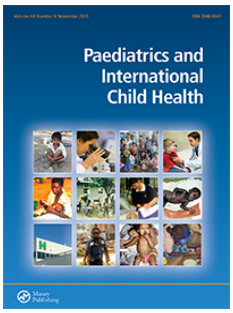

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ARTICLE

Therapeutic hypothermia for moderate and severe hypoxic ischaemic encephalopathy in newborns using low-cost devices – ice packs and phase changing material

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ABSTRACT

Background: Different methods have been used for therapeutic hypothermia for neonates with moderate-to-severe hypoxic ischaemic encephalopathy (HIE). As standard cooling devices are expensive, there is a need to establish the safety and efficacy of low-cost devices such as ice packs (IP) and phase changing material (PCM).

Aim: To assess the efficacy and safety of therapeutic hypothermia (TH) and the clinico-laboratory profile of neonates who underwent cooling with IP or PCM.

Methods: The study was retrospective. TH for moderate-to-severe HIE was initiated with IP between 2012 and 2014 and with PCM (MiraCradle^{TM}) from September 2014. A standard protocol for inclusion and management during TH was used for all newborns. All data were collected by means of a local cooling registry.

Results: Sixty-two cooled newborns (IP 29, PCM 33) were included in the study. Mean gestational age was 38.6 (1.7) weeks and mean birthweight 2920.6 g (450.7); 66.1% were inborn and 91.9% had moderate encephalopathy. Mean (SD) core temperature during cooling was 33.47°C (0.33) for PCM and 33.44°C (0.34) for IP. Adverse events observed during TH were thrombocytopenia (54.8%), coagulopathy (30.6%), shock (30.6%), skin changes (12.9%) and persistent pulmonary hypertension (8.1%). Forty-nine infants were discharged, two died and 11 were discharged against medical advice. TH was prematurely stopped in seven newborns with serious adverse events such as disseminated intravascular coagulation (DIC), gangrene and arrhythmia (IP 5, PCM 2).

Conclusion: Low-cost devices are safe and effective alternatives for maintaining TH in low-resource settings with adequate monitoring.

Abbreviations: DAMA, discharged against medical advice; DIC, disseminated intravascular coagulation; HELIX, Hypothermia for Encephalopathy in Low- and Middle-Income Countries Trial; HIE, hypoxic ischaemic encephalopathy; IP, ice packs; LMIC, low- and middle-income countries; NICHD, National Institute of Child Health and Human Development; PCM, phase changing; TH, therapeutic hypothermia (TH); TOBY, total body hypothermia for neonatal encephalopathy.

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KEYWORDS
Hypoxic ischaemia; brain; hypothermia; induced; ice packs; phase changing material

Introduction

Neonatal mortality accounts for two-thirds of infant mortality in India and other low- and middle-income countries (LMIC) [1,2]. Perinatal asphyxia contributes to 21% of all neonatal deaths. Therapeutic hypothermia (TH) initiated within 6 h and maintained for 72 h after an asphyxial insult has been shown to reduce the combined outcome of mortality or major neurodevelopmental disability at 18 months of age (RR 0.75, 95% CI 0.68–0.83) [3,4].

Different methods have been used to induce moderate hypothermia, including selective head cooling, head cooling combined with body cooling and body cooling alone [5–10].

Because of the prohibitive expense of servo-controlled devices, several low-cost devices such as ice packs (IP) [6,7] and phase changing material (PCM) [8,9] have been used for cooling. The Indian guidelines for neonatal resuscitation 2017 [11], however, still do not list TH as a standard treatment in perinatal asphyxia. More studies are necessary in India to establish the safety, efficacy and feasibility of low-cost devices for TH before it can become the standard of care in similar LMICs.

This study was therefore undertaken with the primary objective of assessing the efficacy and safety of low-cost devices for TH and to describe the clinico-laboratory profile of infants who have undergone TH in a tertiary care NICU. The secondary objective was to

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compare the two low-cost methods of cooling with IP and PCM.

Methods

This was a retrospective analysis of newborns cooled at St John's Medical College Hospital, Bengaluru, a tertiary-care centre in southern India. Newborns who received TH from April 2012 to July 2016 were included in the study. Ice packs (plastic containers filled with cooling gel used in vaccine carriers) were used for cooling newborns between 2012 and 2014, and PCM (MiraCradle^{TM}, Pluss Polymers, New Delhi, India) from September 2014. Data were retrieved from chart analysis and from the cooling registry in the unit.

TH was initiated in all neonates with a gestation of ≥35 weeks, who weighed >1.8 kg, presented within 6 h of life and fulfilled the cooling criteria modified from the National Institute of Child Health and Human Development (NICHD) criteria [3].

For inborn infants, the physiological criteria were any one of the following: arterial blood gas (cord/first postnatal hour) pH < 7.0 or absolute base excess ≥-12 or Apgar score ≤5 at 5 min or requiring positive pressure ventilation for at least 10 min at birth. The neurological criteria were the presence of seizures or evidence of moderate or severe encephalopathy. Encephalopathy staging was based on the modified Sarnat staging used in the NICHD study [3]. The standardised neurological criteria were used to assess newborns every hour until 6 h of life.

For outborn infants, the physiological criteria were relaxed to include those who did not cry immediately after birth or required resuscitation or Apgar score < 5 at 5 min (if available). Infants requiring respiratory support, including mechanical ventilation, were also included.

Written informed consent was obtained from the parent/s before initiation of TH.

With IP, TH was initiated by placing three-to-six cloth-covered IPs in contact with the infant on the head, abdomen and back, and, in the PCM group, blocks of PCM with a melting point of 29°C (MiraCradle^{TM}) were used.

PCM are material composed of salt hydride, fatty acids and esters which act as heat buffers by virtue of their ability to convert to liquid form when brought into contact with a warmer object such as the human body by absorbing and storing heat. Two types of PCM blocks were used: FS-29 (Form Stable melting point 29°C) and FS-21 (Form Stable melting point 21°C) [10]. When not in use, the PCM blocks were stored in the refrigerator at 2°C–8°C, and, when taken out for use, were ensured to be in a solid state. For insulation, the newborn was placed in a cradle on a conduction mattress on top of the PCM under a radiant warmer.

The core body temperature was continuously measured by a rectal probe attached to a multi-channel monitor. The target temperature of 33.5°C was achieved as soon as possible and maintained in the range of 33.2–33.8°C.

When temperatures were ≤33.2°C, IPs were removed one-by-one and, when the temperature touched 33.8°C, more ice packs were added. If the temperature was ≤33.2°C in the PCM group, lateral positioning using linen sheets as a barrier followed by increasing heat output by a radiant warmer in manual mode from 10% to 40% was undertaken gradually to prevent the temperature from falling further. Removal of the sheet barriers or use of FC-21 was employed beyond 33.8°C. The temperature was maintained between 33°C and 34°C for 72 h and then the infant was slowly rewarmed at the rate of 0.2–0.5°C per hour to a normal temperature of 36.5°C.

Continuous vital monitoring was undertaken for all the newborns and temperatures were recorded every 15 min in the charts. Blood counts, prothrombin time and activated partial thromboplastin time, serum creatinine, serum electrolytes, liver enzymes and C-reactive protein were monitored during cooling. Feeds were commenced when the newborns were haemodynamically stable after 48 h of TH. Sedation was administered as required using either opioids for ventilated newborns or paracetamol for shivering. Other supportive treatments including invasive ventilation (with an endotracheal tube *in situ*), fluid management, shock, electrolyte imbalance and sepsis were managed as per standard recommendations which did not change during the study period. HIE staging was undertaken according to the Sarnat classification [12]. The ambient temperature of the unit was maintained between 24°C and 26°C by centralised air conditioning.

Outcome measures

The primary outcome was the number of newborns successfully cooled and discharged. The number of deaths and DAMA (discharged against medical advice), duration of hospital stay, short-term complications owing to the disease process itself and to cooling were documented. As a secondary outcome, the two devices—IP and PCM—were compared for ability and ease in maintaining temperature in the target range.

Sample size

The sample size was calculated on the basis of the pilot data for 20 newborns in the same centre undergoing TH which showed that 4% of the temperature readings were outside the target range (33–34°C). To estimate this rate of non-compliance with 20% relative precision and a 95% confidence interval, the sample size required was 2305 temperature readings.

Table 1. Neonates. baseline characteristics.

Variables	Ice packs, *n* = 29	PCM, *n* = 33	*p*-value	Total, *n* = 62
Inborn, *n* (%)	17 (58.6)	24 (72.7)	0.36	41 (66.1)
Gestational age, wks, mean (SD)	39 (1.3)	38.3 (1.9)	0.17	38.6 (1.7)
Male, *n* (%)	18 (62.1)	16 (48.5)	0.40	34 (54.8)
Small for gestational age, *n* (%)	5 (20.7)	4 (12.1)	0.70	9 (14.5)
Birthweight, g, mean (SD)	2860 (391.8)	2973 (496.8)	0.33	2920 (447.1)
Normal delivery, *n* (%)	24 (82.7)	18 (54.5)	0.36	42 (67.7)
APGAR at 5 mins, mean (SD)*	5.8 (1.3)	5.6 (1.4)	0.80	5.8 (1.3)
Cord pH, mean (SD)*	6.9 (0.1)	6.9 (0.1)	0.28	6.9 (0.1)
Base excess, mean (SD)*	19.8 (4.8)	20.7 (3.8)	0.30	20.3 (4.2)
Seizures, *n* (%)	6 (20.6)	4 (12.1)	0.49	10 (16.1)
Moderate encephalopathy, *n* (%)	27 (93.0)	30 (91.0)	0.75	57 (91.1)

*Inborn.

With 72 readings per newborn, this would need recordings for 32 newborns.

Statistical analysis

The data were analysed using the SPSS 16.0 software. Mean (SD), median (IQR) and frequency were calculated. The χ^2 test was used for qualitative variables, Pearson's co-efficient for correlation between the two methods and the *t*-test or Mann–Whitney U-test for quantitative variables.

Ethics

The ethics committee of St John's Medical College approved the study before it commenced.

Results

Sixty-two cooled newborns (IP 29, PCM 33) were included in the study. The mean gestational age was 38.6 (1.7) weeks and mean birthweight 2920.6 g (450.7); 66.1% were inborn and 91.9% had moderate encephalopathy (Table 1).

Altogether, 49 newborns (79%) were successfully cooled and discharged (Table 2). Death and DAMA occurred in 3.2% and 17.7%, respectively. Significantly more newborns were discharged from the PCM than the IP group (90.9% *vs* 65.5%, $p = 0.03$).

TH was stopped prematurely in five (17.2%) newborns in the IP group as three had disseminated intravascular coagulation (DIC), one had bradyarrhythmia (heart rate <60/min) and one developed ischaemic gangrene of the hand secondary to peripheral arterial line insertion. In the PCM group, TH was stopped prematurely in two (6.2%) newborns because of DIC. Tables 3 and 4 compare temperature and clinico-pathological profiles in the IP and PCM groups.

Table 2. Outcome.

	Ice packs *n* = 29	PCM *n* = 33	*p*-value
Discharged, *n* (%)	19 (65.5)	30 (90.9)	**0.03***
DAMA, *n*	9	2	
Death, *n*	1	1	
Duration of hospital stay, days, mean (SD)	11.8 (8.7)	10.3 (5.1)	0.40

DAMA, discharged against medical advice; *statistically significant.

The median time to reach the target rectal temperature from initiation was less in the PCM group (30 min, IQR 20–40) than in the IP group (35 min, IQR 25–45). In the PCM group, 3.7% of readings were <33°C compared with 4.8% in the IP group ($p = 0.1$), and 4.8% of readings were >34°C compared with 2.7% in the IP group ($p = 0.001$). The mean (SD) temperature during cooling was comparable between the two groups [33.47 (0.33°C) and 33.44 (0.34°C), respectively]. Rectal temperatures during the induction and maintenance phases of cooling using IP and PCM are shown in Figure 1.

Adverse events observed during TH were thrombocytopenia (54.8%), coagulopathy (30.6%), shock (30.6%), skin changes (12.9%) and persistent pulmonary hypertension (8.1%) (Table 4). Times to achieve full feeds with IP and PCM were 4.80 (1.6) and 4.96 (1.5) days, respectively. Rates of re-warming with PCM and IP were 0.2°C/h and 0.26°C/h, respectively, not significantly different. TH with PCM was less labour-intensive with the mean use of F-21 per day being 5.2 (1.5) times compared with 8.1 (4.1) times per day ($p < 0.05$) for changing ice packs.

Discussion

Low- and middle-income countries have about a 10 times higher burden of HIE but have been deprived of the benefits of TH, primarily because of the high costs associated with advanced servo-controlled cooling devices. This study demonstrates that low-cost methods such as IP and PCM are equally effective in maintaining a target temperature of 33–34°C for a total of 72 h. This is comparable to mean temperatures attained in other studies of low-cost devices—33.45°C (0.26) [10] and 33.8°C (0.4) [6]—and also servo-controlled devices [33.4 (0.4)] [14,15]. Both methods effectively reduced rectal temperature to the target temperature within the specified time limit, which was comparable with results of other studies at a median (IQR) of 30 min (10–90) [9]. Another Indian study reported a median time of 60 min (IQR 60–180) [10].

Table 3. Temperature comparison between the two methods.

Variable	Ice packs	PCM	*p*-value
Rectal temperature at initiation of cooling, °C, mean (SD)	36.3 (0.94)	36.1 (0.94)	0.36
Median time to reach target temperature, mins, median (IQR)	35 (25–45)	30 (20–40)	0.25
Mean temperature during cooling, °C, mean (SD)	33.44 (0.34)	33.47 (0.33)	**0.004***
Labour intensity, mean no. of changes/day of IP and F-21, mean (SD)	8.14 (4.14)	5.28 (1.54)	**0.04***
Temperature readings outside target, %:			
< 33°C	4.8	3.7	0.1
> 34°C	2.7	4.8	**0.001***
Rate of rewarming, °C/hour	0.26	0.2	**0.001***

*Statistically significant.

Table 4. Clinico-laboratory profile of newborns undergoing therapeutic hypothermia.

Events	Ice packs, *n* (%)	PCM, *n* (%)	*p*-value	Total, *n* (%)
Respiratory				
No. receiving invasive ventilation	11 (37.9)	12 (36.36)	0.89	23 (37)
Cardiovascular				
Shock*	14 (48.2)	15 (45.4)	0.82	29 (46.7)
Bradycardia†	9 (31.0)	11 (33.3)	1.0	20 (32.2)
PPHN‡	2 (6.9)	3 (9.09)	1.0	5 (8.0)
Haematological				
Coagulopathy	8 (27.5)	11(33.3)	0.78	19 (30.6)
Thrombocytopenia, platelet count < 150 × 10^9/L	15 (51.7)	17 (51.5)	0.97	32 (51.6)
Anaemia, Hb < 13 g/dL	7 (24)	4 (12.1)	0.30	11 (17.7)
Other				
Seizure	17 (58.6)	14 (42.4)	0.30	31 (50.0)
Acute kidney injury	3 (10.3)	4 (12.1)	1.0	7 (11.2)
Sepsis, culture-positive	2 (6.9)	0	0.21	2 (3.2)
Hyperbilirubinaemia requiring phototherapy	4 (13.7)	7 (21.2)	0.66	11 (17.7)
Days to achieve full feeds, mean (SD)	4.8 (1.6)	4.96 (1.5)	0.72	4.9 (1.6)
Metabolic				
Hyperglycaemia§	7 (24.0)	4 (12.1)	0.31	11 (17.7)
Hypoglycaemia**	11(37.9)	8 (24.4)	0.27	19 (30.6)
Hyponatraemia††	10 (34.4)	9 (27.3)	0.58	19 (30.6)
Hypocalcaemia‡‡	2 (6.9)	5 (15.0)	0.26	7 (11.2)
Other adverse events	12 (41.3)	5 (15.15)	**0.02**	17 (27.4)
Cardiac arrhythmia, bradycardia < 60/min	1 (3.4)	0		
Bleeding	4 (13.7)	3 (9.0)		
Skin changes	6 (20.6)	2 (6.0)		
Gangrene of the hand	1 (3.4)	0		

*Requiring bolus or inotrope; †heart rate < 90/min; ‡persistent pulmonary hypertension of the newborn; right-to-left shunting in the absence of congenital heart disease; §blood glucose >7 mmol/L; **blood glucose <2.8 mmol/L; ††serum sodium <135 mmol/L; ‡‡total serum calcium <1.75 mmol/L; *p*-value in bold type is statistically significant.

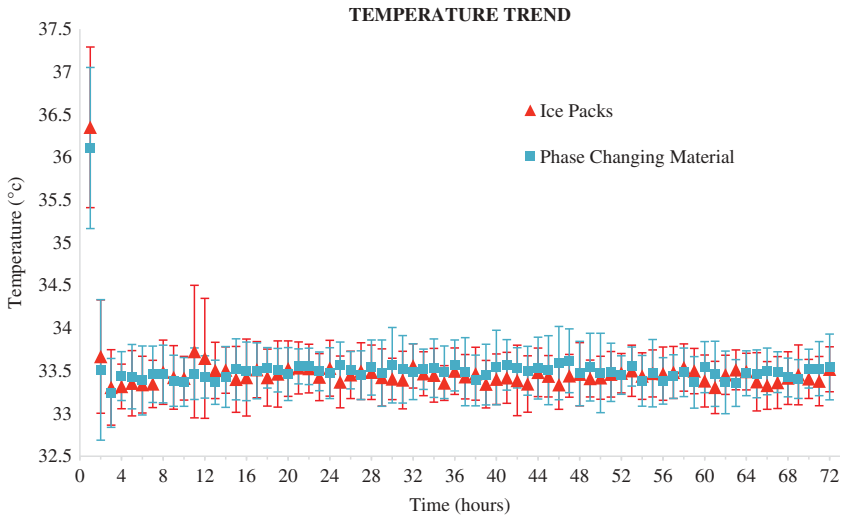

Figure 1. Mean (SD) rectal temperature profile during the induction and maintenance phases.

There were more readings of <33°C in the IP group, whereas in the PCM group more temperatures of >34° C were recorded. The rate of re-warming was more gradual with PCM as the protocol was changed to a slower re-warming process.

Adverse events were comparable with the TOBY (Total Body Hypothermia for Neonatal Encephalopathy) Trial [14] which showed a significant increase of thrombocytopenia and coagulopathy (58% and 41%, respectively). The incidence of bradycardia was 29% with IP and 33.3% with PCM. However, the incidence of skin changes, particularly subcutaneous fat necrosis, was greater with IP. There was an increased incidence of other adverse events in the IP group, probably because TH was a new modality in the centre at that time. Duration of hospital stay was significantly shorter than in the NICHD trial (11 days *vs* 19.9) [3]. This might reflect earlier discharge policies in India where neonatal care is often not insured and families bear the burden of care. The complications of sepsis, acute kidney injury and jaundice were not significantly different in the two groups. The times taken to achieve full feeds were also similar with the two methods.

The use of PCM was less labour-intensive than that of IP. Other Indian studies have observed a similar pattern in PCM [10]. This has major implications for LMICs in which most NICUs have a sub-optimal nurse: newborn ratio.

The improved outcomes with PCM compared with IP possibly reflect improved experience of its use over time rather than better efficacy of PCM as both methods were found to be equally effective in maintaining temperatures.

The strengths of the study are the relatively large number of newborns included, evaluation of two different low-cost devices and reliable and detailed collection of data.

Whether TH is effective in India in reducing mortality or neurodevelopmental deficits would be best established by a randomised controlled trial.

The absence of a control group is a limitation of the study. However, in view of the proven benefits of TH in various well conducted trials including in India [3,8], it was considered unethical to withhold it for half of the population, and TH was implemented with close monitoring and vigilance after informed consent had been obtained. Long-term neurodevelopmental outcomes were not studied; however, all the cooled newborns are under developmental follow-up.

The study shows that therapeutic hypothermia can be undertaken in LMIC using low-cost devices, IP or PCM, as an effective and relatively safe strategy. Currently, TH is practiced in many centres in India, in some for research purposes and in others as a service [7–10]. However, TH is still not practised routinely in India [11] as there is concern that outcomes may be poorer [9]. An inferior quality of newborn care and differences in co-morbidities are possible reasons for these poorer outcomes. Caution should be exercised before over-enthusiastic and premature implementation of this therapeutic modality [13] without an adequate quality of general care. A multicentre RCT–HELIX trial [16] is under way in India to study the efficacy of a servo-controlled device.

Considering that perinatal asphyxia contributes to 150,000 deaths/year [1] in India, TH has the potential to save 38,000 lives per year in addition to being a major advance in reducing the hidden burden of disability in countries such as India. With the approximate cost of Miracradle^{TM} being INR160,000 (€1750) including the PCMs, conduction mattress and insulating cradle, there is also a need for manufacturers to keep costs affordable for low-resource countries. This study adds to the growing body of evidence that, in LMIC, TH is feasible using low-cost devices with results which are comparable to those of multicentre international studies. However, in view of the need for continuous clinical and laboratory monitoring, trained health-care personnel, the need for ventilation and other supportive infrastructure, TH should be offered only in tertiary-care centres providing good newborn care using established protocols.

Ice packs and phase changing material are safe and effective alternatives for therapeutic hypothermia in low-resource settings. The use of PCM is less labour-intensive than that of IP and is associated with fewer serious adverse events. TH for moderate-to-severe encephalopathy is feasible and effective in the Indian setting in a tertiary-care NICU with close clinical and laboratory monitoring.

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Authors' contributions

YNP designed the study, collected and analysed the data, drafted the initial manuscript and approved the final manuscript; PNSR and AS conceived the study and reviewed and revised the manuscript for intellectual content; SN supervised the data collection, analysed the data and approved the final manuscript; and KCB and BSC supervised the data collection and approved the final manuscript

Disclosure statement

No potential conflict of interest was reported by the authors.

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