

# Hypothermia for encephalopathy in low-income and middle-income countries: feasibility of whole-body cooling using a low-cost servo-controlled device

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## ABSTRACT

Although therapeutic hypothermia (TH) is the standard of care for hypoxic ischaemic encephalopathy in high-income countries, the safety and efficacy of this therapy in low-income and middle-income countries (LMICs) is unknown. We aimed to describe the feasibility of TH using a low-cost servo-controlled cooling device and the short-term outcomes of the cooled babies in LMIC.

**Design** We recruited babies with moderate or severe hypoxic ischaemic encephalopathy (aged <6 hours) admitted to public sector tertiary neonatal units in India over a 28-month period. We administered whole-body cooling (set core temperature 33.5°C) using a servo-controlled device for 72 hours, followed by passive rewarming. We collected the data on short-term neonatal outcomes prior to hospital discharge.

**Results** Eighty-two babies were included—61 (74%) had moderate and 21 (26%) had severe encephalopathy. Mean (SD) hypothermia cooling induction time was 1.7 hour (1.5) and the effective cooling time 95% (0.08). The mean (SD) hypothermia induction time was 1.7 hour (1.5 hour), core temperature during cooling was 33.4°C (0.2), rewarming rate was 0.34°C (0.16°C) per hour and the effective cooling time was 95% (8%). Twenty-five (51%) babies had gastric bleeds, 6 (12%) had pulmonary bleeds and 21 (27%) had meconium on delivery. Fifteen (18%) babies died before discharge from hospital. Heart rate more than 120 bpm during cooling ( $P=0.01$ ) and gastric bleeds ( $P<0.001$ ) were associated with neonatal mortality.

**Conclusions** The low-cost servo-controlled cooling device maintained the core temperature well within the target range. Adequately powered clinical trials are required to establish the safety and efficacy of TH in LMICs.

**Clinical trial registration number** NCT01760629.

## What is already known on this topic?

- ▶ Therapeutic hypothermia (TH) improves neurodevelopmental outcomes after moderate or severe neonatal encephalopathy in high-income countries.
- ▶ Core temperature needs to be maintained within a narrow target range for optimal neuroprotection.

## What this study hopes to add?

- ▶ Effective TH can be provided using a low-cost servo-controlled cooling device in low-income and middle-income countries.
- ▶ Bleeding problems, particularly gastric bleeds, frequently occur in babies with encephalopathy undergoing cooling therapy in these settings and are associated with high mortality.

Hypoxic ischaemic encephalopathy (HIE) accounts for 1 million infant deaths every year, and more than half of the surviving infants develop lifelong neurodisability.<sup>1</sup> Therapeutic hypothermia (TH) reduces mortality and improves survival with normal neurological outcome after HIE in high-income countries<sup>2–5</sup> and is now offered as standard care in these settings.<sup>6</sup>

There are several challenges in extrapolating the safety and efficacy data of cooling therapy from high-income countries to low-income and middle-income countries (LMICs), which shoulder 99% of the disease burden.<sup>1</sup>

First, the population comorbidities are very different, and there is far higher incidence of foetal growth restriction, meconium aspiration and perinatal sepsis in LMICs; these may reduce the neuroprotective effect of cooling. Second, in high-income countries, cooling is provided only in specialist cooling centres with facilities for optimal intensive care support and with high nursing to patient ratios. Such facilities and staffing resourcing levels are not available in most LMIC neonatal units. Finally, for effective neuroprotection, it is essential to rapidly reduce the core body temperature and precisely maintain this within the target range (33°C to 34°C) for 72 hours. Deviations from these regimes with overcooling or undercooling, or prolonging the duration of therapy, may be potentially harmful.<sup>7</sup> Thus, in high-income countries, TH is administered using sophisticated and expensive servo-controlled devices,<sup>8</sup> which are unaffordable in LMICs.

Despite the lack of evidence, TH is an increasingly used routine clinical practice in LMIC. A recent survey of cooling practices in India<sup>9</sup> suggested that most units offering cooling therapy use various improvised local solutions including air conditioning, ice packs and phase-changing materials to manually achieve cooling, but the efficacy of these methods is still debatable, and they may be associated with increased monitoring and staffing requirements.<sup>8</sup> Here, we report the feasibility and effectiveness of using an affordable servo-controlled system for whole-body cooling in public sector neonatal units in India and the short-term outcomes of the cooled babies.

## METHODS

We recruited term babies (aged <6 hours; birth weight  $\geq 1.8$  kg) requiring resuscitation at birth and with moderate or severe HIE, from five large public sector hospitals in India (Madras Medical College, Chennai; Indira Gandhi Institute of Child Health, Bangalore; Lokmanya Tilak Municipal General Hospital, Mumbai; Jawaharlal Nehru Institute of Postgraduate Medical Education and Research, Puducherry and Government Medical College, Calicut), between April 2013 and August 2015. These hospitals are funded by the Indian government and offer free healthcare to low-income populations. All centres are regional neonatal intensive care units with facilities for cardiorespiratory support and neonatal surgery. However, invasive blood pressure monitoring, inhaled nitric oxide and amplitude-integrated electroencephalography (aEEG) are not available. We trained the medical staff at the recruiting centres in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) neurological staging of neonatal encephalopathy (table 1) prior to the start of the study.<sup>2</sup>

We excluded babies who were born in moribund condition, as well as those who had any major life-threatening congenital malformations, or if the cooling device was not available (ie, already in use) at the time of recruitment. The University College London ethics committee

and the ethics committee of each participating hospital approved the study. We obtained informed parental consent prior to recruitment.

## Procedures

We initiated cooling by keeping the baby naked with a nappy on the cooling mattress, inserting a core temperature monitoring probe, turning off radiant warmers and switching on the machine (Tecotherm HELIX, Inspiration Healthcare) (figure 1). The device had a single set temperature of 33.5°C. Following a rapid induction phase, the device maintained core body temperature between 33°C and 34°C for 72 hours, servo-controlled to rectal or oesophageal temperature. After 72 hours of cooling, we removed the mattress and rewarmed the baby passively using three layers of clothing, without using a radiant warmer. Once the baby's temperature reached 36.5°C, we restarted the overhead radiant warmer (servo-controlled to avoid hyperthermia). We documented the vital parameters every 15 min during the first hour and then hourly until 90 hours after the start of cooling.

Clinical management protocols were unaltered by study participation. We monitored the haemogram, biochemistry, blood cultures (where available) and liver function throughout the first 4 days. We obtained antenatal and delivery data on all babies. We also collected data on medications (antibiotics, anticonvulsants, inotropes and sedatives), ventilation and the use of blood products up to hospital discharge.

## Sample size and statistical analysis

We expected the cooling device to have comparable efficacy to the standard servo-controlled cooling device used in high-income countries—that is, over 90% effective cooling time (percentage of time during which the rectal temperature is effectively within the target temperature (33°C to 34°C) during the entire cooling period).<sup>8</sup> Assuming an effective cooling time of 90%, to estimate this percentage with an uncertainty of  $\pm 7\%$  (with a 95% confidence level), 74 babies needed to be recruited. We increased the sample size to 82 to allow for a 10% rate of early mortality (prior to the completion of cooling).

The associations between clinical variables and mortality were examined. The unpaired t-test or Mann-Whitney test was used to compare the continuous variables between survivors and non-survivors, whereas Fisher's exact test was used to compare categorical variables between groups. We used IBM SPSS (V.24; IBM, New York, USA) and STATA (V.15; StataCorp, Texas, USA) for all data analysis.

## RESULTS

Out of 173 babies screened, 91 did not meet the eligibility criteria (age >6 hours; mild encephalopathy; non-availability of the device). We enrolled the remaining 82 into this study after informed parental consent (49 babies from Institute of Child Health, Madras Medical College,

**Table 1** Classification of neonatal encephalopathy (NICHD neurological examination)

Categories (total 6)	Signs of NE in each category (circle the most appropriate level)			
	Normal	Mild NE	Moderate NE	Severe NE
<b>1. Level of consciousness</b>				
	Alert, responsive to external stimuli (state dependent, eg, postfeeds)	Hyperalert, has a stare, jitteriness, high-pitched cry, exaggerated responds to minimal stimuli, inconsolable	Lethargic	Stupor/coma
<b>2. Spontaneous activity</b>				
	Changes position when awake	Normal or decreased	Decreased activity	No activity
<b>3. Posture</b>				
	Predominantly flexed when quiet	Mild flexion of distal joints (fingers, wrist usually)	Moderate flexion of distal joint, complete extension	Decerebrate
<b>4. Tone</b>				
	Strong flexor tone in all extremities+strong flexor hip tone	Normal or slightly increased peripheral tone	Hypotonia (focal or general) or hypertonia	Flaccid rigid
<b>5. Primitive reflexes (circle only the highest level in each sign; the maximum score is only one in any one category)</b>				
Suck	Strong, easily illicit	Weak, poor	Weak but has a bite	Absent
Moro	Complete	Partial response, low threshold to illicit	Incomplete	Absent
<b>6. Autonomic system (circle only the highest level in each sign; the maximum score is only one in any one category)</b>				
Pupils	In dark: 2.5–4.5 mm In light: 1.5–2.5 mm	Mydriasis	Constricted	Deviation/dilated/non-reactive to light
Heart rate	100–160 bpm	Tachycardia (HR >160)	Bradycardia (HR <100)	Variable HR
Respiration	Regular respirations	Hyperventilation (RR >60/min)	Periodic breathing	Apnoea or requires ventilator
<b>Total score</b>				
*Seizure	None	None	Yes/no	Yes/no

Infant who has seizure will be moderate or severe NE depending on the neurological exam. Seizure with normal or mild NE or moderate NE on neurological exam will be 'moderate NE'. Seizure with severe NE will be 'severe NE'. The level of encephalopathy will be assigned based on which level of signs (moderate or severe) predominates among the six categories. If moderate and severe signs are equally distributed, the designation is then based on the highest level in category no 1: the level of consciousness.

HR, heart rate; NE, neonatal encephalopathy; NICHD, National Institute of Child Health and Human Development; RR, regular respiration.

Chennai; 14 babies from Indira Gandhi Institute of Child Health, Bangalore; 10 babies from Lokmanya Tilak Municipal General Hospital, Mumbai; 9 babies from Jawaharlal Nehru Institute of Postgraduate Medical Education and Research, Puducherry). Sixty-one (74%) babies had moderate and 21 (26%) had severe encephalopathy. Fifteen (18%) babies died before discharge from hospital (5 (8%) babies with moderate encephalopathy and 10 (47%) with severe encephalopathy).

Overall, 19 (24%) babies were inborn at the recruiting centre, 57 (73%) were born at another hospital and 2 (3%) were born at home. The majority of babies (66%–85%) were born via spontaneous vaginal delivery, 8 (9.8%) via emergency caesarean section, 2 (3%) via non-emergency caesarean section and 2 (3%) via instrumental vaginal delivery. The mean (SD) maternal age was 22.8 (2.9) years, and mean gestational age was 38.7 (1.3)

weeks. Mean birth weight was 2901 (365) g and head circumference 33.7 (0.7) cm. Mean (SD) Apgar scores were 4.5 (1.3) at 5 min and 6.3 (1) at 20 min. Sixty-four babies were men (65%).

Clinical seizures were present within the first 6 hours in 68 (87%) babies. Pregnancy complications were reported in 5 (7%) cases and delivery complications in 9 (12%). Meconium stained liquor was reported in 19 (27%) babies and maternal fever during labour occurred in 3 (4%) cases. The baseline characteristics of survivors and non-survivors are given in [table 2](#).

#### Therapeutic effectiveness of the cooling device

Mean (SD) age at the start of cooling was 3.7 (1.4) hours. Target cooling temperature was achieved within 1 hour of start of cooling in 37 (45%) of the babies and within 2 hours for 63 (77%) of the babies. Three babies (4%)

## Tecotherm-Helix Set up



**Figure 1** Setting up of Tecotherm HELIX cooling device.

took more than 3 hours to reach target cooling temperature. The mean (SD) baseline temperature before start of cooling was 35.5°C (1.5), and babies took on average 1.7 hour (1.5) to reach target temperature range (defined as time at which core temperature dropped below 34°C).

During cooling treatment, mean (SD) temperature was 33.4°C (0.24), and cooling phase lasted on average 72.2 hours (2.1). Time within target core temperature (effective cooling time) of 33°C to 34°C was 95% (0.08). Passive rewarming phase lasted on average 11.3 hours

(5.8) with an average rewarming rate of 0.34°C (0.16) per hour. Of 71 babies, 35 (50%) took more than 10 hours to reach normothermia. Rectal temperature probes were used in 75 babies (91%), and oesophageal probes were used in 7 babies (9%). The effectiveness during cooling and rewarming is presented in [figure 2](#).

### Clinical status and ongoing care

The majority of babies were on intravenous (only) fluids for the first 4 days (varying from 76 (93%) on day 1 to

**Table 2** Baseline characteristics of survivors and non-survivors

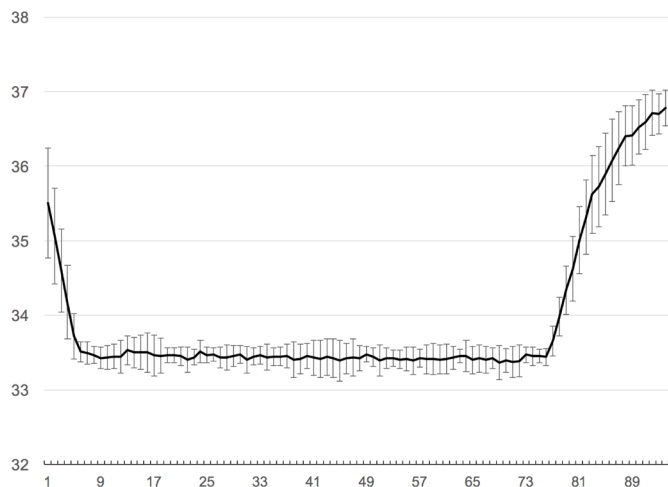
	Survivors (n=67)	Non-survivors (n=15)	P values
Maternal age (years)	22.6±3.0	24.0±1.8	0.37
Gestational age (weeks)	38.8±1.3	38.0±1.2	0.14
Age at start of cooling (hours)	3.6±1.4	4.1±1.4	0.22
Birth weight (g)	2912±364	2855±388	0.58
Head circumference (cm)	33.7±0.8	33.9±0.4	0.49
1 min Apgar— median (IQR)	1 (0)	2 (2)	0.33
5 min Apgar— median (IQR)	4 (0)	4.5 (2)	0.60
10 min Apgar— median (IQR)	5.0 (0)	5.0 (0)	0.36
20 min Apgar— median (IQR)	7.0 (0)	NA	–
Gender (male)	45/66 (68%)	8/15 (53%)	0.37
Severe encephalopathy	11/67 (16%)	10/15 (67%)	<0.001
Seizures within 6 hours of birth	55/64 (86%)	13/14 (93%)	0.68
Complications in pregnancy	4/64 (6%)	1/12 (8%)	1.00
Complications during delivery	9/64 (14%)	0/13 (0%)	0.34
Meconium stained liquor	13/60 (22%)	6/11 (55%)	0.06
Maternal fever during labour	2/64 (3%)	1/13 (8%)	0.43
Place of delivery			
Inborn	15/65 (23%)	4/13 (31%)	
Outborn— hospital	48/65 (74%)	9/13 (69%)	0.81
Outborn— home	2/65 (3%)	0/13 (0%)	
Delivery method			
Prelabour LSCS	2/65 (3%)	0/13 (0%)	
Emergency LSCS	6/65 (9%)	2/13 (15%)	0.82
Spontaneous vaginal delivery	55/65 (85%)	13/13 (85%)	
Instrumental vaginal delivery	2/65 (3%)	0/13 (0%)	
Neonatal complications			
Gastric bleeds	14/38 (37%)	11/11 (100%)	<0.001
Pulmonary haemorrhage	1/38 (3%)	5/11 (45%)	0.001
PPHN	1/38 (3%)	6/11 (55%)	<0.001
Thrombocytopenia	42/67 (63%)	10/15 (67%)	1.00
Metabolic acidosis	26/67 (39%)	9/15 (60%)	0.16
Treatment duration (days)			
Invasive ventilation	1.4±1.8	3.3±1.5	0.002
Sedation	0.9±1.5	1.4±1.8	0.40
Inotropic support	3.1±1.3	3.9±0.3	0.04
Anticonvulsive drugs	2.9±1.7	3.9±0.3	0.07

LSCS, lower segment caesarean section; PPHN, persistent pulmonary hypertension. Mean values ± SD or proportion (percentage), unless specified otherwise.

54 (66%) on day 4). Three babies (4%) received enteral feeds via nasogastric tube on day 1 and, by day 4, there were 2 (2%) babies on full nasogastric feeds and 17 (21%) receiving a combination of intravenous plus nasogastric intake.

Thirty-seven babies (46%) required invasive ventilation during the first 24 hours. Most babies required treatment

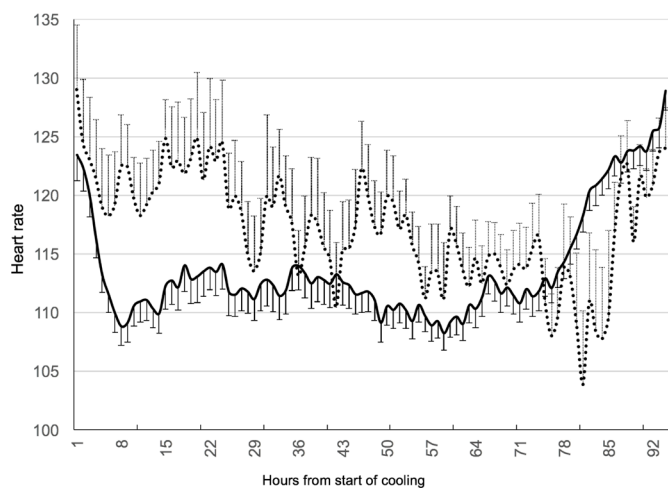
with anticonvulsive drugs (59 (77%) on day 1 to 52 (72%) on day 4), using mainly phenobarbitone (53% on day 1 to 64% of the babies on day 4) or multiple drugs (13% to 18% of the babies). Sixty-three (82%) babies required some inotropic support on day 1, decreasing to 48 babies (68%) on day 4. Main inotropes used were a combination of dopamine and dobutamine. Requirement of



**Figure 2** Mean (SD—error bars) temperature during cooling and rewarming.

inotropic support during the first 4 days was higher for non-survivors (mean 3.9 days vs 3.0 days,  $P=0.000$ , 95% CI  $(-1.64$  to  $-0.3)$ ), but only 25% (12/48) of babies requiring inotropic support on day 4 died. Sedation was used in 22 (37%) babies. This corresponded to 14 (19%), 18 (25%), 17 (24%) and 18 (26%) between days 1 and 4, respectively). When using sedation, choral hydrate and fentanyl were the preferred sedatives (53% and 41%, respectively).

The mean (SD) heart rate of the babies who died was 121 bpm (17 bpm), which was higher than those who survived, who had a mean (SD) heart rate of 111 bpm (13 bpm) ( $P=0.008$ ) (figure 2). The babies who died were more likely to have a heart rate higher than 120 bpm (93% vs 51%;  $P=0.005$ ) and more persistently elevated heart rate ( $>120$  bpm) (median of 5 hours compared with a median of 1 hour) than those who survived ( $P=0.01$ ). Duration of heart rate above 120 bpm did not appear to be associated with sedation or sedation days, neither did



**Figure 3** Mean (SD—error bars) heart rate (bpm) during cooling and rewarming. The dotted line represents non-survivors, and the continuous line represents survivors.

sedation (lack of) seem to be associated with mortality. Figure 3 presents the average heart rate during treatment.

Only one baby had hypoglycaemia (blood sugar level below 45 mg/dL (2.5 mmol/L)), which occurred on day 1. Metabolic acidosis (absolute base excess  $<-10$ ) persisted for more than 24 hours in 4 (13%) babies. Fifty-two babies (64%) had thrombocytopenia (platelet count below  $100 \times 10^9/L$ ). C reactive protein was available only for 20 babies, and the mean (SD) on days 1 to 4 were 4.8 (3.0), 8.4 (12.8), 22.9 (22.1) and 48.6 (62.7), respectively. There was no growth in any of the 49 blood cultures (automated) obtained at the time of recruiting.

Gastric bleed (defined as fresh blood  $>5$  mL from nasogastric tube) was recorded in 25/49 (51%) and pulmonary haemorrhage (defined as copious bloody secretions with clinical deterioration requiring change(s) in ventilatory management) in 6/49 (12%) of the babies (table 3). There was no significant difference between those with and without gastric bleeds for any of birth weight, sedation or severity of encephalopathy. However, there was a highly significant association between gastric bleeds and mortality. No patients without gastric bleeds died, whereas almost half (44%) of patients with a gastric bleed died. The bleeds were treated with blood product transfusions (fresh frozen plasma, packed cell transfusions and platelets).

Persistent pulmonary hypertension (defined as severe hypoxaemia disproportionate to the severity of lung disease with a significant pre–postductal saturation difference on pulse oximetry) occurred in 7/49 (14%) of the babies. Persistent pulmonary hypertension was managed by vasopressors and by optimising conventional ventilation. Inhaled nitric oxide was not available.

## DISCUSSION

The data presented here have several important messages for the clinicians in LMICs and will inform the design of future cooling trials in these settings. First, TH can be effectively delivered using a low-cost servo-controlled whole-body cooling device without the need for additional nursing resources. Whereas concerns about the loss of therapeutic effectiveness and increased workload associated with high oscillations during manual cooling have been described previously,<sup>8</sup> the effective cooling times achieved in our study were reassuring that a low-cost servo-controlled cooling device may offer a promising alternative. In addition, a high thermal efficacy and stability of the device used in this study suggests that this method may not only hold better therapeutic effect but also sustain or even reduce staff demand. As the study used a pragmatic approach, the treatment requirements and decisions were continued from what had been locally practised until the study. Although we have not formally collected feedback from staff on the challenges of delivering TH, we observed a fast-paced learning curve which was facilitated by the ease of operation of a simplified

**Table 3** Comparison of babies with encephalopathy with and without gastric bleeds

Variable	No gastric bleed		Gastric bleed		P values	Mean/proportion difference (95% CIs)
	n	Summary	n	Summary		
Mean (SD) birth weight (g)	24	2925±249	25	2967±386	0.66	42 (228 to -146)
Sedation during cooling	19	4 (21%)	18	5 (28%)	0.71	7% (-20% to 33%)
Mortality	24	0 (0%)	25	11 (44%)	<0.001	44% (22% to 63%)

equipment, suggesting there was no increase in the required intensity of care.

Our servo-controlled device is based on Tecotherm-Neo, a widely used whole-body cooling device in high-income countries. Although the device has similar safety features, cost reduction was achieved by simplifying the design with a single set target temperature of 33.5°C. The coolant was tap water, mixed with locally available surgical spirit (90% alcohol). The device lacked a rewarming mode, hence the rewarming was passive by removing the baby from the cooling mattress. This increased the rewarming duration and the variability of core temperature during rewarming. The device has been modified to include a constant rewarming since then and is currently being CE (Conformité Européene) marked. It is likely that the eventual costs (approximately US\$1000) of this device would be one-tenth of high-income country cooling devices.

Second, the short clinical term morbidity of babies with encephalopathy in this setting was different to high-income countries. There was a very high incidence of gastric bleeds (25/49, 51%), although we did not have data on gastric bleeds for all the participants and we had data for more non-survivors than survivors. The reason for gastric bleeds is unclear, and none of the babies had evidence of perforation or necrotising enterocolitis. It is possible that the bleeds were multiple in utero ischaemic events; however, no relation with birth weight and gastric bleed was seen on regression model. There was no relation of sedation and gastric bleeds indicating that stress of cooling was an unlikely contributor to these bleeds.

Coagulopathy is a well-known complication of hypoxic ischaemic encephalopathy, and gastrointestinal bleeding has been reported in up to 25% of the babies undergoing TH in high-income countries.<sup>10 11</sup> Cooling studies from LMICs have not yet reported such bleeds as yet. In these settings, it is possible that gastric bleeds were not specifically looked for or recorded in the case record forms and hence were overlooked. The incidence of pulmonary bleed was also much higher than the published data from high-income countries.<sup>12</sup>

We also observed a persistently higher heart rate above 120 bpm during cooling in non-survivors, which was independent of sedative use. Association of tachycardia during cooling and increased mortality in neonatal encephalopathy has been reported previously.<sup>13</sup> It is possible that this elevated heart rate is a reflection of the underlying disease severity and cardiac dysfunction.

There are several limitations of this feasibility study. We were unable to perform autopsy in any of the babies due to a lack of parental consent and, hence, were unable to find the cause of the gastric bleeds. As there was no control arm, it is unclear if the gastric bleeds were related to the underlying condition or to the cooling therapy. Although blood cultures were obtained, we have not performed detailed screening for infection using polymerase chain reaction methods, and hence we might have missed co-existent sepsis. Finally, we have not performed any neuro-imaging or assessed the neurodevelopmental outcomes.

A number of small randomised controlled trials of cooling therapy have been reported from LMIC. The pooled data from these studies do not suggest an improvement in neonatal mortality.<sup>14</sup> Only one of these studies had reported neurodevelopment outcomes at 18 months or more, and the authors claimed that cooling significantly reduced death and neurodisability.<sup>15</sup> An indigenous (China) servo-controlled head cooling device was used in this study. This study was of poor quality, and relevance of the findings remains unclear. Since then, one more pilot randomised control involving 60 encephalopathy babies (30 each allocated to cooling and usual care) from India has been reported. Authors claimed adverse outcomes (death or neurodisability at 30 months) in 6/30 (20%) of cooled babies and 18/30 (60%) of usual care babies (P=0.0015). Adverse outcomes related to cooling were minimal. Selective head cooling was attempted using ice in this study, which had been previously shown to be unreliable in administering effective TH.<sup>16</sup> Hence, it is unclear if any survival benefits in this study were related to the intervention.

Most studies in LMICs have used water bottles, ice or frozen gels pack to induce TH.<sup>17-22</sup> While such manual methods are suitable and safe when there is close nursing monitoring to ensure that core temperature is maintained in the target range,<sup>23</sup> most LMIC neonatal units do not have adequate nursing resources. We have previously reported the use of phase change material for TH in India.<sup>24</sup> Given that the phase change materials are inexpensive (US\$20) and widely available, cooling devices can be easily developed from these. However, in our experience, the cooling efficacy of phase change materials was weak and required low ambient temperatures to induce cooling, which limits the wider use.<sup>24</sup> Nevertheless, cooling devices using phase change material is now commercially marketed in India, and several centres are using these devices.<sup>25</sup>

Considering the differences in comorbidities, maternal ill health and healthcare resources in LMICs, adequately powered and designed clinical trials are required to answer the question of whether TH is safe and beneficial for babies with moderate or severe encephalopathy in these settings.<sup>7</sup> Despite the lack of evidence, many centres in India and other LMICs are now routinely offering cooling therapy to babies with neonatal encephalopathy using a wide range of indigenous cooling devices.<sup>9</sup>

The data presented in this feasibility study will inform the study design of future cooling trials in LMIC. Our inclusion criteria were purely clinical so as to increase the generalisability of the therapy in LMIC, where blood gas and aEEG are not routinely available. A large pragmatic trial of hypothermia for neonatal encephalopathy is currently underway in India, Bangladesh and Sri Lanka.<sup>26</sup> A total of 408 babies with moderate and severe encephalopathy will be randomised to whole-body cooling using a servo-controlled cooling device or usual care. All babies have detailed infection screen and 3 Tesla MRI and spectroscopy in addition to detailed neurodevelopmental assessment at 18 months. The study protocol of the HELIX trial is available online and may be useful for clinicians in LMIC who wish to offer TH in these settings.

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**Contributors** VO analysed and interpreted the data and wrote the initial drafts of the manuscript. KK, NE, MS and KC assisted in the study design and supervised the recruitment and data collection in Chennai. JS, NB and PBan led the recruitment at Bangalore. MC and RS assisted in the data collection and interpretation of data. JMo, KD and SM assisted in the study design and supervised the recruitment and data collection in Mumbai. SB and VM assisted in the study design and supervised the recruitment and data collection in Pondicherry. VM and MN assisted in the study design and supervised the recruitment and data collection in Calicut. P.J.L., PM, GA and JMe assisted in the data interpretation and preparation of the manuscript. PM undertook the statistical analysis. SR, SS and ST (chief investigator) conceived the idea, designed the study and interpreted the data. All authors contributed to the development of the manuscript and approved the final version for publication.

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