Narrative review

Neuroprotective strategies of neonatal encephalopathy in low-resource settings

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Abstract

Objective: Perinatal asphyxia followed by hypoxic ischemic encephalopathy is a major contributor to neonatal death. In high-income countries therapeutic hypothermia is the standard of care. However, safety and efficacy of cooling have not been proven in low- and middle income countries, who bear most of the burden of neonatal encephalopathy. This article reviews the entry criteria of cooling in developing countries and the feasibility, safety and efficacy of different low-cost cooling techniques. Furthermore, we discuss whether other neuroprotective therapies could be used.

Methods: We searched in PubMed and other databases for studies regarding entry criteria, low-cost cooling techniques and other neuroprotective therapies for neonatal encephalopathy in low- and middle income countries.

Results: A 5-minute Apgar score less than six and a Thompson score more than six are useful entry criteria for cooling in low-resource settings. Effective cooling was feasible with different low-cost cooling techniques, but a servo-controlled device maintained the most stable temperature profile and seems to be the most safe and easiest to use device. Only a few studies were powered to assess efficacy. None of the studies could show a significant decrease in mortality rate. When the rate of death and developmental delay were combined, they could notice a significant decrease in the hypothermia group. A promising drug to provide neuroprotection in low-resource settings is 2-iminobiotin.

Conclusions: To assess safety and efficacy of therapeutic hypothermia and other neuroprotective drugs in low-resource settings we need more adequately powered clinical trials.

Introduction

Globally, progress has been made in reducing under-five mortality, but the decline in neonatal mortality stays much more behind (1). One of the major causes of neonatal death is perinatal asphyxia followed by hypoxic ischemic encephalopathy (HIE) (2). Therapeutic hypothermia reduces mortality and neurodevelopmental disability after neonatal encephalopathy and is now widely used as standard treatment in high income countries (HIC) (3-5). It is still unknown if cooling would also benefit neonates in low- and middle income countries (LMIC), where the burden of neonatal encephalopathy is about ten times higher (6,7). A systematic review of Pauliah et al. could not show the same significant reduction in neonatal mortality in LMIC as seen in HIC (8). This absence of treatment effect may be due to heterogeneity and poor design of the included studies, inefficiency of low-cost cooling techniques, lack of adequate neonatal intensive care or differences in study populations.

It is therefore important to investigate these different possibilities. Firstly, we identified which entry criteria for hypothermia could be useful in low resource settings. Secondly, we will summarize which low-cost cooling techniques do exist, whether it is feasible to provide accurate cooling with these techniques and whether they are safe and effective. Furthermore, it is also of interest whether other neuroprotective therapies could be used in LMIC. Last, it must be said that prevention still remains the key stone in perinatal asphyxia.

Materials and methods

We searched for relevant literature in medical databases PubMed, Embase, Cochrane and Trip Database. We used the following search terms: infant, newborn, neonate, hypoxia-ischemia, encephalopathy, hypothermia, developing countries, low- and middle income countries. We analysed the literature published before February 2021 and selected relevant literature based on title and abstract. In addition, we searched in the reference list of the selected articles to identify other possible relevant studies. We used the following inclusion criteria: (1) patients are term or near-term infants with perinatal asphyxia followed by HIE born in LMIC (2) intervention with hypothermia (3) outcomes regarding feasibility, adverse effects and/or mortality. A second type of literature that was searched for were articles regarding possible entry criteria for initiation of hypothermia in low-income countries. Thirdly, we searched for relevant literature regarding neuroprotective therapies other than hypothermia.

Results

Literature search

A total of thirteen studies were selected after applying our inclusion criteria. In addition, we included one thesis research. Characteristics of the included studies are shown in Table 1 (9-22).

Entry criteria in LMIC

Perinatal asphyxia and subsequently the presence of encephalopathy are evaluated to see if infants are eligible for hypothermia. Perinatal asphyxia is mostly defined by a 5-minute Apgar score less than six or the need for ventilation for at least ten minutes. To assess neonatal encephalopathy the Thompson score (Table 2) is more usable in developing countries compared to the Sarnat grading system (Table 3) (23-24). It is a quick and simple clinical grading method that requires no comprehensive training and no specific equipment. A study from Horn et al. showed that a Thompson score of more than six is a sensitive predictor of an abnormal 6-hour aEEG (amplitude integrated electroencephalography) or a moderate-severe encephalopathy (25). Biselele et al. stated that the timing of scoring is also important because it changes during the first six hours after birth. They concluded that more newborns will be eligible for hypothermia if Thompson scoring is done within the first three hours (26).

Secondly, it is of great importance to initiate cooling within six hours of birth. In low-resource settings this time frame may have been passed before hypothermia could be started (27). A study in Congo showed that more than

Table 1: Characteristics of the included studies.

Author, year	Country	Sample size	Cooling method	Inclusion criteria	Exclusion criteria
Robertson et al., 2008 (9)	Uganda (LIC)	21 HT 15 ST	Water bottles	- Gestational age ±37 weeks - 5 min Apgar <6 and/or need for resuscitation - Encephalopathy: Thompson score >5	- Apnea or cyanosis - Absent cardiac output >10 min after birth - Birthweight <2kg
Thomas et al., 2011 (10)	India (LMIC)	20	Ice packs	- Gestational age ±35 weeks - 5 min Apgar ≤5, need for ventilation ±10 min or perinatal predisposition to perinatal asphyxia and cord or postnatal blood gas pH <7 or base deficit ±12 - Encephalopathy (modified Sarnat criteria)	- Small for gestational age - Chromosomal or major congenital anomaly - Severely asphyxiated infants
Bharadwaj et al., 2012 (11)	India (LMIC)	62 HT 62 ST	Ice packs	- Gestational age >37 weeks - 10 min Apgar ≤6, need for ventilation ±10 min, fetal distress, organ dysfunction, history of acute perinatal event and arterial blood gas pH ≤7 or base deficit ±12 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Major congenital anomaly - No spontaneous respiration by 20 min after birth - Outborn
Joy et al., 2013 (12)	India (LMIC)	58 HT 58 ST	Ice packs	- Gestational age ±37 weeks - 10 min Apgar ≤5, need for ventilation ±10 min, fetal distress, organ dysfunction, history of acute perinatal event and cord of peripheral blood gas pH ≤7 or base deficit ±12 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Major congenital anomaly - No spontaneous respiration by 20 min after birth - Outborn
Gane et al., 2014 (13)	India (LMIC)	60 HT 60 ST	Ice packs	- Gestational age ±37 weeks - 10 min Apgar ≤5, need for ventilation ±10 min, fetal distress, organ dysfunction and cord of arterial blood gas pH ≤7 or base deficit ±16 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Major congenital anomaly - No spontaneous respiration by 20 min after birth
Thayyil et al., 2013 (14)	India (LMIC)	33	Phase changing materials	- 5 min Apgar <6 - Encephalopathy: Thompson score >5	
Thomas et al., 2015 (15)	India (LMIC)	41	Phase changing materials	- Gestational age >35 weeks - 5 min Apgar <5, need for ventilation >10 min, cord or postnatal blood gas pH <7 or base deficit >12 - Moderate or severe encephalopathy (modified Sarnat criteria)	
Thomas et al, 2018 (16)	India (LMIC)	103	Phase changing materials	- Gestational age ±35 weeks - Birth weight ±1800 grams - 5 min Apgar <5, need for resuscitation >10 min or cord blood pH <7.0 or base deficit >12 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Chromosomal disorder - Major congenital anomaly
Prashantha et al., 2018 (17)	India (LMIC)	33 PCM 29 IP	Phase changing materials and ice packs	- Gestational age ±35 weeks - Birth weight > 1800 grams - 5 min Apgar ≤5, need for ventilation ±10 min or pH ≤7 or base deficit ±12, - Moderate or severe encephalopathy (modified Sarnat criteria)	
Catherine et al., 2021 (18)	India (LMIC)	78 HT 84 ST	Phase changing materials	- Term infants - 10 min Apgar ≤6, need for ventilation ±10 min, fetal distress or organ dysfunction and cord blood pH ≤7 or base deficit ±12 - Moderate or severe encephalopathy (modified Sarnat criteria)	- Major congenital anomaly - No spontaneous respiration by 20 min after birth
Biselele et al., 2014 (19)	DR Congo (LIC)	12	Servo-controlled device	- Gestational age ±36 weeks - 5 min Apgar ≤5 or need for ventilation ±10 min - Encephalopathy: Thompson score ±7	- Congenital malformations - Birth weight < 2000 grams - Symptomatic infection
Oliveira et al., 2018 (20)	India (LMIC)	82	Servo-controlled device	- Birth weight ±1800 grams - Requirement of resuscitation at birth - Moderate or severe encephalopathy (modified Sarnat criteria)	- Born in moribund conditions - Major life-threatening congenital malformations
Enweronu et al., 2019 (21)	Ghana (LMIC)	13	Passive cooling	- Gestational age ±36 weeks - Birth weight ±2000 grams - Postnatal age <24h - 5 min Apgar <6 and need for resuscitation - Encephalopathy: Thompson score ±7 or suspected clinical seizures	- Infants in whom death was felt imminent and infants with major congenital malformations were excluded
Bhat et al., 2006 (22)	India (LMIC)	20 HT 15 ST	Not described	- Severe perinatal asphyxia	

LIC: low income country, LMIC: lower-middle income country, HT: hypothermia, ST: standard therapy, PCM: phase changing materials, IP: ice packs

40% of infants with HIE were inborn or reached the hospital within 6 hours to receive neuroprotective treatment (28). The mean time until admission to the neonatal unit was 1.3±0.2h for the inborn neonates and 2.5±0.3h for the outborn neonates. Thomas et al. reported cooling of inborn and outborn neonates starting at a mean time of respectively 3±1h and 3.5±1h after birth (10). In four other included studies, cooling was started at a mean age of 3.6h, 3.2h, 3.7h and 3.9h (11,13,19,20).

Exclusion criteria are listed in Table 1. Only one study excluded infants with a symptomatic infection (19). It remains unwritten whether a very high Thompson score could be used as an exclusion item. Biselele et al. reported that all neonates with Thompson score of more than 15 died (28). In a study of Horn et al. 75% of the infants with this score died within the first days or had a severely aberrant aEEG (25).

Feasibility of low-cost cooling methods

Different low-cost cooling devices are used for therapeutic hypothermia in studies of LMIC (Figure 1). Feasibility outcomes of the included studies are listed in Table 4.

1. Passive cooling

Passive cooling is a physiological response seen in infants with neonatal encephalopathy and was recently investigated in a Ghanaian study (29,21). Core temperatures between 33-34°C were only maintained in 18±14% of the time during 72h (21). In 71±22% of the time they recorded temperatures above 34°C and excessive cooling with temperatures less than 33°C was seen 11±18% of the time.

2. Water bottles

A feasibility study in Uganda by Robertson et al. used a mattress made of three water bottles filled with cool tap water (25-26°C) (9). To maintain the core temperature between 33-34°C they added or removed sheets, blankets or water bottles. With this simple and inexpensive method (US$10) infants underwent whole-body cooling during 72h. In comparison they also documented to what degree infants with neonatal encephalopathy cool passively. The mean rectal temperature was 33.6±0.69°C in the infants cooled with water bottles and 36.3±0.64°C in the passively cooled infants. Close nursing monitoring was required and water bottles needed to be changed every 8-12h.

3. Ice packs

Two feasibility studies in India worked with cloth covered ice gel packs to achieve hypothermia (10,11). Gel packs were placed over the back, head, abdomen and axillae and could be added or removed when the rectal temperature changed. The packs were obtained from an immunization clinic at no added cost and could be reused. The mean time taken to reach the target temperature was 52±25 minutes in Thomas et al. and 120 min in Bharadwaj et al. During cooling they registered a mean rectal temperature of respectively 32.9±0.11°C and 33.7±1.02°C. The study of Gane et al. also used ice packs and temperature fluctuation above and under 33.5°C was 0.8°C (13). On an average, this technique required four gel packs per infant and packs had to be changed every 3-4h. Furthermore, one nurse was needed for three infants.

4. Phase changing materials (PCM)

Four of the included studies involved the feasibility of whole-body cooling using phase changing materials. When an infant lies on a bed made of PCM, heat is absorbed from the infant and transferred to the materials until it reaches its melting point. A bed made of PCM approximately costs 40 euros and can be reused for at least twenty infants. With this method two studies of Thomas et al. reached the target temperature in 60 and 90 minutes (15,16). The mean rectal temperature during 72h of cooling was 33.44±0.26°C in the study of 2015 and 33.5±0.39°C in the one of 2018. The target temperature was maintained 96.2% and 89.2% of the time, respectively. In Thayyil et al. the median time to reach the target temperature was 30 minutes and mean rectal temperature was 33.5±0.3°C (14). Prashantha et al. compared PCM with ice packs and documented a median time to reach the target temperature of respectively 30 and 35 minutes and a mean core temperature of 33.47±0.33°C and 33.44±0.34°C (17). This technique did not require frequent changes, but nurses still needed to intensively monitor the temperature.

5. Servo-controlled devices

In an Indian study by Oliveira et al. they used a simplified servo-controlled device based on a model used in high-income countries to provide whole-body cooling (20). The cooling device was set at a target temperature of 33,5°C. By simplifying the design costs could be reduced to approximately US$1000. A temperature between 33-34°C was reached after 102 minutes and could be maintained in 95% of the time. Mean core temperature was 33.4±0.2°C. In the Democratic Republic of Congo Biselele et al. used refrigerated gel bags or neofan in combination with a servo-controlled radiant warmer (19). It took 62 minutes to reach a temperature of 33-34°C. The mean core temperature during 72h was 33.76±0.28°C. A servo-controlled device omits the need for manual adjustments, but nurses still need to closely monitor the temperature.

Adverse events

In addition to the feasibility of low-cost cooling devices, we also need to consider their safety. The reported adverse events including their proportions are summarized in Table 5. The most frequent adverse events were thrombocytopenia, sinus bradycardia, coagulopathy, sepsis, shock/hypotension, hypoglycemia and skin changes. The percentage of skin changes was higher when using ice packs as compared to using PCM (17). Only a few of the included studies had a control arm to compare adverse events between therapeutic hypothermia and standard therapy in LMIC. Robertson et al. documented more seizures in the hypothermia group, but seizures cannot be attributed as a complication of cooling (9). Of the 33 infants participating in the study of Thayyil et al. 3 of the cooled infants developed sepsis, but no one in the control arm did (14). When comparing ice gel packs with standard care Bharadwaj et al. and Joy et al. did not find significant differences in adverse events (11-12).

Table 2: Thompson score.

	0	1	2	3
Tone	Normal	Hypertonia	Hypotonia	Flaccid
Level of consciousness	Normal	Hyperalert, stare	Lethargic	Comatose
Fits	None	< 3/day	>2/day	
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent ± bites	
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)
Fontanel	Normal	Full, not tense	Tense	

Table 3: Sarnat grading system.

	Stage 1 (mild)	Stage 2 (moderate)	Stage 3 (severe)
Level of consciousness	Hyperalert	Lethargic/obtunded	Stuporous
Muscular tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch	Overactive	Overactive	Decreased/absent
Segmental myoclonus	Present	Present	Absent
Suck	Weak	Weak/absent	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	Overactive	Weak/absent
Tonic neck	Slight	Strong	Absent
Pupils	Mydriasis	Miosis	Variable
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial/salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal/decreased	Increased/diarrhea	Variable
Seizures	None	Common/focal or multifocal	Uncommon
EEG	Normal/decreased	Early low voltage continuous delta and theta, later periodic, seizures focal 1-1.5 Hz spike-wave	Early periodic pattern with isopotential phases, later isopotential
Duration	<24 h	2-14 days	Hours-weeks

Table 4: Feasibility outcomes of the included studies.

Author, year	Cooling method	Mean age at start	Mean time to reach target T°	Mean rectal T°	Maintaining target T° during 72h
Robertson et al., 2008 (9)	Water bottles			33,6±0.69°C (HT) 36,3±0.64°C (ST)	
Thomas et al., 2011 (10)	Ice packs	3.4h	52 min	32.9±0.11°C	
Bharadwaj et al., 2012 (11)	Ice packs	3.6h	120 min	33.7±1.02°C	
Gane et al., 2014 (13)	Ice packs	3.2h		33.5±0.8°C	
Thayyil et al., 2013 (14)	Phase changing materials		30 min	33.5±0.3°C (HT) 36.4±0.5°C (ST)	
Thomas et al., 2015 (15)	Phase changing materials		60 min	33.44±0.26°C	96.2%
Thomas et al, 2018 (16)	Phase changing materials		90 min	33.5±0.39°C	89.2%
Prashantha et al., 2018 (17)	Phase changing materials and ice packs		30 min (PCM) 35 min (IP)	33.47±0,33°C (PCM) 33.44±0.34°C (IP)	
Biselele et al., 2014 (19)	Servo-controlled device	3.9h	62 min	33.76±0.28°C	
Oliveira et al., 2018 (20)	Servo-controlled device	3.7h	102 min	33.4±0.2°C	95%
Enweronu et al., 2019 (21)	Passive cooling			35.0±1.0°C	18±14%

T°: temperature, HT: hypothermia, ST: standard therapy, PCM: phase changing materials, IP: ice packs

Mortality and developmental delay

The mortality rate and neurological outcomes documented in our studies are listed in Table 6. Only three of the included studies had an adequate sample size and a control arm to evaluate the efficacy of therapeutic hypothermia in LMIC (11,12,18). The mortality rate in all of the three studies was lower in the hypothermia group compared to the group with standard care, but none of the results were significant. In the studies of Bharadway et al. and Joy et al. neurological status at discharge was significantly better in the hypothermia group (11-12). Catherine et al. also showed a small but not significant reduction in neurological abnormality (18).

Neurodevelopmental assessment at 6, 12 and 18 months was done by respectively Bharadwaj et al., Gane et al. and Catherine et al. (Table 7) (11,13,18). They could all show significantly less neurological abnormality in the hypothermia group. The number of deaths at follow-up was again lower, but not significant, when infants were cooled. When they combined the rate of death and neurological outcome at 12 months of age Gane et al. noticed a significant decrease that favours cooling (95% CI 0.18-0.68) (13). When the studies of Bharadwaj et al. and Catherine et al. combined their results there were also significantly more survivors without neurological abnormality at discharge (95% CI 1.18-1.88) and at 6-18 months (95% CI 1.17-1.60) when infants were cooled in comparison with standard care (18).

Other neuroprotective therapies

The neuroprotective effect of various drug therapies has been investigated in in-vitro and animal models as well as clinical trials (30-32). Suggested drugs like xenon and erythropoietin are not affordable in LMIC. Xenon, erythropoietin, magnesium and allopurinol are also given on top of hypothermia, making them no better option for use in LMIC. More promising drugs are melatonin and 2-iminobiotin. The neuroprotective effect of melatonin has been documented

Table 5: Adverse effects reported in the included studies.

Author, year	*Cooling method*	*Adverse events*
Robertson et al., 2008 (9)	Water bottles	- seizures (28% HT, 13% ST)
Thomas et al., 2011 (10)	Ice packs	- thrombocytopenia (25%) - sinus bradycardia (25%) - deranged bleeding parameters (20%) - aposteatonecrosis (15%) - hyperglycemia (15%) - hypoglycemia (10%) - hypoxemia (5%) - life-threatening coagulopathy (5%) - many of the infants shivered
Bharadwaj et al., 2012 (11)	Ice packs	- thrombocytopenia (12.9% HT, 8.06% ST) - sepsis (11.3% HT, 9.7% ST) - pneumonia (9.7% HT, 17.2% ST) - hypoglycemia (9.6% HT, 12.9% ST) - shock (8.1% HT, 14.5% ST) - hypocalcemia (6.45% HT, 12.9% ST) - bleeding (6.45% HT, 4.8% ST) - skin changes (6.45% HT, 0 ST) - pulmonary haemorrhage and hypertension (1.6% HT, 4.8% ST) - acute renal failure (1.6% HT, 3.2% ST) - necrotizing enterocolitis (1.6% HT, 1.6% ST) - arrhythmia (1.6% HT, 0 ST)
Joy et al., 2013 (12)	Ice packs	- shock (12.06% HT, 13.79% ST) - hypoglycemia (10.34% HT, 13.79% ST) - bleeding (6.89% HT, 8.62% ST) - bradycardia (3.45% HT, 0 ST)
Thayyil et al., 2013 (14)	Phase changing materials	- sepsis (18% HT, 0 ST) - seizures (47% HT, 44% ST)
Thomas et al., 2015 (15)	Phase changing materials	- subcutaneous fat necrosis (2.4%)
Thomas et al, 2018 (16)	Phase changing materials	- coagulopathy (21.4%) - sepsis (20.4%) - shock/hypotension (18%) - thrombocytopenia (10.7%) - hyperglycemia (8.7%) - hyponatremia, hyperkalemia (5.8%) - hypoglycemia (6.8%) - persistent pulmonary hypertension (4.9%) - subcutaneous fat necrosis (2.9%) - bleeding (1.9%) - leukopenia (1.9%) - arrythmia (1.9%) - acute kidney injury (1%)
Prashantha et al., 2018 (17)	Phase changing materials and ice packs	- thrombocytopenia (51.5% PCM, 51.7% IP) - shock (45.4% PCM, 48.2% IP) - seizures (42.4% PCM, 58.6% IP) - bradycardia (33.3% PCM, 31% IP) - coagulopathy (33.3% PCM, 27.5% IP) - hyponatremia (27.3% PCM, 34.4% IP) - hypoglycemia (24.4% PCM, 37.9% IP) - hyperbilirubinemia (21.2% PCM, 13.7% IP) - hypocalcemia (15% PCM, 6.9% IP) - anemia (12.1% PCM, 24% IP) - hyperglycemia (12.1% PCM, 24% IP) - acute kidney injury (12.1% PCM, 10.3% IP) - persistent pulmonary hypertension (9.1% PCM, 6.9% IP) - bleeding (9% PCM, 13.7% IP) - skin changes (6% PCM, 20.6% IP) - sepsis (0 PCM, 6.9% IP) - cardiac arrhythmia (0 PCM, 3.4% IP) - gangrene of the hand (0 PCM, 3.4% IP)
Biselele et al., 2014 (19)	Servo-controlled device	- shivering (16.7%) - subcutaneous fat necrosis (8.3%)
Oliveira et al., 2018 (20)	Servo-controlled device	- thrombocytopenia (64%) - gastric bleeds (51%) - persistent pulmonary hypertension (14%) - metabolic acidosis (13%) - pulmonary bleeds (12%) - hypoglycemia (1.2%)

HT: hypothermia, ST: standard therapy, PCM: phase changing materials, IP: ice packs

in a few animal studies (33-35). One small clinical trial investigated oral administration of melatonin without additional hypothermia after asphyxia and showed promising results (36). Neuroprotective effects of 2-iminobiotin have also been shown in animal models (37-38). Currently, a Congolese trial is investigating the safety as well as the efficacy of 2-iminobiotin in neonates with moderate to severe perinatal asphyxia born in Kinshasa (39). To date, they could not attribute any of the adverse events to the administration of 2-iminobiotin (40).

Discussion

Perinatal asphyxia followed by hypoxic ischemic encephalopathy is a major contributor to neonatal death (1,2). In high-income countries therapeutic hypothermia has become the standard treatment for HIE, however in low- and middle income countries efficacy and safety of hypothermia have not been proven (8). Since most of the burden of neonatal encephalopathy occurs in LMIC, it is essential to further investigate neuroprotective treatments in low-resource settings.

Entry criteria in LMIC

Before initiation of cooling, inclusion and exclusion criteria in low-resource settings have to be considered. A low Apgar score, requirement for resuscitation and a Thompson score of more than six are useful criteria for inclusion. Whether a very high Thompson score could also be used as an exclusion item remains in discussion. In these circumstances it could be better to discuss the poor prognosis with the parents and to only offer maximal comfort therapy. Perinatal infection is another exclusion criterion which requires some thought. Infections can increase brain vulnerability to hypoxic-ischemic insult and cooling in the presence of it might even be more harmful (41-43). Lastly, hypothermia needs to be started within 6 hours after birth. Lack of proper transportation facilities in LMIC can be a hazard for this entry criterion as well as delays in healthcare provision in the hospital itself. A study in Congo, which has the most daunting infrastructure on the African continent, provided these data and showed that more than 40% of infants with HIE were inborn or reached the hospital within 6 hours to receive neuroprotective treatment (28).

Feasibility of low-cost cooling methods

To provide hypothermia the included studies used passive cooling, water bottles, ice packs, phase changing materials and servo-controlled devices. In order to be effective, the target temperature between 33-34°C must be quickly reached and maintained during the next 72 hours. Wide fluctuations in temperature not only increase the risk of complications when the temperature drops below 33°C, but also compromise the degree of neuroprotection when the temperature rises above 34°C (44). The median time to reach 33-34°C ranged from 30 to 120 minutes. The most stable temperature profile could be maintained by the servo-controlled devices and PCM. With PCM however ambient temperatures below 28°C and intensive nursing are required (14). Cooling using water bottles and ice packs also requires a high nursing input and moreover frequent changing to ensure temperature is maintained within target range. However, most of the neonatal units in LMIC have a shortage of adequate nursing resources which makes it hard to achieve tight temperature control (45). This may offset the cost benefit of an inexpensive cooling method because of the negative consequences of wide temperature fluctuations. Close monitoring of the temperature is also needed with a servo-controlled device, but it is the only device that omits the need for manual adjustments which makes it less labour-intensive. Although it's more expensive (US$1000) compared to the other cooling methods, it seems to be the most safe and easiest to use device in LMIC.

Safety and efficacy

It's hard to draw conclusions about the safety and efficacy in reducing mortality or neurodevelopmental delay of each device, since most of the studies were not powered for this. Overall, the adverse events documented in our included studies were in concordance with studies from HIC (46-49). However caution must be paid when using ice packs because they seem to increase the risk of skin injuries. Shivering was also seen in a few of our studies which could be caused by undersedation or the method of cooling (10). Regarding the efficacy, none of the studies could show a significant decrease in mortality rate. But when the rate of death and developmental delay were combined, three adequately powered studies could notice a significant decrease in the hypothermia group compared to the normothermia group (11,13,18). However developmental scoring in two studies was done at 6-12 months old and may not describe the permanent neurological outcome (11,13). The lack of follow up is a limitation in all of the studies, except for the study of Catherine et al. In the study of Robertson et al. more infants in the cooling group died (9). Two deaths could be caused by infection according to the author. But maybe death was rather due to the severity of the encephalopathy, since all of the seven infants with Sarnat stage III died and six of them were randomized in the hypothermia group.

We urgently need more adequately powered clinical trials to assess whether hypothermia is also beneficial in LMIC. A large trial in India who enrolled 408 neonates with moderate or severe neonatal encephalopathy is currently on his way. It will compare neonates who are randomly allocated to the cooling group using a servo-controlled device or to the standard care group. This study will be powered to examine whether whole body cooling in LMIC can reduce death or neurodisability at 18 months (50).

Other neuroprotective therapies

It is also of interest whether other neuroprotective therapies might result in better outcomes in LMIC because of easier use and less risk of complications. Promising drugs are melatonin and 2-iminobiotin. Melatonin itself is cost-effective and has a good safety profile. Unfortunately, the available intravenous formulation contains ethanol which is not acceptable for neonatal administration. 2-Iminobiotin, a vitamin B7 analogue, is a non-expensive and safe drug that can be easily administered intravenously and stored in higher temperatures. The efficacy of iminobiotin in comparison to standard care is currently investigated in a Congolese study (39). A follow-up study is also planned to evaluate the neurological development in the first 2 years after birth. This cheap, safe and easily administered alternative to hypothermia could be a possible breakthrough in low-resource settings.

Development of potential neuroprotective treatments could be speed up when HIC and LMIC collaborate (27). Tagin et al. discussed the strong potential for complementary contributions between HIC and LMIC. Developed countries have the established expertise in performing medical studies and developing countries have the higher incidence of neonatal encephalopathy.

A broader perspective

It may be wrong to apply cooling without improving prenatal care, obstetrics, monitoring, resuscitation and respiratory management (51). Prenatally, chronic insults like malnutrition and intra-uterine growth restriction may contribute to the higher incidence of perinatal asphyxia (52). Improving prenatal follow-up, nutritional behavior and treatment of underlying diseases are therefore essential, as well as adequate management protocols and qualified personnel during labor. After birth, adequate intensive care support including proper monitoring, mechanical ventilation, sedation and oxygen-use is needed (27). Scaling up quality of obstetric and neonatal care may result in an even greater reduction in asphyxia-related mortality and morbidity (53).

Conclusion

There is a growing body of evidence that providing therapeutic hypothermia to infants with neonatal encephalopathy is feasible using low-cost cooling methods in developing countries. Adequately powered clinical trials are needed to assess whether these cooling methods are also safe and effective in reducing mortality and morbidity. Future studies should also investigate whether neuroprotective drugs, like 2-iminobiotin, might result in better outcomes in low-resource settings. But efforts should also be made in developing preventive strategies and strengthening obstetrics and neonatal care. Developments in the prevention as well as the treatment of neonatal encephalopathy could make a great contribution in achieving the 2030 sustainable developmental goal 3.

Table 6: Outcome at discharge: deaths and neurological abnormality

Author, year	Cooling method	Sample size	Mortality rate	Neurological abnormality
Robertson et al., 2008 (9)	Water bottles	21 HT 15 ST	33,3% in the HT group 6,7% in the ST group	
Thomas et al., 2011 (10)	Ice packs	20	5%	
Bharadwaj et al., 2012 (11)	Ice packs	62 HT 62 ST	4,8% in the HT group 9,7% in the ST group (95% CI 0.13-1.91)	16.1% in the HT group 40.3% in the ST group (95% CI 0.21-0.76)
Joy et al., 2013 (12)	Ice packs	58 HT 58 ST	1.7% in the HT group 6.9% in the ST group (p value 0.17)	36.8% in the HT group 79.4% in the ST group (p value <0.001)
Thayyil et al., 2013 (14)	Phase changing materials	33	24% in the HT group 13% in the ST group	
Thomas et al., 2015 (15)	Phase changing materials	41	Not reported	
Thomas et al, 2018 (16)	Phase changing materials	103	6.8%	
Prashantha et al., 2018 (17)	Phase changing materials and ice packs	33 PCM 29 IP	3.2%	
Catherine et al., 2021 (18)	Phase changing materials	78 HT 84 ST	28,2% in the HT group 34.5% in the ST group (95% CI 0.52-1.29)	33.3% in the HT group 35.7% in the ST group (95% CI 0.61-1.43)
Biselele et al., 2014 (19)	Servo-controlled device	12	16.7%	
Oliveira et al., 2018 (20)	Servo-controlled device	82	18%	
Enweronu et al., 2019 (21)	Passive cooling	13	23%	
Bhat et al., 2006 (22)	Not described	20 HT 15 ST	15% in the HT group 33% in the ST group (p value >0.05)	HT group < ST group (p value <0.001)

HT: hypothermia, ST: standard therapy, PCM: phase changing materials, IP: ice packs, CI: confidence interval

Table 7: Outcome at follow up: deaths and neurological abnormality

Author, year	Cooling method	Age at follow-up	Sample size	Mortality rate	Neurological abnormality
Bharadwaj et al., 2012 (11)	Ice packs	6 months	57 HT 59 ST	5.3% in the HT group 10.2% in the ST group (95% CI 0.14-1.97	3.5% in the HT group 20.3% in the ST group (95% CI 0.04-0.74)
Gane et al., 2014 (13)	Ice packs	12 months	53 HT 50 ST	7% in the HT group 13.8% in the ST group (95% CI 0.16-1.59)	9.4% in the HT group 36% in the ST group (95% CI 0.10-0.65)
Catherine et al., 2021 (18)	Phase changing materials	18 months	76 HT 79 ST	28.9% in the HT group 36.7% in the ST group (95% CI 0.50-1.24)	6.6% in the HT group 21.5% in the ST group (95% CI 0.12-0.79)

HT: hypothermia, ST: standard therapy, CI: confidence interval

Figure 1 : *Figure 1: Low-cost cooling devices. (a) Water bottles. (b) Ice packs. (c) Phase changing materials. (d) Servo-controlled devices. Reproduced with permission of Thayyil Sudhin and Thomas Niranjan (20,45).*

REFERENCES:

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: An updated systematic analysis. Lancet. 2015;385(9966):430-440.
2. Hug L, Alexander M, You D, Alkema L. National, regional, and global levels and trends in neonatal mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. Lancet Glob Heal. 2019;7(6):710-720.
3. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013;(1):CD003311.
4. Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O. Effects of hypothermia for perinatal asphyxia on childhood outcomes. Obstet Gynecol Surv. 2014;69(11):639-641.
5. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Eunice Kennedy Shriver NICHD Neonatal Research Network: Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med. 2012;366:2085-2092.
6. Lawn J, Shibuya K, Stein C. No cry at birth: Global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. Bull World Health Organ. 2005;83(6):409-417.
7. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86(6):329-338.
8. Pauliah SS, Shankaran S, Wade A, Cady EB, Thayyil S. Therapeutic Hypothermia for Neonatal Encephalopathy in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. PLoS One. 2013;8(3).
9. Robertson NJ, Nakakeeto M, Hagmann C, Cowan FM, Acolet D, Iwata O, et al. Therapeutic hypothermia for birth asphyxia in low-resource settings: a pilot randomised controlled trial. Lancet. 2008;372(9641):801-803.
10. Thomas N, George KC, Sridhar S, Kumar M, Kuruvilla KA, Jana AK. Whole body cooling in newborn infants with perinatal asphyxial encephalopathy in a low resource setting: A feasibility trial. Indian Pediatr. 2011;48(6):445-51.

11. Bharadwaj SK, Vishnu Bhat B. Therapeutic hypothermia using gel packs for term neonates with hypoxic ischaemic encephalopathy in resource-limited settings: A randomized controlled trial. J Trop Pediatr. 2012;58(5):382-388.
12. Joy R, Pournami F, Bethou A, Bhat VB, Bobby Z. Effect of therapeutic hypothermia on oxidative stress and outcome in term neonates with perinatal asphyxia: a randomized controlled trial. Journal of Tropical Pediatrics. 2013;59(1)17–22.
13. Gane BD, Bhat V, Rao R, Nandhakumar S, Harichandrakumar K, Adhisivam B. Effect of therapeutic hypothermia on DNA damage and neurodevelopmental outcome among term neonates with perinatal asphyxia: a randomized controlled trial. Journal of Tropical Pediatrics. 2014;60(2):134–40.
14. Thayyil S, Shankaran S, Wade A, Cowan FM, Ayer M, Satheesan K, et al. Whole-body cooling in neonatal encephalopathy using phase changing material. Arch Dis Child Fetal Neonatal Ed. 2013;98(3):280-1.
15. Thomas N, Chakrapani Y, Rebekah G, Kareti K, Devasahayam S. Phase changing material: An alternative method for cooling babies with hypoxic ischaemic encephalopathy. Neonatology. 2015;107(4):266-270.
16. Thomas N, Abiramalatha T, Bhat V, Varanattu M, Rao S, Wazir S, et al. Phase Changing Material for Therapeutic Hypothermia in Neonates with Hypoxic Ischemic Encephalopathy-A Multi-Centric Study. Indian Pediatr. 2018;55(3):201-205.
17. Prashantha YN, Suman Rao PN, Nesargi S, Chandrakala BS, Balla KC, Shashidhar A. Therapeutic hypothermia for moderate and severe hypoxic ischaemic encephalopathy in newborns using low-cost devices–ice packs and phase changing material. Paediatr Int Child Health. 2018;39(4):234-239.
18. Catherine RC, Ballambattu VB, Adhisivam B, Bharadwaj SK, Palanivel C. Effect of therapeutic hypothermia on the outcome in term neonates with hypoxic ischemic encephalopathy - a randomized controlled trial. Journal of Tropical Pediatrics. 2021;67(1)
19. Biselele T, Naulaers G, Horn A, Paula B, Bambi J, Kayembe C. Use of cooling treatment in infants with HIE in the Democratic Republic of Congo. Unpublished doctoral dissertation. 2014.
20. Oliveira V, Kumutha JR, Narayanan E, Somanna J, Benkappa N, Bandya P, et al. Hypothermia for encephalopathy in low-income and middle-income countries: feasibility of whole-body cooling using a low-cost servo-controlled device. BMJ Paediatr Open. 2018;2(1):e000245.
21. Enweronu-Laryea C, Martinello KA, Rose M, Manu S, Tann CJ, Meek J, et al. Core temperature after birth in babies with neonatal encephalopathy in a sub-Saharan African hospital setting. J Physiol. 2019;15:4013-4024.
22. Bhat MA. Re: Therapeutic hypothermia following perinatal asphyxia. Archives of Disease in Childhood- Fetal and Neonatal Edition. 2006;91(6):F464–F
23. Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteno CD, et al. The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr Int J Paediatr. 1997;86(7):757-761.
24. Sarnat HB, Sarnat MS. Neonatal Encephalopathy Following Fetal Distress: A Clinical and Electroencephalographic Study. Arch Neurol. 1976;33(10):696-705.
25. Horn AR, Swingler GH, Myer L, Linley LL, Raban MS, Joolay Y, et al. Early clinical signs in neonates with hypoxic ischemic encephalopathy predict an abnormal amplitude-integrated electroencephalogram at age 6 hours. BMC Pediatr. 2013;13:52.
26. Biselele T, Naulaers G, Tady B. Evolution of the Thompson score during the first 6 h in infants with perinatal asphyxia. Acta Paediatr Int J Paediatr. 2014;103(2):145-148.
27. Tagin M, Abdel-Hady H, Rahman SU, Azzopardi DV, Gunn AJ. Neuroprotection for perinatal hypoxic ischemic encephalopathy in low- and middle-income countries. J Pediatr. 2015;167(1):25-28.
28. Biselele T, Bambi J, Naulaers G, Tabu G, Kapinga J, Bola V, et al. Observational study shows that it is feasible to provide neuroprotective treatment for neonatal encephalopathy in low-income countries. Acta Paediatr Int J Paediatr. 2018;107(8):1345-1349.
29. Burnard ED, Cross KW. Rectal temperature in the newborn after birth asphyxia. Br Med J. 1958;2(5106):1197-9.
30. Perrone S, Stazzoni G, Tataranno ML, Buonocore G. New pharmacologic and therapeutic approaches for hypoxic-ischemic encephalopathy in the newborn. J Matern Neonatal Med. 2012;25(Suppl1):83-88.
31. Albrecht M, Zitta K, Groenendaal F, van Bel F, Peeters-Scholte C. Neuroprotective strategies following perinatal hypoxia-ischemia: Taking aim at NOS. Free Radic Biol Med. 2019;142:123-131.
32. Solevåg AL, Schmölzer GM, Cheung PY. Novel interventions to reduce oxidative-stress related brain injury in neonatal asphyxia. Free Radic Biol Med. 2019;142:113-122.
33. Robertson NJ, Faulkner S, Fleiss B, Bainbridge A, Andorka C, Price D, et al. Melatonin augments hypothermic neuroprotection in a perinatal asphyxia model. Brain. 2013;136(1):90-105.
34. Berger HR, Nyman AKG, Morken TS, Vettukattil R, Brubakk AM, Widerøe M. Early metabolite changes after melatonin treatment in neonatal rats with hypoxic-ischemic brain injury studied by in-vivo 1H MR spectroscopy. PLoS One. 2017;12(9):e0185202.
35. Aridas JDS, Yawno T, Sutherland AE, Nitsos I, Ditchfield M, Wong FY, et al. Systemic and transdermal melatonin administration prevents neuropathology in response to perinatal asphyxia in newborn lambs. J Pineal Res. 2018;64(4):e12479.
36. Fulia F, Gitto E, Cuzzocrea S, Reiter RJ, Dugo L, Gitto P, et al. Increased levels of malondialdehyde and nitrite/nitrate in the blood of asphyxiated newborns: Reduction by melatonin. J Pineal Res. 2001;31(4):343-9.
37. Van Den Tweel ERW, Van Bel F, Kavelaars A, Peeters-Scholte C, Haumann J, Nijboer C, et al. Long-term neuroprotection with 2-iminobiotin, an inhibitor of neuronal and inducible nitric oxide synthase, after cerebral hypoxia-ischemia in neonatal rats. J Cereb Blood Flow Metab. 2005;25(1):67-74.
38. Bjorkman ST, Ireland Z, Fan X, van der Wal WM, Roes KCB, Colditz PB, et al. Short-term dose-response characteristics of 2-iminobiotin immediately postinsult in the neonatal piglet after hypoxia-ischemia. Stroke. 2013;44(3):809-11.
39. A multiple-centre Phase 2 trial comparing the efficacy of 2-Iminobiotin (2-IB) treatment to standard care in neonates with gestational age of ≥36 weeks with moderate to severe perinatal asphyxia in DR Congo. (https://www.clinicaltrialsregister.eu, EudraCT 2015-003063-12).
40. Biselele TBJ, Tabu G, Kapinga J, Bola V, Makaya P, Tady B, et al. Safety and pharmacokinetics of 2-iminobiotin in neonates after perinatal asphyxia in DR of Congo, Abstract during the 10th International Conference .
41. Stridh L, Mottahedin A, Johansson ME, Valdez RC, Northington F, Wang X, et al. Toll-Like Receptor-3 Activation Increases the Vulnerability of the Neonatal Brain to Hypoxia-Ischemia. J Neurosci. 2013;33(29):12041-51.
42. Osredkar D, Thoresen M, Maes E, Flatebø T, Elstad M, Sabir H. Hypothermia is not neuroprotective after infection-sensitized neonatal hypoxic-ischemic brain injury. Resuscitation. 2014;85(4):567-72.
43. Biggar WD, Barker C, Bohn D, Kent G. Partial recovery of neutrophil functions during prolonged hypothermia in pigs. J Appl Physiol. 1986;60(4):1186-9.
44. Shankaran S, Laptook A, Wright LL, Ehrenkranz RA, Donovan EF, Fanaroff AA, et al. Whole-body hypothermia for neonatal encephalopathy: Animal observations as a basis for a randomized, controlled pilot study in term infants. Pediatrics. 2002;110(2.1):377-85.
45. Montaldo P, Pauliah SS, Lally PJ, Olson L, Thayyil S. Cooling in a low-resource environment: Lost in translation. Semin Fetal Neonatal Med. 2015;20(2):72-79. d
46. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005;353(15):1574-84.
47. Azzopardi D, Strohm B, Edwards AD, Halliday H, Juszczak E, Levene M, et al. Treatment of asphyxiated newborns with moderate hypothermia in routine clinical practice: How cooling is managed in the UK outside a clinical trial. Arch Dis Child Fetal Neonatal Ed. 2009;94(4):260-4.
48. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic Hypothermia after Neonatal Encephalopathy: Outcomes of neo.nEURO.network RCT. Pediatrics. 2010;126(4):771-8.
49. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: A randomized controlled trial. Arch Pediatr Adolesc Med. 2011;165(8):692-700.
50. Thayyil S, Oliveira V, Lally PJ, Swamy R, Basset P, Chandrasekaran M, et al. Hypothermia for encephalopathy in low and middle-income countries (HELIX): Study protocol for a randomised controlled trial. Trials. 2017;18(1).
51. Robertson NJ, Hagmann CF, Acolet D, Allen E, Nyombi N, Elbourne D, et al. Pilot randomized trial of therapeutic hypothermia with serial cranial ultrasound and 18-22 month follow-up for neonatal encephalopathy in a low resource hospital setting in uganda: Study protocol. Trials. 2011;12:138.
52. Bamji MS, Muthy PVVS, Williams L, Vishnu M, Vardhana Rao MV. Maternal nutritional status & practies & perinatal, neonatal mortality in rural Andhra Pradesh, India. Indian J Med Res. 2008;127(1):44-51.
53. Lawn JE, Kinney M, Lee ACC, Chopra M, Donnay F, Paul VK, et al. Reducing intrapartum-related deaths and disability: Can the health system deliver? International Journal of Gynecology and Obstetrics. 2009;107(Suppl1):123-40.