed in this trial [11].

The extremely low attrition in this RCT [11] was achieved by research nurses maintaining contact with the families of enrolled infants between discharge and follow-up. Special search teams were constituted to track families who failed to follow-up as scheduled. These teams were able to make home visits not only to local families, but even to those who had migrated.

Very few limitations could be identified in this trial [11], none of them serious. For example, although the analysis was described as intention-to-treat, the calculations were based on the number whose primary outcome was available, rather than the number randomized. As in many multi-centric trials, only aggregated data across study sites was presented, making it difficult for readers to judge whether data are driven by experiences in a limited number of sites with larger proportion of enrolments. This is important because in this trial [11], two sites accounted for 55% of the enrolled neonates, whereas 3 sites, each enrolled less than 10% of the sample size. One site enrolled only 12 neonates.

Since many of the enrolled neonates had clinical seizures, it can be argued that EEG data would be important. A systematic review showed that abnormal amplitude integrated electroencephalogram (aEEG) at 72 hours had high reliability to predict death or moderate/severe disability [15]. Another systematic review of 37 publications also confirmed that aEEG at 24 and 72h, had high predictive value for adverse neurodevelopmental outcomes [14]. However, this RCT [11] did not perform EEG.

The robust methodology and multiple refinements in this trial [11] generate high level of confidence in the results. There was no difference between the RCT arms for the primary outcome. Among the long-term outcomes, all-cause mortality at 18 months was increased with no benefit in the other two outcomes. Among the 17 short-term outcomes, 7 were worse in TH group, with no benefit in the other 10. Among 13 additional clinical outcomes, only one viz. disabling cerebral palsy showed a statistically significant reduction with TH, whereas there was no difference in the other 12. The multiple MRI findings were all comparable between the groups. In addition to the outcomes presented above, the supplementary files [11], have a plethora of additional data including hematological parameters, biochemical values, and clinical support requirements, recorded at 24h, 48h, 72h, and 96h. A wealth of MRI data (too extensive to present here) is also included. Overall, none of these showed any benefit of TH.

The authors also undertook multiple subgroup analyses of one secondary outcome "mortality at discharge." Three comparisons stood out. First, the increased mortality at discharge was driven by outborn neonates. Surprisingly, there was increased mortality in

Table I: Critical Appraisal of the Study

Clinical question	The research question in the PICOT format is: "In full-term newborns having moderate or severe encephalopathy (*P=Population*), what is the effect of therapeutic hypothermia (*I=Intervention*), compared to no hypothermia (*C=Comparison*), on mortality or disability (*O=Outcome*) at 18-22 months of age (*T=timeframe*)?
Study design	Randomized controlled trial with allocation of individual neonates to the trial arms.
Study setting	Tertiary level neonatal care units based in three developing countries viz. India, Sri Lanka, and Bangladesh. All the participating neonatal units fulfilled the ILCOR criteria for safe administration of TH. In addition, all had adequately trained manpower to look after sick neonates.
Study duration	Recruitment of neonates was done from August 2015 to February 2019. Follow-up was conducted till 18-22 months of age.
Inclusion criteria	Newborns (gestation >36wk, birth weight >1800g), with neonatal encephalopathy defined by the presence of two criteria viz. *i*) Evidence of perinatal asphyxia (defined as need for ongoing resuscitation at 5min of life, or a 5-minute Apgar score <6, or absence of crying by 5min of age for home-delivered neonates; and *ii*) Evidence of moderate or severe encephalopathy between 1-6h of life (determined by clinical examination and modified Sarnat staging).
Exclusion criteria	Neonates without heartbeat at 10min of life inspite of appropriate resuscitation, and those having major life-threatening congenital malformation, were not included. Neonates whose parents declared inability to attend scheduled follow-up assessment visits, were also excluded.
Recruitment procedure	Not described in detail.
Intervention and Comparison groups	Neonates in the TH arm underwent controlled reduction of core (rectal) temperature to 33·5°C, starting within 1-6h of birth, for a total of 72 h. Thereafter, automated re-warming at the rate of 0·5°C every hour was initiated, until normothermia was achieved. Neonates experiencing shivering or unexplained tachycardia were sedated. TH was ceased if there was refractory hypotension, or a life-threatening/massive haemorrhage.Those in the Comparison arm did not receive hypothermia. Both groups received the usual care as per the clinical condition, including respiratory support, cardio-vascular support, avoidance of iatrogenic hyperthermia, careful clinical and lab monitoring, and correction of abnormalities detected.
Outcomes	The primary outcome in this RCT was death or (moderate/severe) disability. There were three long-term secondary outcomes viz. all-cause mortality at 18mo of age, severe disability among survivors, and microcephaly at 18-22mo of age. There were 17 short-term secondary outcomes evaluated before discharge viz. mortality, length of hospital stay, abnormal neurological examination at discharge, culture-proven early-onset neonatal sepsis, pneumonia, necrotizing enterocolitis, renal failure, cardiac arrhythmia, major intracranial hemorrhage, pulmonary hemorrhage, gastric bleeding, persistent hypotension, prolonged coagulation necessitating treatment, severe thrombocytopenia, persistent metabolic acidosis, and subcutaneous fat necrosis.Additional clinical outcomes included survival without disability, moderate disability, disabling cerebral palsy, Bayley-III cognitive, motor, and language composite scores, persistent seizures, gross motor function classification system level, visual deficit, and auditory deficit. Anthropometric measurements included microcephaly, wasting, and stunting. Infants underwent MRI at 7-14d of age, to identify markers of neuronal damage including brain injury scores on conventional MRI, thalamic N-acetyl aspartate (NAA) concentrations; lactate:NAA ratio, NAA:creatine ratio, and NAA:choline peak area ratio; and whole brain white matter fractional anisotropy.
Follow-up protocol	Enrolled neonates were followed-up at 18-22mo of age. Detailed neurological examination was done by a neuro-developmental pediatrician, who administered Bayley Scales in local languages. In infants who could not be examined either at the site, or at home, families were contacted over telephone, and information on mortality ascertained.
Sample size	The investigators assumed an effect size of 30% reduction in the primary outcome (from 50% to 35%) with TH. Calculating for 5% alpha error, 20% beta error, and 10% attrition, the required sample size was 408 infants. The trial achieved this sample size.
Data analysis	Intention-to-treat analysis was planned. Appropriate statistical methods and tests were used to examine the data.
Comparison of groups at baseline	Maternal age, gravidity, parity, and pregnancy complications were evenly distributed between the groups. Delivery characteristics including mode, place, and red-flag events were also comparable. There were no differences in the trial arms for various neonatal characteristics including gender, gestational age, birth weight, anthropometric parameters, features of birth asphyxia, stage of encephalopathy, seizures, and core temperature.
Summary of results (TH vs control arm)	Primary outcome: • Death or (moderate/severe) disability: RR1·06 (95% CI 0·87,1·30)

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Secondary outcomes:

- All-cause mortality at 18mo of age: RR 1·35 (95% CI 1·04,1·76)*
- Severe disability among survivors: RR 0·61 (95% CI 0·34,1·11)
- Microcephaly at 18-22mo of age: RR 1·09 (95% CI 0·74,1·62)
- Mortality before discharge: RR 1·50 (95% CI 1·10,2·04)*
- Length of hospital stay: Median difference 2.20 (95% CI 0.70, 3.80)*
- Abnormal neurological examination at discharge: RR 0·93 (95% CI 0·70,1·24)
- Culture-proven early-onset neonatal sepsis: RR 1·22 (95% CI 0·54,2·77)
- Pneumonia: RR 1·06 (95% CI 0·63,1·77)
- Necrotizing enterocolitis: RR 5·10 (95% CI 0·60,43·2)
- Renal failure: RR 1·40 (95% CI 0·76,2·59)
- Cardiac arrhythmia: 5/202 vs 0/206; RR not calculable
- Major intracranial hemorrhage: RR 0·51 (95% CI 0·09,2·75)
- Pulmonary hemorrhage: RR 1·53 (95% CI 0·99,2·37)
- Gastric bleeding: RR 1·86 (95% CI 1·28,2·69)*
- Persistent hypotension: RR 1·84 (95% CI 1·17,2·88)*
- Prolonged coagulation: RR 1·55 (95% CI 1·16,2·07)*
- Severe thrombocytopenia: RR 2.24 (95% CI 1.26, 4.00)*
- Persistent metabolic acidosis: RR 1·95 (95% CI 1·24,3·08)*
- Subcutaneous fat necrosis: 1/202 vs 0/206; RR not calculable
- Survival without disability: RR 1·23 (95% CI 0·89,1·68)
- Moderate disability: 0/111 vs 3/135; RR not calculable
- Disabling cerebral palsy: RR 0.53 (95% CI 0.28, 0.98)*
- Bayley-III score <70 and 70-84, compared against ≥85: RR 0·61 (95% CI 0·32,1·18) and 1·28 (95% CI 0·77,2·11), respectively
- Motor score: RR 0.52 (95% CI 0.27, 1.00) and 0·95 (95% CI 0·33,2·72), respectively
- Language score: RR 0·73 (95% CI 0·43,1·21) and 0·73 (95% CI 0·50,1·05), respectively
- Persistent seizures: RR 0·40 (95% CI 0·11,1·44)
- Gross motor function classification system level: Median difference 0
- Visual deficit (blindness): RR 0·61 (95% CI 0·21,1·72)
- Auditory deficit: RR 0·60 (95% CI 0·16,2·37)
- Microcephaly: RR 1.01 (95% CI 0.58, 1.76)
- Wasting: RR 1.04 (95% CI 0.75, 1.45)
- Stunting: RR 1.11 (95% CI 0.87, 1.41)

MRI findings:

- Basal ganglia or thalamic injury: RR 0.84 (95% CI 0.54, 1.30)
- White matter injury: RR 1.06 (95% CI 0.94, 1.20)
- Cortical injury: RR 0.80 (95% CI 0.54, 1.18)
- Subdural bleeds: RR 1.19 (95% CI 0.75, 1.87)
- Mean (SD) thalamic N-acetyl aspartate (NAA) concentration: 8·06 (1·8) vs 8·04 (1·6)
- Median (IQR) Lactate:NAA ratio: 0·14 (IQR 0·106,0·200) vs 0·14 (IQR 0·099,0·175)
- Mean (SD) NAA:creatine ratio: 1·51 (SD 0·29) vs 1·51 (SD 0·26)
- Mean (SD) NAA:choline peak area ratio: 0·83 (SD 0·18) vs 0·85 (SD 0·16)
- Whole brain white matter fractional anisotropy: No significant difference
- Mean (SD)fractional anisotropy values over posterior limbs of the internal capsule: 0·32 (0·05) vs 0·32 (0·06)

Serious adverse events: RR 1.53 (95% CI 0.26, 9.06)

**Statistically significant.*

the TH group, among infants without sepsis, and those having no perinatal sentinel events. It is unclear why the primary outcome was not similarly analyzed.

Given that this methodologically robust RCT [11] showed contrary results to several other studies, (thereby challenging the hitherto accepted practice of TH in HIE), several questions emerge.

First, how do the results of this trial [11] compare with other data? A Cochrane review published in 2013 (11 RCT, 1505 participants) demonstrated statistically and clinically important reduction in mortality or major neuro-developmental disability at 18 months of age [16]. However, this review is outdated and merits no further consideration. A very recent systematic review with literature search updated to April 2020 [17], identified 28 RCTs among nearly 3600 neonates with moderate to severe HIE. Meta-analysis showed that the pooled relative risk of mortality was (statistically and clinically) significantly reduced with TH. However, in addition to some methodological flaws, the authors did not specify the time-frame at which mortality was determined [17]. This makes it difficult to interpret the data from the review [17]. On the plus side, the authors did not identify significant publication bias (i.e. lower probability of publication of trials showing no beneficial effects of TH).

Since the publication of the systematic review [17], additional trials have emerged. A recent RCT conducted in Chennai [18] examining the same outcomes as this trial [11] in over 160 neonates, reported a statistically significant difference in mortality or abnormal neurological outcome, at 18mo, although there was no significant difference within 28d. Another RCT [19] in a single Indian institution among 50 neonates with moderate or severe HIE, examining MRI changes in the posterior limb of the internal capsule, reported a statistically significant beneficial effect with TH, although this could be analyzed in less than half the recruited infants. Conventional MRI findings also suggested that TH was beneficial. Yet another RCT among 120 neonates with HIE at JIPMER Puducherry, reported lower mortality with TH [20], and also less frequency and severity of acute renal injury. Markers of myocardial injury (cardiac enzyme levels at 72h) and ECG as well as echocardiography findings were more favorable in those receiving TH [21]. An RCT in 40 Chinese infants [22], also reported lower incidence of severe disability, better psychomotor development scores, and higher neuro-development scores at 15 months of age in those receiving TH. These infants also had better neonatal neuro-behavioural score at 28 days of age. However, there was no difference in mortality and no difference in the levels of neuronal biomarkers after 72 hours of treatment. Overall, none of these RCTs had the methodological rigour associated with this trial [11].

Despite the overall benefit reported in systematic reviews of TH [16,17], not all trials showed the same effect. Even trials showing benefit differed in its magnitude. A group of authors tried to analyze the reason for statistically significant differences in the efficacy of TH in two fairly large trials [23]. Despite similar inclusion criteria, there were differences in the sickness level of included neonates, severity of HIE, use of anti-convulsant medication, sedation, and many in one of the trials had received cooling before randomization itself.

To be fair, this is not the first robust piece of evidence that failed to find a beneficial effect of TH. A systematic review focusing on studies conducted only in low-and middle-income countries, identified 7 trials [24]. These trials included 567 infants, of whom 15% had only mild encephalopathy. Various formal and non-formal cooling systems were used. However, there was no statistically significant decrease in neonatal mortality with TH. The authors attributed this to heterogeneity, poor methodological quality, inappropriate cooling devices, or inadequate intensive care facilities. However, they also considered population-based differences (compared to high-income countries) such as perinatal infection, obstructed labor, intrauterine growth retardation, etc.

There are other indirect pieces of evidence suggesting limitations to the effects of TH. A community-based study in the UK followed up 145 survivor children, 6-7 years after being randomized to TH or otherwise, to determine their health-related quality of life (HRQL) [25]. However, no statistically significant differences were observed. A similar analysis on healthcare resource utilization and costs among 130 survivors aged 6-7 years (from the same cohort), showed lower resource utilization in the TH arm, though the differences were not statistically significant [26]. Another indirect evidence is that hypothermia for longer than 72 hours, cooling to temperature lower than 33.5°C, or both together, did not add further benefit in terms of mortality or severe disability at 18 months of age [27,28].

The second important question is, what could be the explanation for the results of this trial being remarkably different? One possible explanation is that previous trials often included neonates with mild HIE also, whereas this trial [11] included only those with moderate or severe HIE. In this context, a systematic review [29] identified 13 studies wherein almost one in six included neonates had mild HIE. On meta-analysis, about 22% of the infants who underwent TH had only mild HIE. Another systematic review also identified 117 babies with mild HIE who had been inadvertently included in 5 TH trials [30].

Another potential explanation is that, the mechanism (and consequences) of perinatal asphyxia in low-resource settings may be different from developed country settings. In this context, the trial authors [11] themselves suggested that the included babies underwent subacute, or partial prolonged hypoxia (based on MRI findings). Further, the occurrence of seizures in many infants in this trial [11] suggested intra-partum hypoxia before birth, which could reduce the neuro-protective effects of TH. There is also data that, among neonates with birth asphyxia, the presence of hyperoxemia at admission increases the risk of HIE [17]. This is referred to as the oxygen paradox, wherein excess oxygen supplementation following hypoxia worsens the outcome. In this trial [11], over 70% enrolled neonates were born at other institutions, wherein less-skilled physicians may have used excess oxygen to manage the hypoxia. One wonders whether this could be a contributing factor.

Conclusion: This very well-designed and well-executed landmark RCT confirmed that therapeutic hypothermia (for 72h) in full-term neonates having moderate or severe encephalopathy did not reduce the composite outcome of mortality or disability at the age of 18-22 mo. On the contrary, short-term, as well as long-term mortality were increased. Several other clinically important outcomes were also worse in those receiving TH, making it a harmful intervention. An urgent review of the clinical practice of offering TH is warranted at the institutional, as well as national levels.

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Neonatologist's Viewpoint

Therapeutic hypothermia (TH) is the only intervention well-proven to improve intact survival in neonates with moderate-severe hypoxic ischemic encephalopathy [1]. It is the standard of care in high income countries (HICs) and is recommended by the International Liaison Committee on Resuscitation (ILCOR) 2020 in low- and middle-income countries (LMICs), though it is a weak recommendation with low evidence [2]. A recent meta-analysis of 675 infants from 7 RCTs from LMICs showed a 50% reduction in mortality in LMICs and found higher effect size in LMICs as compared to HICs [3]. The results of the HELIX trial with 408 infants are in contradiction to this and the conclusion and the commentaries by the authors have cast a cloud on the practice of TH in LMICs [4].

The HELIX trial, an apparently well-conducted trial with excellent follow-up rates, did not find a difference in the primary outcome of disability-free survival at 18 months and has recommended to stop TH in LMICs [4]. However, there are several issues in the trial that need further clarification. The first is the case-mix. Unlike most other hypothermia trials from India, two-third of the infants were outborn who reached the cooling center at a median time of >3 hours. The screening for enrolment is unlikely to have been optimal considering that only 2296 infants were screened in 3.5 years in seven very high-volume public health facilities, where the annual NICU admission is often double this number. Further, the lack of an objective risk assessment score raises concerns that the babies in the study, particularly in the hypothermia arm, were sicker, indicating a selection bias. The complications in pregnancy and emergency cesarean section were higher in the hypothermia arm. This is especially a cause for perturbation in this study, where the authors state that "*professionals showed a strong bias towards cooling therapy*" coupled with "*parental decisions that were heavily influenced by a trust in doctors to make the right decision on their behalf"* [5].

The second issue is the fidelity to the intervention. Early initiation of cooling and the 'time to target temperature' is critical to improved outcomes. Cooling beyond 6 hours has been found to be of no benefit [6]. In fact, a recent study suggests cooling to be done before 3 hours. In the HELIX trial, the inclusion criteria states that baby should be "randomized" within 6 hours of birth and the mean randomization time is mentioned; the time to target temperature is not mentioned. Review of **Fig. 1** shows that the mean time of achieving 33.5º is 6 hours post-randomization. The mean age at admission to the cooling unit in outborn babies who constitute 2/3rd of the subjects being 3 hours suggests that most infants in the intervention arm achieved the target temperature at approximately 9 hours. This could be one major difference from other studies that have shown benefit, where the time to target temperature has been less than two hours [7,8]. The rate of rewarming was also 0.5 per hour as against the currently recommended 0.25 per hour [9].

A higher proportion of babies in the hypothermia arm were treated with inotropes, sedatives/analgesics and antibiotics [4]. Assessment of shock is a challenge during therapeutic hypothermia [10], and it is plausible that medications are confounders in this study.

The next issue is the high mortality in both arms. Of the seven centers, five centers that contributed >90% of the subjects had high regional neonatal mortality. High regional neonatal mortality, which is a reflection of the quality of care coupled with the learning curve of a new intervention, may not permit the true benefits of an intervention to surface.

This is in contrast to Indian RCTs that have reported low mortality (1.7-28%) during TH [3]. Characteristics of the HELIX hospitals with quality-of-care measures such as survival rates, shared use of thermal control device and infection control rates in the supple-mentary appendix would have helped understand the generalizability of the study. The wide variation in survival in centers across India that has been highlighted in other collaborative studies [11] and the results of the HELIX trial cannot be extrapolated to centers with low mortality rates.

It is worth noting note that the primary composite outcome of death or disability in hypothermia arm was similar to the control arm despite higher mortality, suggesting that there is indeed some benefit of hypothermia in preventing brain damage [4]. Severe disability among survivors were halved and disabling cerebral palsy was reduced by 47% [11% vs 21%; RR (95% CI) 0.53 (0.28-0.98)].

Considering the above issues, the sweeping recommendation of the authors not to offer TH in all tertiary care intensive care facilities is unfounded on evidence. However, what the HELIX trial has shown that it is not the time for all NICUs to embrace TH without setting the infrastructure, resources and quality care for safe implementation of TH. With the high burden of asphyxia-related mortality and morbidity, we need to explore and study how to make TH safe in LMICs. Collaborative efforts by hospitals that have low mortality with cooling therapy, constant vigil, a national database, benchmarking and efforts to get outborn babies early to cooling hospitals that have shown good outcomes are some of the steps way forward. I feel that it is certainly not the time to write the epitaph on cooling in LMICs.

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Pediatric Neurologist's Viewpoint

Protection of the developing brain had been the holy grail of neonatal practice over the years. The important goals of early and accurate identification of the insults to the fetal and neonatal brain, understanding the complex neurobiology of these insults and developing appropriate mitigation strategies still remain elusive. The utility of classical clinical approach is often very minimal in the newborn in view of the limited repertoire of neurological signs and symptoms [1].

Early identification and stratification of the insults to the immature brain, based on the potential for future neurodevelopmental disabilities, will help the clinicians predict the clinical and developmental outcomes much more accurately. Families too can take better learned decisions regarding the continuation of life support in the NICU. It will also help the research community to develop better targeted acute interventions for the really vulnerable babies improving the benefit: risk ratio. However, the current understanding of neonatal neurology is far from satisfactory to make such accurate assumptions. Some

general categorizations are possible based on the clinical data and investigations.

Neonatal encephalopathy at term with documented evidence for intrapartum sentinel hypoxic/ischemic events is possibly such a group. This cohort is usually much more homogenous in developed countries, where there are robust protocols for antenatal care and intrapartum monitoring. In populations with poor maternal health status, antenatal care and intrapartum monitoring, the clinical syndrome of neonatal encephalopathy might be the composite end result of multiple on going and one-time insults to the developing brain occurring throughout the antenatal and perinatal periods. Without reliable biomarkers, either imaging or biochemical, it will be difficult to stratify this cohort into much more homogenous groups.

The story of neuroprotective interventions for majority of the acquired brain insults has not been very encouraging till now. Most of the proposed ones fell by the wayside while moving from bench to the bedside, mainly due to the undesirable side effects or lack of the predicted clinical benefits [2]. However, TH for moderate/severe hypoxic ischemic encephalopathy in term newborn babies has shown to be consistently effective in reducing long term disabilities in several well-conducted trials and is currently considered the standard of care in most of the developed world [3,4]. TH has also shown to be effective in reducing the burden of neonatal seizures in this group [5].

The recently published HELIX trial [6] – a randomized controlled trial conducted in a few large public hospitals in South Asia, has raised major safety concerns for therapeutic hypothermia in LMICs. The HELIX trial data suggested that therapeutic hypothermia alongside optimal tertiary neonatal intensive care significantly increased the incidence of death relative to a control group without any reduction in brain injury on MRI or improvement in the combined outcomes of death or disability after neonatal encephalopathy [6]. There are two very important aspects here – lack of efficacy and potential for harm. The latter has much more serious implications, in view of the potentially higher risk of occurrence in routine clinical practice compared to the controlled settings of a randomized trial.

Why did the HELIX trial show a potential for serious harm? Such a serious safety signal was not apparent in any of the previous studies conducted in the developed world. The reasons might be neurobiological as the authors are trying to argue. The clinical syndrome of neonatal encephalopathy in LMICs might represent a totally different cohort compared to the developed world for the reasons described above. Moreover, there might be some inherent genetic variations affecting the suscepti-bility to hypoxic ischemic injury as well as response to cooling in this population. The pragmatic design and processes used in this trial, developed probably to suit the already existing practices in the study centers [6], might also have contributed to this outcome. However, one factor clearly emerging out of this well-conducted study is that safety margins are very narrow for the current practice of therapeutic hypothermia for neonatal encephalopathy. The tendency to offer this intervention across all settings might result in considerable harm, especially in the LMICs.

What's the way forward? We can look at the HELIX data more closely to identify any potential subgroups with higher or lower safety margins compared to the total cohort. Such an analysis might possibly give us more insights into the complex neurobiology of neonatal encephalopathy/ therapeutic hypothermia and might also help us modify the current clinical care protocols. It might also lead to further studies to identify new biomarkers and to explore better preventive and interventional strategies for neonatal encephalopathy. There is an urgent need to set up large prospective multicentric neonatal brain consortiums in the country with standardized protocols for clinical care, data capture and outcome analysis. Such an approach might possibly help us stratify neonatal encephalopathy into more homogenous groups for better targeted interventions.

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