RESEARCH PAPER

Phase Changing Material for Therapeutic Hypothermia in Neonates with Hypoxic Ischemic Encephalopathy – A Multi-centric Study

Niranjan Thomas[1], Thangaraj Abiramalatha[1], Vishnu Bhat[2], Manoj Varanattu[3], Suman Rao[4], Sanjay Wazir[5], Leslie Lewis[6], Umamaheswari Balakrishnan[7], Srinivas Murki[8], Jaikrishnan Mittal[9], Ashish Dongara[10], Prashantha YN[4] and Somashekhar Nimbalkar[11]

From Departments of Neonatology; [1]CMC, Vellore, Tamil Nadu; [2]JIPMER, Puducherry; [3]Jubilee Mission Medical College and Research Institute, Thrissur, Kerala; [4]St. John's Medical College Hospital, Bengaluru; [5]The Cradle (by Apollo), Gurgaon; [6]KMC, Manipal; [7]Sri Ramachandra Medical College Chennai; [8]Fernandez Hospital, Hyderabad; [9]Neoclinic, Jaipur; [10]Narayana Multispeciality hospital, Ahmedabad, Gujarat; and [11]Department of Pediatrics, Pramukhswami Medical College, Karamsad, Gujarat; India.

Correspondence to: Dr. Niranjan Thomas, Department of Neonatology, Christian Medical College, Vellore 632 004, Tamil Nadu, India. niranjan@cmcvellore.ac.in.

Received: February 17, 2017; Initial review: June 19, 2017; Accepted: November 27, 2017.

Objective: To assess the feasibility and safety of cooling asphyxiated neonates using phase changing material based device across different neonatal intensive care units in India.

Design: Multi-centric uncontrolled clinical trial.

Setting: 11 level 3 neonatal units in India from November 2014 to December 2015.

Participants: 103 newborn infants with perinatal asphyxia, satisfying pre-defined criteria for therapeutic hypothermia.

Intervention: Therapeutic hypothermia was provided using phase changing material based device to a target temperature of 33.5±0.5ºC, with a standard protocol. Core body temperature was monitored continuously using a rectal probe during the cooling and rewarming phase and for 12 hours after the rewarming was complete.

Outcome measures: *Feasibility measure* **-** Time taken to reach target temperature, fluctuation of the core body temperature during the cooling phase and proportion of temperature recordings outside the target range**.** *Safety measure* **-** adverse events during cooling

Results: The median (IQR) of time taken to reach target temperature was 90 (45, 120) minutes. The mean (SD) deviation of temperature during cooling phase was 33.5 (0.39) ºC. Temperature readings were outside the target range in 10.8% (5.1% of the readings were <33ºC and 5.7% were >34ºC). Mean (SD) of rate of rewarming was 0.28 (0.13)ºC per hour. The common adverse events were shock/ hypotension (18%), coagulopathy (21.4%), sepsis/probable sepsis (20.4%) and thrombocytopenia (10.7%). Cooling was discontinued before 72 hours in 18 (17.5%) babies due to reasons such as hemodynamic instability/refractory shock, persistent pulmonary hypertension or bleeding. 7 (6.8%) babies died during hospitalization.

Conclusion: Using phase changing material based cooling device and a standard protocol, it was feasible and safe to provide therapeutic hypothermia to asphyxiated neonates across different neonatal units in India. Maintenance of target temperature was comparable to standard servo-controlled equipment.

Keywords: *Cooling devices*, *Perinatal asphyxia, Treatment.*

Published online: December 14, 2017. PII:S097475591600103

Therapeutic hypothermia (TH) reduces mortality and neurodevelopmental morbidity in asphyxiated neonates and is now the standard of care for asphyxiated neonates in high-income countries [1]. As servo-controlled equipment are expensive, many innovative low-cost methods have been developed for cooling and are being used in low- and middle-income countries (LMICs). A recent systematic review of TH in LMICs concluded that TH was not associated with a statistically significant reduction in neonatal mortality or neurodevelopmental morbidity [2]. One among the reasons stated was the probable inefficiency of the low technology cooling devices. The review emphasized the need for further studies on safety and efficacy of TH in LMICs using low-cost device before it could be offered in routine clinical practice [2].

Accompanying Editorials: Pages 197-200

Phase changing material (PCM) is one such low-cost technology used for cooling asphyxiated neonates [3,4]. MiraCradle - Neonate Cooler is a PCM-based cooling device that has recently been developed and used in India. Though we have previously reported successful use of PCM-based device to provide TH, the question remains whether the same results can be replicated in

other centers [4]. Hence we prospectively collected data from eleven centers to analyze the feasibility and safety of providing TH using the PCM-based device.

METHODS

This was a multi-centric, uncontrolled clinical trial, done in 11 centers in India from November 2014 to December 2015. We used Miracradle - Neonate Cooler (Pluss Advanced Technologies) to provide TH. The manufacturer of the device and Christian Medical College (CMC) Vellore, the development partner, conducted a workshop at CMC, Vellore in August 2014. In this workshop, neonatologists from all the 11 centers were trained on providing TH using PCM-based device, and various clinical aspects of TH were discussed. The study centers were level-3 neonatal intensive care units (NICUs) from both public and private sector who were already using cool gel packs for TH in neonates and/or expressed interest in using the PCM-based device for the purpose. None of the centers were using servo-controlled equipment for TH. Thereafter, the cooling device was supplied to all the centers along with relevant user instructions.

We developed a registry to record the temperature, complications and other relevant data of the cooled infants. The document was supplied in hard as well as soft copy to all the centers and the data was collected prospectively over the study period. All the centers got approval from their institutional ethical board to use the equipment and collect the data for publication.

We included infants ≥35 weeks gestational age and ≥1800 grams with a minimum of one physiological (Inborn babies – cord blood pH <7 or base deficit >12; 5-minute APGAR <5; need for resuscitation for >10 minutes. Outborn babies – a history of not having cried/ breathed immediately after birth; given assistance for breathing soon after birth; 5-minute APGAR <5) and one neurological criteria (moderate or severe encephalopathy as per modified Sarnat staging [5]; seizures).

Babies were excluded from the study if they had chromosomal disorder or major congenital anomaly or inability to start cooling before 6 hours of age.

The target temperature was 33.5±0.5°C. TH was started within 6 hours after birth and continued for 72 hours, followed by slow rewarming over 10-12 hours at the rate of 0.2-0.5°C per hour. Core body temperature was monitored continuously using a rectal probe during the cooling and rewarming phase and for 12 hours after the rewarming was complete. The rectal probe was inserted to a depth of 2-3 cm and it was sterilized with ethylene oxide gas after use.

MiraCradle-Neonate Cooler has a cradle made of non-conducting material, PCM blocks kept in the hollowed-out area and a conducting mattress above the PCM blocks, on which the baby is nursed. The PCM blocks are stored in the refrigerator (2-8°C) and should be solid when taken for use. They were disinfected with surgical spirit. Two types of PCM blocks were used, FS-29 (FS, form stable) with melting point of 29°C and FS-21 with melting point of 21°C.

During the induction phase, both FS-29 and FS-21 were used to decrease the baby's core temperature to the target range as quickly as possible. When the temperature reached 33.8°C, the FS-21 was removed and only FS-29 was used during the maintenance phase. The upper and lower alarm limits were set on the multi-parameter monitor at 33.8°C and 33.2°C, respectively. If the baby's temperature reached ≥33.8°C, FS-21 was added till the temperature came down to 33.5°C.

If the temperature reached ≤33.2°C (lower alarm limit), steps taken to increase the core temperature were placing a sheet between the PCM bed and the baby, covering the baby with another sheet or switching on the radiant warmer. The radiant warmer was used in manual mode with an output of 10% to start with, and adjusted in increments or decrements of 5% depending on the baby's temperature.

Continuous monitoring of vital parameters was done. The study infants had a central venous line and an arterial line whenever feasible. Blood counts, prothrombin time (PT) and activated partial thromboplastin time (aPTT), serum creatinine, serum electrolytes, liver enzymes and C-reactive protein (CRP) were monitored during cooling.

Sedation was not routinely given during cooling. Sedation/analgesia was given according to the protocol of the unit. All the other treatment modalities including ventilation, medications (antibiotics, anticonvulsants and inotropes) and use of blood products were done as per the protocol of individual units.

RESULTS

The study enrolled 103 neonates [JIPMER, Puducherry (25), CMC Vellore (23), JMMC, Thrissur (15), SJMC, Bangalore (n=10), The Cradle, Gurgaon (10), KMC, Manipal (9), SRMC, Chennai (3), Fernandez Hospital Hyderabad (3), Cloudnine Hospital Gurgaon (2), Neo Clinic Jaipur (2) and Shaiva Critical Care Ahmedabad (1)]. The mean (SD) gestational age and birth weight was 38.5 (1.5) and 2925 (458), respectively. Three (2.9%) infants had mild, 81 (78.6%) had moderate and 19

(18.4%) infants had severe encephalopathy; 58 (56.3%) babies had seizures.

The temperature and cooling profile is provided in ***Table* I** and ***Web Fig*. 1.** Cooling had to be discontinued in 18 (17.5%) infants. The reasons included hypotension (8), PPHN (4), withdrawal by parents (5) and bleeding (1). In the subset of babies in whom cooling was withdrawn, the mean (SD) temperature during the cooling phase was 33.5 (0.48)°C and 15.0% of the readings were outside the target range (10.6% readings were <33°C and 4.9% were >34°C).

***Table* II** shows the adverse events in the cooled neonates. The most frequent events were related to hypotension, coagulopathy and sepsis. Seven (6.8%) babies died before discharge; 4 babies due to severe encephalopathy, 2 due to severe persistent pulmonary hypertension (PPHN) and 1 baby due to sepsis.

DISCUSSION

In this study, we observed that cooling of asphyxiated neonates using PCM-based cooling device can be done without major complications in level 3 NICUs in India, with a well-defined protocol in place. Most of the infants had a low temperature at the initiation of cooling (35.2±1.3ºC). This might be a result of asphyxia or because of failure to switch on warmer in asphyxiated babies (before initiation of TH) to prevent inadvertent hyperthermia, which has been shown to worsen outcome in these babies [6].

TH could be initiated within the 6 hours window period in all the centers. The time taken to reach target temperature (up to 120 minutes) in our study was higher than that in the NICHD trial using servo-controlled equipment, where the target temperature was reached in all babies within 90 minutes [5]. The induction phase should be as short as possible, as a longer time to reach the target temperature delays the onset of TH. The core temperature of the neonates in our study could be maintained within the target range during the cooling phase in all the centers. The fluctuation (SD) of the temperature during cooling phase (0.39°C) in our study was less when compared to the fluctuations reported by the TOBY (0.5°C) and NICHD (0.45°C) trials using servo-controlled systems [5,7].

While temperature readings <33°C increase the rate of complications of cooling, temperature >34°C would decrease the efficacy of TH. Hence maintaining the core temperature within the target range is essential. In our study, temperature readings outside the target range were higher as compared to that seen in single-center study using the same PCM-based device (3.4% and 1.4% respectively) [4]. The temperature fluctuations beyond the target range might be reduced with more intense nursing input to maintain the target temperature and with experience. However, only 6 (5.8%) babies had temperature recorded <32°C compared to 10% in the NICHD study [8].

The study has some limitations. There was no control group. The nursing interventions were not objectively

TABLE I TEMPERATURE AND COOLING PROFILE OF ENROLLED NEONATES (*N*=103)

Variables	*Value*
Age of initiation of cooling (h)	2.9 (1.9)
Rectal temperature at initiation of cooling (ºC)	35.2 (1.3)
*Time taken to reach target temperature (min)	90 (45, 120)
Temperature during cooling phase, (ºC)	33.5 (0.39)
Temperature readings outside the target range	
% below 33ºC	5.1
% above 34ºC	5. 7
Rewarming rate (ºC/ h),	0.28 (0.14)

*Values in mean (SD) or *Median (IQR).*

TABLE II ADVERSE EVENTS DURING COOLING PERIOD IN ENROLLED NEONATES (*N*=103)

Adverse event	*n (%)*
Cardiovascular	
Hypotension	11 (10.7)
Shock/Hemodynamic instability	8 (7.8)
Arrythmia	2 (1.9)
Persistent pulmonary hypertension of newborn	5 (4.9)
Sinus bradycardia (<80/min)	-
Hematological	
Coagulopathy	22 (21.4)
Thrombocytopenia	11 (10.7)
Bleeding	2 (1.9)
Leucopenia	2 (1.9)
Metabolic	
Dyselectrolytemia (Hyponatremia/hyperkalemia)	6 (5.8)
Hypoglycemia	7 (6.8)
Hyperglycemia	9 (8.7)
Others	
Sepsis (Culture positive or probable)	21 (20.4)
Acute kidney injury	1 (1)
Subcutaneous fat necrosis	3 (2.9)
Death	7 (6.8)

WHAT IS ALREADY KNOWN?

- Phase Changing Material (PCM)-based system is a low-cost technology that has recently been developed.

WHAT THIS STUDY ADDS?

- Therapeutic hypothermia using PCM-based device is feasible and safe when practiced in level 3 NICUs in India.
- PCM-based device is comparable to standard servo-controlled equipment in maintaining the target temperature.

measured. We did not have follow-up data as we looked only at the feasibility and short-term outcome.

Though the PCM-based device provides a stable temperature during cooling, comparable to servo-controlled equipment, the extent of nursing interventions required would be greater than while using the automated equipment. The nursing input was not measured systematically in our study. However, the nursing efforts required would be less than while using frozen cool gel packs (FGP). In the study by Bharadwaj, *et al*. [9], the FGPs needed to be changed once in 3-4 hours. Whereas while using the PCM, the FS-21 blocks may need to be placed 2-3 times in 24 hours when temperature increases to 33.8ºC while the FS-29 do not need to be changed for the 72 hours cooling period. Thus the two major drawbacks of low-cost cooling methods such as FGP, water bottles and cooling fans namely the wider fluctuations of target temperature and the labor-intensive nursing are less with the PCM-based cooling device [10].

Most of the complications reported in cooled neonates are likely to be due to the asphyxia *per se* rather than cooling. In the recent Cochrane review [1], only thrombocytopenia and sinus bradycardia were significantly higher in babies being cooled, compared to non-cooled neonates. The complications in our study were much less as compared to the TOBY trial [7]. This could be due to fewer babies with severe encephalopathy in our study (only 10% as compared to the 60% in the TOBY trial). Three babies had subcutaneous fat necrosis in our study, which was similar to the 2.8% reported in the Swiss Cooling Registry [11]. There was a high rate of discontinuation of cooling before 72 hours in our study due to reasons such as hemodynamic instability/ refractory shock, PPHN and bleeding. This was probably because some of the centers were relatively inexperienced in TH and had a low threshold to withdraw cooling.

Though our study shows that TH can be practiced safely, adequate supportive care, continuous vitals monitoring and monitoring of laboratory parameters are imperative during cooling. All cooled neonates should preferably have central venous and arterial lines. TH cannot be recommended in level 2 NICUs, as cooling without adequate supportive care and back up of invasive ventilation may be unsafe.

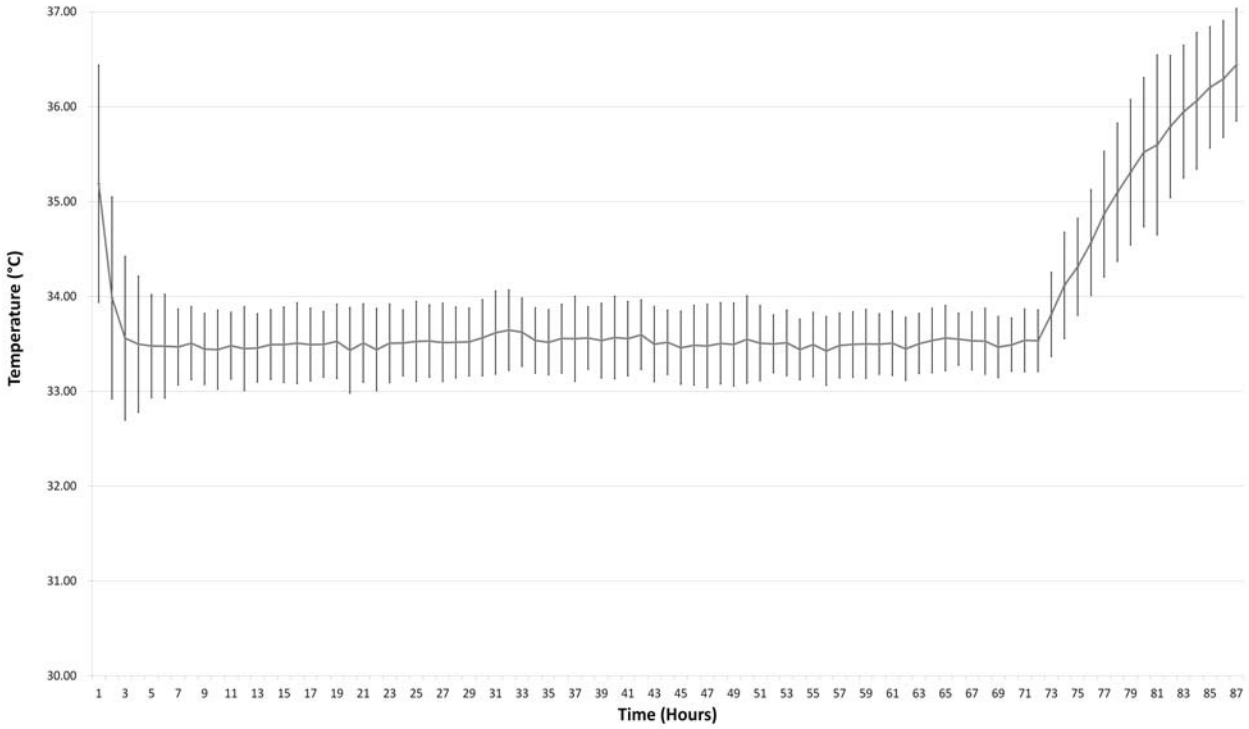
We conclude that therapeutic hypothermia of neonates with HIE using PCM-based cooling device is feasible and safe when practiced in level 3 NICUs in India. PCM-based device seems to be comparable to standard servo-controlled equipment in maintaining the target temperature.

Contributors: NT: concept, design, data collection, data analysis, manuscript writing and review; AT, VB, MV, SR, SW, LL, UB, SM, JM, AD, PYN and SN: design, data collection, data analysis, manuscript writing and manuscript review; All authors approved the final version.
Funding: The Miracradle-Neonate Cooler was supplied by Pluss Advaced technologies free-of-cost to all the participating centers. The workshop where the participants were trained (including travel and accommodation) in using the Miracradle was funded by Christian Medical College Vellore, Adit foundation and Indian Overseas Bank (funds from the latter two raised by Pluss Advaned technologies, the manufacturer of Miracradle).
Competing interests: NT was involved in the concept and design of the Miracradle. None stated for other authors.

REFERENCES

1. 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.
2. 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:e58834.
3. 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:F280-1.
4. 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;107:266-70.

5. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, *et al*. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005;353:1574-84.
6. Laptook A, Tyson J, Shankaran S, McDonald S, Ehrenkranz R, Fanaroff A, *et al*. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics. 2008;122:491-9.
7. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, *et al*. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009; 361:1349-58.
8. Shankaran S, Laptook AR, McDonald SA, Higgins RD, Tyson JE, Ehrenkranz RA, *et al*. Temperature profile and outcomes of neonates undergoing whole body hypothermia for neonatal hypoxic-ischemic encephalopathy. Pediatr Crit Care Med. 2012;13:53-9.
9. 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;58:382-8.
10. Higgins RD, Raju T, Edwards AD, Azzopardi DV, Bose CL, Clark RH, *et al*. Hypothermia and other treatment options for neonatal encephalopathy: An executive summary of the Eunice Kennedy Shriver NICHD workshop. J Pediatr. 2011;159:851-8.
11. Grass B, Weibel L, Hagmann C, Brotschi B, National Asphyxia and Cooling Register Group. Subcutaneous fat necrosis in neonates with hypoxic ischaemic encephalopathy registered in the Swiss National Asphyxia and Cooling Register. BMC Pediatr. 2015;15:73.



***Web Fig.* 1** *Temperature (mean±SD) of cooled babies.*