RESEARCH PAPER

Whole Body Cooling in Newborn Infants with Perinatal Asphyxial Encephalopathy in a Low Resource Setting: *A Feasibility Trial*

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Objective: To determine the feasibility and safety of whole body cooling in newborn infants with perinatal asphyxial encephalopathy in a low resource setting.

Design: Feasibility trial.

Setting: Tertiary care perinatal centre.

Subjects: Infants born at ≥ 35 weeks gestation with perinatal asphyxia were included in the study.

Interventions: Infants were cooled to a rectal temperature of 33±0.5°C for 72 hours using cloth-covered ice-gel packs. Vital parameters were monitored continuously.

Outcome measures: The primary outcome was the achievement of target temperature within 1 hour of initiation of treatment and maintaining the target temperature for 72 hours. Adverse events and possible complications of hypothermia were the secondary outcomes measured.

Results: Twenty infants were included in the study. The mean time taken to achieve target rectal temperature was 52±25 minutes. The mean rectal temperature during cooling was 32.9±0.11°C. The target temperature could be maintained for 72 hours without difficulty in all babies. Adverse events observed during cooling were thrombocytopenia (25%), sinus bradycardia (25%), deranged bleeding parameters (20%), aposteatonecrosis (15%), hyperglycemia (15%), hypoglycemia (10%), hypoxemia (5%), life-threatening coagulopathy (5%) and death (5%). Shivering was noted in many of the babies, especially in the initial phase of cooling.

Conclusion: Whole body cooling in term infants with perinatal asphyxia is achievable, safe and inexpensive in a low-resource setting.

Key words: *Asphyxia, Feasibility, India, Management, Newborn, Therapeutic hypothermia.*

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Brain cooling initiated within 6 hours and maintained for 72 hours after an asphyxial insult has been shown to reduce mortality and morbidity among newborn survivors of perinatal asphyxia [1-7]. Meta-analyses, including the Cochrane systematic review on cooling for hypoxic ischemic encephalopathy conclude that there is evidence that therapeutic hypothermia is beneficial to term newborns with hypoxic ischemic encephalopathy [8-10]. Cooling reduced mortality without increasing major disability among survivors. However, most studies have been done in developed countries using expensive equipment.

The present trial was conducted to evaluate whether whole body cooling (WBC) could be achieved in a low-resource setting using simple and easily available cooling materials.

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METHODS

The study was conducted in the neonatal unit of the Christian Medical College, Vellore between October 2007 to September 2008 after approval from the Institutional Review Board. Term and near-term babies (gestational age ≥35 weeks) were recruited, and included both inborn and outborn babies with perinatal asphyxia.

Inborn babies were included in the study if the following criteria were satisfied: umbilical cord or a postnatal (in the first hour of life) arterial blood gas pH of < 7.0 or base deficit ≥12 along with any two of the following: (*a*) Apgar score ≤5 at 5 minutes; (*b*) Ventilation initiated at birth and continued for at least 10 minutes; and, (*c*) Perinatal predisposition to perinatal asphyxia (any one) - intrapartum fetal distress, cord prolapse, placental abruption, maternal respiratory arrest, and uterine rupture/dehiscence.

The criteria for outborn babies was a history of not having cried/breathed immediately after birth with evidence of encephalopathy at admission and any or all of the following features: (*a*) not breathing normally at five minutes of birth; (*b*) given assistance for breathing soon after birth; (*c*) flaccid since birth; (*d*) poor feeding; and, (*e*) Apgar score of 5 or less at 5 minutes.

Babies were excluded from the study if they were small for gestational age, had chromosomal or major congenital anomaly, refusal of consent, or inability to start cooling by 5 hours of age. As per the unit protocol, severely asphyxiated babies (no spontaneous respiration by 30 minutes of life) were not ventilated.

After obtaining informed consent from the parents of eligible babies, a neurological examination was performed using a standardized neurological examination that was based on the modified Sarnat criteria and used in the NICHD study [6,11]. The infant warmer was turned off and cooling achieved by placing 3-5 cloth-covered cooling ice packs over the back, head, abdomen and the axillae of the baby. These packs were plastic containers filled with cooling gel used in vaccine carriers and were stored in the freezer of the refrigerator. These packs were reused after adequate cleaning.

A rectal probe (Philips-ref no 21090 A or Drager-ref no 4329848-08) to monitor core temperature was inserted 5 cm within the rectum and connected to a multi-parameter monitor (Philips Intellivue MP20 or Drager vista XL). The desired rectal temperature was 33±0.5°C. The temperature was continuously monitored and recorded every 15 minutes for 4 hours and then subsequently every hour for 80 hours. The skin temperature was measured simultaneously. During the cooling process, if the infant's rectal temperature approached 33.5°C, more cloth-covered cooling-gel packs were placed on the body, and these were removed one by one when the rectal temperature dropped to 33°C. After 72 hours of hypothermia, re-warming was achieved by removing the packs, turning on the warmer and raising the temperature of the baby by not more than 0.5°C per hour. The environmental temperature of the nursery was also recorded during the study period. The nurse to patient ratio was 1:3. All infants had a central venous line and arterial access. Continuous monitoring of vital parameters was done. All treatment including medications (antibiotics, anticonvulsants, inotropes and sedatives), ventilation, and use of blood products were as per existing treatment protocols. Neurological examination was repeated at 24 and 72 hours. Serum electrolytes, blood urea, serum creatinine, prothrombin time (PT), activated partial thromboplastin time (aPTT), liver enzymes and blood counts were monitored at 0, 24, 48 and 72 hours. Blood gas was done at 0, 2, 8, 12, 24, 48 and 72 hours. An ECG was obtained if the heart rate was less than 80/min.

An external data and safety monitoring committee was notified within 48 hours if any of the following adverse events occurred: cardiac arrhythmia requiring medical treatment; persistent hypoxemia (transcutaneous oxygen saturation of 85% or a paO_2 <50 mm Hg in spite of a FiO_2 of 1 on mechanical ventilation); hypotension despite adequate inotropic support (dopamine at 10 µg/kg/min and dobutamine at 20 µg/kg/min); skin changes (sclerema, aposteatonecrosis); thrombocytopenia ($<100\times10^3/\mu L$); life-threatening coagulopathy; arterial thrombosis; hepatic and renal failure; electrolyte disturbances; and, death.

Statistical analysis: The sample size was calculated using the design of Gehan (1961). With a 10% precision and a 20% desired effectiveness, the sample size was calculated as 20. The analysis of the data was done using the SPSS 16.0 software. Mean, median, mode, standard deviation and frequency were calculated. Tests for significance used were Pearson's coefficient and Mann-Whitney U test.

RESULTS

Twenty infants were recruited in the study, of whom 11 (55%) were outborn, and 12 (60%) were female. Maternal and neonatal details are provided in ***Tables* I** and **II**. Most mothers were primigravid (90%), had no complications of pregnancy, and went into spontaneous labour. Fetal heart deceleration was seen in the majority of inborn babies and 45% were born normally. Cooling was started at a mean of 3.4 ± 1.2 hours after birth. Majority of the infants recruited developed moderate encephalopathy.

At the start of cooling, the mean rectal temperature was 36.0±0.8°C and the mean skin temperature was 35.8±0.97°C. The mean time taken to reach target rectal temperature was 52±25 minutes. A Kaplan-Meier survival analysis was done with "time to attain target temperature" as the event. By the end of 15 minutes, 30% had achieved the target temperature; the median time to event was 45 minutes (95% CI 34.3-55.8). At 60 and 90 minutes from commencement of cooling, only 35% and 5% of the newborns, respectively had not achieved the target temperature.

TABLE I MATERNAL CHARACTERISTICS OF THE STUDY NEONATES

Primigravia	18 (90%)
Complications of pregnancy	
Gestational diabetes mellitus	1 (5%)
Pregnancy induced hypertension	2 (10%)
None	17 (85%)
Peripartum complications (inborn)	
Fetal heart rate deceleration	7 (77.7%)
Hemorrhage	1 (11.1%)
Meconium stained amniotic fluid	1 (11.1%)
Spontaneous onset of labor	18 (90%)
Duration of labour (h)	13±10
Mode of delivery	
Normal	9 (45%)
LSCS	8 (40%)
Forceps	2 (10%)
Vacuum	1 (5%)
Inborn No (%)	9 (45%)

Pearson's correlation looking at the linear relationship of birth weight and time taken to achieve target temperature showed a positive moderate correlation (r=0.545; P<0.05) suggesting that the larger babies took a longer time to cool. There was no statistical significance between time taken to cool and gestational age, gender, type of labor, place and mode of delivery.

The environmental temperature of the nursery during the study period ranged from 28 to 32ºC.

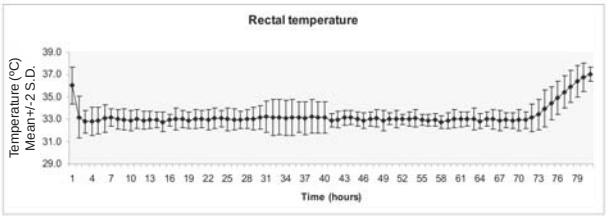
Skin and rectal temperature during cooling: The mean average rectal temperature and mean average skin temperature during the period of cooling were 32.9±0.11°C and 33.1±0.14°C, respectively (***Fig* 1*a,b***). The mean average difference between rectal and skin temperatures was 0.15±0.13°C. (***Fig* 1*b***). The rate of rewarming after 72 hours of cooling was 0.48 ± 0.07°C (***Fig* 1*c***). The variation in the mean rectal temperature from target temperature during the period of cooling was 0.08 ± 0.04°C.

Clinical and laboratory parameters: The mean heart rate, blood pressure and oxygen saturation during cooling is seen in ***Fig.* 3**. The mean heart rate at the start of cooling was 138±15 per minute while the average mean heart rate during the period of cooling was 111±5/min. The mean blood pressure at the start of cooling was 54.7±7.9 mm Hg and the average mean blood pressure during the period of cooling

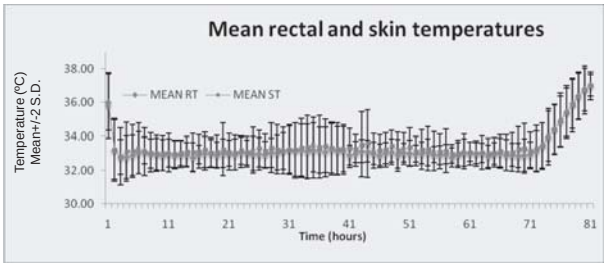
TABLE II CHARACTERISTICS OF THE NEONATES IN THE STUDY

Mean gestational age (wks)	38.5 ± 1.3
Age at starting cooling (h)	3.4 ± 1.2
Inborn	3 ± 1
Outborn	3.5 ± 1
Gender (Inborn: Outborn)	
Male (1:1)	8 (40%)
Female (1:1.4)	12 (60%)
Birthweight (g)	3034 ± 518
Cord blood pH (inborn only)	6.945 ± 0.118
Cord blood BE (inborn only)*	–19.1 ± 3.2
Moderate encephalopathy, No. (%)	16 (80%)
Severe encephalopathy, No. (%)	4 (20%)

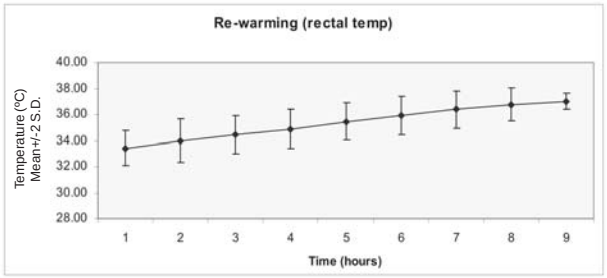
**BE: base excess.*



(*a*) Rectal temperature



(*b*) Trend of rectal and skin temperature



(*c*) Trend during re-warming

FIG. 1 *Trend of rectal and skin temperature during whole body cooling.*

was 55.6 ±1.7 mm Hg. It was noted that many of the babies shivered, especially in the initial few hours.

There was significant acidosis among inborn babies at admission. The acidosis corrected in most instances within 12 hours of the initiation of the procedure, though two babies (10%) had persistent metabolic acidosis requiring sodium bicarbonate infusion. Serum electrolytes and blood urea remained within normal limits. Serum creatinine and blood lactate showed a downward trend as cooling progressed. Two (10%) infants had hypoglycemia, and 3 (15%) had hyperglycemia requiring insulin. Liver enzyme levels were elevated initially but showed a downward trend after 48 hours. The hemoglobin and packed cell volume dropped marginally and the platelet count showed a decreasing trend during cooling.

Serious adverse events: The serious adverse events that occurred during whole body cooling are shown in ***Table* III**. There were no cardiac arrhythmias recorded. However, 5 (25%) babies developed transient sinus bradycardia. Bleeding requiring transfusions was seen in 1 (5%) infant. This infant had prolonged bleeding parameters before starting cooling and a subgaleal bleed that worsened with cooling. Cooling was stopped after 27 hours but the baby continued to deteriorate and died. Skin changes (aposteatonecrosis) seen in 3 babies resolved spontaneously. Neurosonogram was done on all infants in the first week. Periventricular white matter changes were seen in 1(5%) baby while the rest were normal.

DISCUSSION

This study was designed to look at the feasibility of whole body hypothermia in a developing country context. We used reusable ice gel packs obtained from the immunization clinic at no added expense. These were wrapped in clean cloth to prevent cold injury to the skin. The only additional cost involved was the cost of the rectal probes (Rs 900/probe) which were reusable. Using this method we could achieve and maintain the target temperature with ease. Several other researchers have used cold water/ ice gel packs in previous studies either for head cooling or for inducing whole body hypothermia(12-14). Compared to this, the standard equipment used in cooling is expensive: the cooling mattress costs Rs 500,000 while the cool cap costs Rs 3,500,000. Two studies from Africa also looked at using low resource methods of cooling; Robertson, *et al*. [15] used water

TABLE III SERIOUS ADVERSE EVENTS DURING COOLING

Adverse events	No. (%)
Cardiac arrhythmias	Nil
Hypoglycemia (blood sugar <45 mg/dL)	2 (10%)
Hyperglycemia requiring insulin	3 (15%)
Thrombocytopenia(<100 ×10^3/μL)	5 (25%)
Bleeding	1 (5%)
Aposteatonecrosis	3 (15%)
Hypoxemia	1 (5%)
Hepatic dysfunction	1 (5%)
Oliguria (urine output <0.5 mL/kg/h)	1 (5%)

WHAT IS ALREADY KNOWN?

- In developed countries, whole body cooling has been shown to decrease the risk of death or disability in infants with moderate to severe hypoxic-ischemic encephalopathy.

WHAT THIS STUDY ADDS?

- Whole body cooling is feasible and safe in a low resource setting and can be achieved with minimal additional cost.

bottles filled with cool tap water, and Horn, *et al*. [16] devised a servo control fan to maintain hypothermia. Both studies reported that cooling is possible in a low resource setting and can be made inexpensive by innovative means.

We have also demonstrated that it is possible to obtain informed consent and initiate treatment within 5 hours of birth in both inborn and outborn infants. The mean time to achieve target temperature in our study was 52±25 minutes. This was similar to the time taken to achieve cooling in previous studies from China and South Africa [4,15]. Although many studies do not indicate the time taken to reach the target temperature, available data suggests that an upper limit of 90 minutes is more realistic [6]. Though only 65% achieved desired temperature in our trial within one hour, using this criterion of 90 minutes, 95% of our newborn infants reached the target rectal temperature.

Wide variations in temperature during cooling not only increase the adverse effects of cold exposure but also compromise the degree of neuroprotection, because even small changes (as little as 1-2ºC) in brain temperature may modulate the extent of hypoxic ischemic damage [17]. In this trial, the mean rectal temperature was very close to desired temperature with the mean variation in rectal temperature being only 0.08 ± 0.04ºC from the target temperature. It is important to avoid rapid re-warming as this may offset the neuroprotective effect of hypothermia. Our re-warming rate was 0.48 ± 0.07°C per hour, demonstrating that slow and smooth re-warming can be achieved using radiant warmers.

An interesting outcome noted was that the mean average difference between the rectal and skin temperature during the period of cooling was only 0.15±0.13ºC; this implies that the skin temperature is comparable to rectal temperature. A similar finding was reported by Horn, *et al*. [14]. However, further studies are needed to see if using skin temperature alone would suffice in monitoring babies' temperature during therapeutic hypothermia.

The results of this feasibility trial are in concordance with other studies that show that hypothermia is not associated with serious adverse events like cardiac arrhythmias, prolonged acidosis, life threatening bleeding or thrombosis. The fall in the heart rate when the rectal temperature was lowered to the target temperature was consistent with other reports. Thrombocytopenia seen in five of the infants could be attributed to cooling. However, there was no significant clinical bleeding in 4 of these babies. One baby, who had deranged coagulation profile before the start of cooling, developed disseminated intravascular coagulation and subsequently died. Hypoglycemia was seen in two infants requiring higher intravenous carbo-hydrate intake. Hyperglycemia requiring insulin was seen in three babies. This may be attributed to the decrease in insulin secretion during hypother-mia [18]. This effect has not been reported in earlier trials involving newborn infants.

We specifically monitored for skin changes as cloth covered ice-gel packs were used in the initiation and maintenance of cooling. At the start of cooling, there was hyperemia in the areas where the ice-gel packs were placed and this required frequent rotation of the packs to different areas of the body. During the maintenance phase, no skin changes were noted. The aposteatonecrosis that was observed in three babies occurred during the start of cooling and subsequently resolved without intervention or residual scarring. These have been well described as an adverse effect of whole body cooling [6,15,19]. Though shivering was not one of the adverse events

monitored, we noted that many of the babies shivered especially in the initial few hours. The shivering noted in our study may be related to either under sedation or the method of cooling. Shivering was also noted by Horn, *et al*. [16], who also reported hypomagnesemia in all the babies who shivered. There is evidence from studies in adult intensive care units to suggest that shivering may be associated with a worse outcome [20]. Other than sedation, clonidine has been used for this shivering, both in neonates who have been cooled and in post operative adult patients [16,21]. A majority of our cooled babies received phenobarbitone, though we did not routinely give analgesia other than if ventilated. Sedation during cooling is recommended and there is animal evidence to show that the neuroprotective effect of hypothermia may be lost if sedation is not used [22].

This feasibility trial in a developing country using low cost techniques with careful monitoring of temperature establishes that this neuro-protective strategy can be achieved safely and at an affordable cost. There are several issues that need to be addressed in terms of further research in a low resource setting [23]. These include the difference in the population in terms of the high incidence of IUGR, unbooked pregnancies, sepsis and meconium aspiration syndrome, the lack of transport facilities, which may preclude cooling in outborn babies and the difference in severity of encephalopathy seen in cooled babies. There is an urgent need to conduct trials looking at the efficacy and safety of cooling in this setting specifically addressing these issues.

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REFERENCES

1. Battin MR, Dezoete JA, Gunn TR, Gluckman PD, Gunn AJ. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. Pediatrics. 2001;107:480-4.
2. Battin MR, Penrice J, Gunn TR, Gunn AJ. Treatment of term infants with head cooling and mild systemic hypothermia (35ºC and 34.5ºC) after perinatal asphyxia. Pediatrics. 2003;111:244-51.
3. Gluckman P, Wyatt J, Azzopardi D, Ballard R, Edwards D, Ferriero D, *et al*. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005;365:663-70.
4. Lin Z, Yu H, Lin J, Chen S, Liang Z, Zhang Z. Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: an experience from a single neonatal intensive care unit. J Perinatol. 2006;26:180-4.
5. Inder T, Hunt R, Morley C, Coleman L, Stewart M, Doyle L, *et al*. Randomized trial of systemic hypothermia selectively protects the cortex on MRI in term hypoxic-ischemic encephalopathy. J Pediatr. 2004; 145:835-7.
6. Shankaran S, Laptook A, Ehrenkranz R, Tyson J, McDonald S, Donovan E, *et al*. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005;353:1574-84.
7. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, *et al*. TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009;361:1349-58.
8. Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P. Cooling for newborns with hypoxic-ischaemic encephalopathy. Cochrane Database Syst Rev. 2007;4: CD003311.
9. Shah P, Ohlsson A, Perlman M. Hypothermia to treat neonatal hypoxic ischemic encephalopathy: systematic review. Arch Pediatr Adolesc Med. 2007;161:951-8.
10. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, *et al*. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ. 2010;340:c363.
11. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33: 696-705.
12. Thorensen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics. 2000;106:133-4.
13. Horn AR, Woods DL, Thompson C, Elis I, Kroon M. Selective cerebral hypothermia for post-hypoxic neuroprotection in neonates using a solid ice cap. S Afr Med J. 2006;96:976-81.
14. Horn AR, Harrison MC, Linley LL. Evaluating a simple method for neuroprotective hypothermia for newborn infants. J Trop Pediatr. 2009 Sep 30 [Epub ahead of print] doi:10.1093/tropej/fmp089.
15. Robertson NJ, Nakakeeto M, Hagmann C, Cowan FM, Acolet D, Iwata O, *et al*. Therapeutic hypothermia for perinatal asphyxia in low-resource settings: a pilot randomised controlled trial. Lancet. 2008;372:801-3.
16. Horn A, Thompson C, Woods D, Nel A, Bekker A, Rhoda N, *et al*. Induced hypothermia for infants with hypoxic-ischemic encephalopathy using a servo-controlled fan: an exploratory pilot study. Pediatrics. 2009;123:e1090-8.

17. 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;110:377-85.
18. Varon J, Acosta P. Therapeutic hypothermia: past, present, and future. Chest. 2008;133:1267-74.
19. Navarini-Meury S, Schneider J, Bührer C. Sclerema neonatorum after therapeutic whole-body hypothermia. Arch Dis Child Fetal Neonatal Ed. 2007;92:F307.
20. Polderman KH Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med. 2009;37:S186-202.
21. Biolatta F, Ferri F, Giovannini F, Pinto G, Rosa G. Neopam or clonidine in the pharmacological prevention of shivering in patients undergoing conscious sedation for interventional neuroradiology. Anaesthesia. 2005; 60:124-8.
22. Thorensen M, Satas S, Loberg EM, Whitelaw A, Acolet D, Lindgren C, *et al*. Twenty-four hours of mild hypothermia in unsedated newborn pigs starting after a severe global hypoxic-ischemic insult is not neuroprotective. Pediatr Res. 2001;50:405-11.
23. Thayyil S, Costello A, Shankaran S, Robertson NJ. Therapeutic hypothermia for neonatal encephalopathy: implications for neonatal units in India. Indian Pediatr. 2009;46:283-9.