

Original Research Article

Temperature control and short-term outcomes of phase-changing material versus servo-controlled whole-body cooling in neonates with hypoxic-ischemic encephalopathy: a prospective comparative cohort study

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Received: 24 September 2026

Accepted: 21 October 2026

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ABSTRACT

Background: Therapeutic hypothermia improves outcomes in neonates with moderate-to-severe hypoxic-ischaemic encephalopathy (HIE), but access to servo-controlled systems may be limited. Phase-changing material (PCM) devices are a lower-complexity alternative requiring continuous core-temperature monitoring.

Methods: This prospective, single-centre, observational comparative cohort study included 60 neonates with moderate-to-severe HIE treated for 72 hours with either servo-controlled whole-body cooling (n=30) or PCM cooling (n=30). Allocation was non-randomised and determined by device availability at admission. The primary outcomes were time to target temperature (33.5-34.5°C) and proportion of cooling time within the target range. Secondary outcomes included rewarming duration, respiratory and haemodynamic support, complications, treatment completion, seizures, neuroimaging and neurological status at discharge.

Results: Servo-controlled cooling reached target temperature faster than PCM cooling (1.81 ± 0.37 vs 2.53 ± 0.77 hours; mean difference -0.72 hours, 95% CI -1.03 to -0.41; $p < 0.001$) and maintained the target range for a greater proportion of cooling time ($90.94 \pm 4.38\%$ vs $79.52 \pm 6.86\%$; mean difference 11.42 percentage points, 95% CI 8.45 to 14.39; $p < 0.001$). Rewarming duration did not differ significantly (7.10 ± 0.99 vs 7.48 ± 1.16 hours; $p = 0.175$). No statistically significant between-group differences were detected for ventilation, inotropic support, thrombocytopenia, coagulopathy, electrolyte abnormalities, skin complications, completion of 72-hour cooling, seizures, neuroimaging or discharge neurological outcome. In exploratory multivariable analysis, HIE severity, timing of cooling and occurrence of a major adverse event were associated with unfavourable discharge outcome; cooling modality was not (adjusted OR 0.71, 95% CI 0.21-2.38; $p = 0.581$).

Conclusions: In this small, non-randomised cohort, servo-controlled cooling provided faster and more precise temperature control than PCM cooling. PCM cooling was feasible when continuous core-temperature monitoring and intensive neonatal care were available. The study did not establish equivalence of PCM and servo-controlled cooling for clinical or neurological outcomes.

Keywords: Hypoxic-ischaemic encephalopathy, Therapeutic hypothermia, Phase-changing material, Servo-controlled cooling, Neonate

INTRODUCTION

Hypoxic-ischaemic encephalopathy (HIE) remains an important cause of neonatal death and long-term neurological disability. Therapeutic hypothermia is

established treatment for eligible neonates with moderate-to-severe HIE and is generally delivered by controlled whole-body or selective-head cooling systems.^{1,2} The effectiveness of treatment depends not only on achieving therapeutic hypothermia but also on timely initiation and

maintenance of a controlled temperature throughout the 72-hour treatment period.^{3,4}

In many low- and middle-income settings, access to servo-controlled cooling may be constrained by equipment cost, infrastructure requirements and availability of trained personnel. PCM systems have been developed as lower-complexity alternatives.^{5,6} Previous Indian experience has shown that PCM-based devices can provide feasible therapeutic hypothermia with continuous rectal temperature monitoring. Comparative evidence directly evaluating temperature-control performance against servo-controlled whole-body cooling in routine neonatal intensive care remains limited.^{7,8}

This study therefore compared a servo-controlled whole-body cooling system with a PCM-based cooling system in neonates with moderate-to-severe HIE. The primary objectives were to compare time to target temperature and the proportion of cooling time maintained within the target range. Secondary objectives were to compare rewarming, respiratory and haemodynamic support, complications, completion of cooling, seizures, neuroimaging and neurological status at discharge.

METHODS

This was a prospective, single-centre, observational comparative cohort study conducted in the level IIIA neonatal intensive care unit of Shri Shishu Bhawan Super Speciality Hospital for Children and Newborn, Bilaspur, Chhattisgarh, India. The overall study period was from

January 2024 to January 2026, with an initial period for staff training and protocol finalisation, recruitment over 18 months and a subsequent analysis/reporting period.

Neonates with moderate-to-severe HIE were eligible when gestational age was ≥ 34 weeks and predefined evidence of perinatal compromise was present, including Apgar score < 5 at 10 minutes, pH ≤ 7.0 within one-hour, base deficit ≥ 10 mmol/L, assisted ventilation for ≥ 1 hour, and/or clinical seizures or moderate/severe HIE. Exclusion criteria included gestational age < 34 weeks, major congenital or central nervous system anomalies, severe growth restriction (< 1800 g), multiple organ failure, refractory shock, grade IV intraventricular haemorrhage, overwhelming sepsis, uncorrectable coagulopathy, selected chromosomal anomalies including trisomy 13/18, and situations judged to have inevitable death. Severe persistent pulmonary hypertension was treated as a relative contraindication in study protocol.

Sixty eligible neonates were included, 30 in each group. Group allocation was non-randomised and based on the cooling device available at admission, with the stated purpose of avoiding delay in initiating therapeutic hypothermia. Group A received servo-controlled whole-body cooling using the Blanketrol system; Group B received PCM cooling using the MiraCradle system. Both groups were managed according to the same therapeutic hypothermia protocol. Core rectal temperature was continuously monitored. Target temperature was 33.5–34.5°C for 72 hours, followed by controlled rewarming at approximately 0.25–0.5°C/hour to 36.5–37°C.

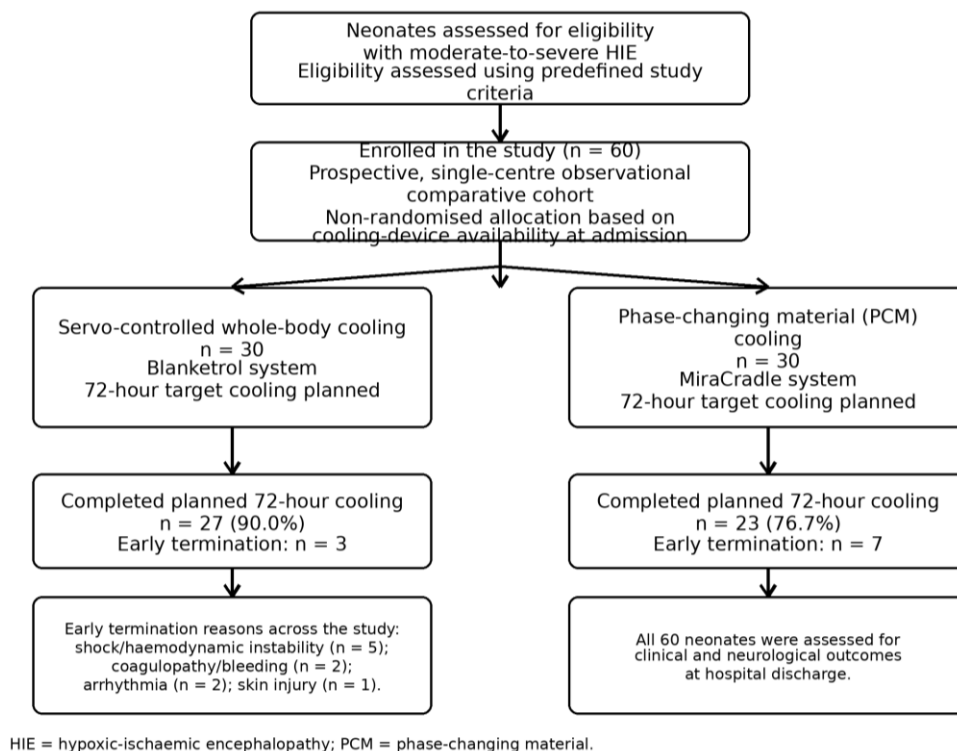


Figure 1: Participant flow through the prospective comparative cohort.

The primary outcomes were time from initiation of cooling to the target temperature and the percentage of the cooling period spent within the target range. Secondary outcomes included rewarming duration; mechanical ventilation; inotropic support; thrombocytopenia; coagulopathy; electrolyte abnormalities; skin complications; completion of 72 hours of cooling; seizures and antiepileptic drug requirement; neuroimaging category; and neurological status at discharge. Unfavourable discharge outcome was defined as an abnormal neurological examination at discharge or death. Long-term neurodevelopmental outcomes were not assessed.

G*Power version 3.1.9.7 was used for a two-independent-proportions calculation with $\alpha=0.05$, power=95% and a 1:1 allocation ratio, yielding a minimum of 11 neonates per group; the sample was increased to 30 per group. Data were analysed using Microsoft excel and SPSS version 25. Continuous variables were compared using an independent-samples t test or Mann-Whitney U test as appropriate; categorical variables were analysed using chi-square or Fisher exact tests. A two-sided $p<0.05$ was considered statistically significant. Exploratory multivariable logistic regression was used to examine factors associated with unfavourable discharge outcome. Because allocation was non-randomised and the sample was small, adjusted associations are interpreted cautiously and are not considered causal effects.

The study protocol was reviewed and approved by the Apollo Hospital's institutional ethics committee (EC/NEW/INST/2019/424) before study initiation and that written informed consent was obtained from parents or legal guardians.

RESULTS

Sixty neonates were analyzed, with 30 in each cooling group. Baseline characteristics were similar between groups. Gestational-age distributions were 34-36 weeks in 8 versus 9 neonates, 37-38 weeks in 12 versus 11, and ≥ 39 weeks in 10 versus 10 in the servo and PCM groups, respectively ($p=0.950$). Birthweight distributions were also similar ($p=0.962$). There were 17 males in the servo group and 16 in the PCM group ($p=0.795$). Caesarean delivery occurred in 17 and 18 neonates, respectively ($p=0.963$). Moderate HIE (Sarnat stage II) occurred in 22 versus 21 neonates and severe HIE (stage III) in 8 versus

9 ($p=0.774$). Cooling initiation was <3 hours in 14 versus 13, 3-6 hours in 12 versus 11, and >6 hours in 4 versus 6 neonates ($p=0.786$). Baseline pH, base deficit and lactate were also comparable.

Servo-controlled cooling reached the target temperature in 1.81 ± 0.37 hours compared with 2.53 ± 0.77 hours with PCM cooling ($p<0.001$). The mean between-group difference was -0.72 hours (95% CI -1.03 to -0.41). Servo-controlled cooling also maintained the target range for $90.94\pm 4.38\%$ of the cooling period compared with $79.52\pm 6.86\%$ with PCM cooling ($p<0.001$), an absolute difference of 11.42 percentage points (95% CI 8.45 to 14.39). Rewarming duration was 7.10 ± 0.99 versus 7.48 ± 1.16 hours ($p=0.175$).

Mechanical ventilation was required in 20/30 (66.7%) servo-cooled neonates and 21/30 (70%) PCM-cooled neonates ($p=0.781$). Inotropic support was used in 9/30 (30%) and 13/30 (43.3%), respectively ($p=0.284$). Thrombocytopenia occurred in 7 (23.3%) vs 11 (36.7%) ($p=0.260$), and coagulopathy in 5 (16.7%) versus 9 (30%) ($p=0.222$). Overall distribution of electrolyte abnormalities did not differ significantly ($p=0.409$). Skin findings absent in 29 servo-cooled and 25 PCM-cooled neonates; erythema/pressure marks occurred in 1 and 4, and skin breakdown in 0 and 1, respectively ($p=0.213$).

Completion of the planned 72-hour course occurred in 27/30 (90.0%) servo-cooled neonates and 23/30 (76.7%) PCM-cooled neonates (chi-square $p=0.166$; Fisher exact $p=0.299$). Ten neonates discontinued cooling early. The recorded reasons were shock/haemodynamic instability in five, coagulopathy/bleeding in two, arrhythmia in two and skin injury in one. The study was not powered to establish differences in these individual adverse events.

Seizure profiles were similar between groups: no seizures in 6 versus 4 neonates, seizure control with a single antiepileptic drug in 17 vs 16, and refractory/multiple-drug treatment in 7 versus 10 ($p=0.619$). Neuroimaging was normal/minimally abnormal in 10 vs 7, mild-to-moderately abnormal in 11 versus 11, severely abnormal in 7 vs 10, and not performed in 2 vs 2 ($p=0.787$). At discharge, 16 (53.3%) servo-cooled and 13 (43.3%) PCM-cooled neonates had a normal neurological examination; 8 (26.7%) and 9 (30.0%) had an abnormal examination; and 6 (20%) and 8 (26.7%) died, respectively ($p=0.721$). Overall, 31/60 (51.7%) had an unfavorable discharge outcome.

Table 1: Baseline characteristics of the study population.

Variables	Servo-controlled, (n=30)	PCM, (n=30)	P value
Gestational age (in weeks)			
34-36	8	9	0.950
37-38	12	11	
≥39	10	10	
Birth weight (in gm)			
<2500	12	13	0.962

Continued.

Variables	Servo-controlled, (n=30)	PCM, (n=30)	P value
2500-3499	14	13	
≥3500	4	4	
Male sex	17	16	0.795
Caesarean delivery	17	18	0.963
Sarnat stage			
II	22	21	
III	8	9	0.774
Cooling initiation (h)			
<3	14	13	
3-6	12	11	
>6	4	6	0.786
pH	6.95±0.07	6.94±0.07	0.500
Base deficit	14.49±2.85	14.22±3.24	0.740
Lactate	10.28±2.46	10.43±1.47	0.775

Table 2: Temperature-control outcomes.

Outcomes	Servo-controlled, (n=30)	PCM, (n=30)	P value	Between-group estimate
Time to target temperature, (h)	1.81±0.37	2.53±0.77	<0.001	MD -0.72 h (95% CI -1.03 to -0.41)
Cooling time within 33.5-34.5°C, (%)	90.94±4.38	79.52±6.86	<0.001	MD +11.42 percentage points (95% CI 8.45 to 14.39)
Rewarming duration, (h)	7.10±0.99	7.48±1.16	0.175	MD -0.38 h (95% CI approximately -0.94 to 0.18)

Table 3: Clinical and safety outcomes.

Outcomes	Servo-controlled, N (%)	PCM, N (%)	P value
Mechanical ventilation	20 (66.7)	21 (70.0)	0.781
Inotropic support	9 (30.0)	13 (43.3)	0.284
Thrombocytopenia	7 (23.3)	11 (36.7)	0.260
Coagulopathy	5 (16.7)	9 (30.0)	0.222
72-hour cooling completed	27 (90.0)	23 (76.7)	0.166
Skin complication: erythema/pressure marks	1 (3.3)	4 (13.3)	0.213
Skin breakdown	0	1 (3.3)	

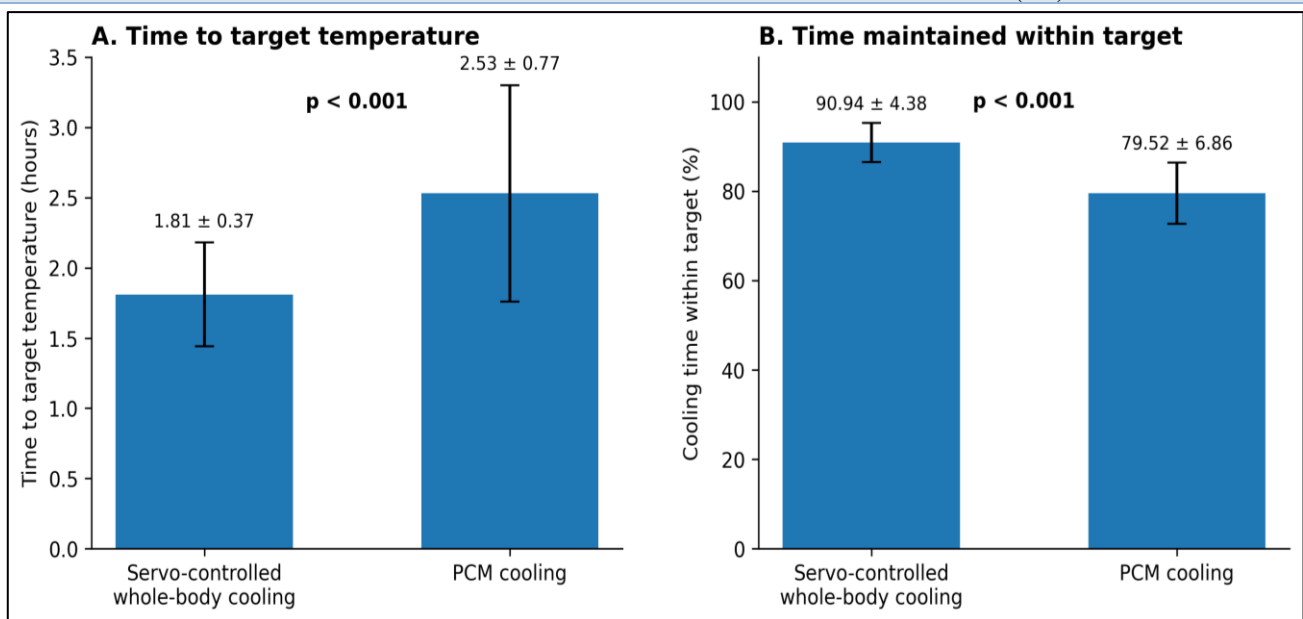


Figure 2 (A and B): Comparison of temperature-control performance between cooling methods.

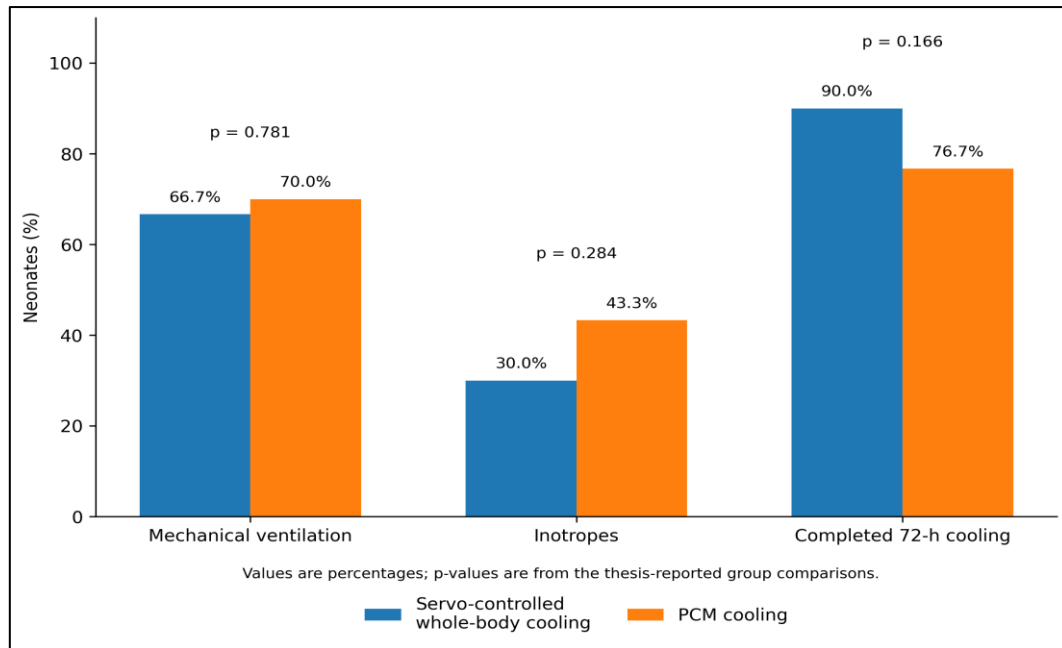


Figure 3: Clinical support and cooling completion.

Table 4: Neurological outcomes and exploratory regression.

Outcomes	Servo-controlled, N (%)	PCM, N (%)	P value
No seizures	6 (20.0)	4 (13.3)	0.619
Single-antiseizure drug control	17 (56.7)	16 (53.3)	
Refractory/multiple-drug seizures	7 (23.3)	10 (33.3)	
Normal/minimal neuroimaging	10 (33.3)	7 (23.3)	0.787
Mild-moderate imaging abnormality	11 (36.7)	11 (36.7)	
Severe imaging abnormality	7 (23.3)	10 (33.3)	
Normal neurological exam at discharge	16 (53.3)	13 (43.3)	0.721
Abnormal neurological exam at discharge	8 (26.7)	9 (30.0)	
Death	6 (20.0)	8 (26.7)	0.581
Adjusted OR for cooling modality (servo vs PCM)	0.71 (0.21–2.38)	Reference	

In univariate analysis, severe HIE was associated with a higher proportion of unfavourable outcomes than moderate HIE (76.5% vs 41.9%; $p=0.016$), and the occurrence of at least one major adverse event was also associated with unfavourable outcome (69.6% vs 40.5%; $p=0.029$). In the reported multivariable model, the overall model was significant ($\chi^2=19.101$, $df=5$, $p=0.002$), with Nagelkerke $R^2=0.364$ and Hosmer-Lemeshow $p=0.353$. Moderate versus severe HIE was associated with lower odds of unfavourable outcome (OR 0.13, 95% CI 0.03–0.53; $p=0.005$). Cooling initiated <3 hours (OR 0.13, 95% CI 0.02–0.81; $p=0.029$) and 3–6 hours (OR 0.08, 95% CI 0.01–0.55; $p=0.011$) were associated with lower odds than initiation >6 hours. Absence of a major adverse event was associated with lower odds (OR 0.27, 95% CI 0.08–0.97; $p=0.044$). Cooling modality was not independently associated with outcome (OR 0.71, 95% CI 0.21–2.38; $p=0.581$). Because major adverse events

occur during treatment, this regression is exploratory and should not be interpreted as a causal model.

DISCUSSION

The principal finding was a difference in temperature-control performance. Servo-controlled cooling reached the target range approximately 43 minutes faster on average and kept neonates within the target range for about 11 percentage points more of the 72-hour cooling period. These findings are consistent with the expected technical advantage of feedback-controlled cooling, in which the device continuously adjusts thermal output according to measured core temperature. Previous comparative work has likewise reported greater precision with servo-controlled systems, while studies of PCM-based systems have demonstrated that clinically useful therapeutic temperatures can be achieved with continuous monitoring.⁹

The present results extend the existing literature by directly comparing the two approaches within the same NICU using a common clinical protocol. Thomas et al reported feasibility of PCM cooling in 103 neonates across Indian level-3 NICUs, supporting the practicality of PCM devices when continuous rectal temperature monitoring is available.⁸ Studies comparing active, passive and manual approaches have similarly highlighted the importance of accurate temperature measurement and the risk of temperature variability with less automated methods. In the current cohort, PCM cooling achieved and maintained therapeutic hypothermia for most of the treatment period, but its temperature performance was less consistent than servo-controlled cooling.¹⁰

The clinical outcomes should be interpreted differently from the temperature outcomes. No statistically significant difference was observed in ventilation, inotropic support, haematological complications, electrolyte abnormalities, skin complications, completion of 72-hour cooling, seizures, neuroimaging or neurological status at discharge. These findings do not demonstrate equivalence between the two cooling modalities. The study was small, non-randomised and not designed or powered as an equivalence or non-inferiority trial. A lack of statistical significance for clinical outcomes therefore cannot be interpreted as proof that the methods have the same clinical effect.¹¹

The exploratory regression identified HIE severity and timing of cooling as important correlates of discharge outcome. This is biologically plausible because the severity and duration of hypoxic-ischaemic injury influence neurological prognosis, and earlier initiation of therapeutic hypothermia is a core principle of treatment. However, these associations should not be interpreted as causal estimates because treatment allocation was non-randomised and residual confounding is possible. The inclusion of major adverse events in the model also requires caution because these events occur after treatment begins and may lie on the pathway between baseline risk, treatment course and outcome.¹²

The practical implication is that PCM cooling can be considered a feasible method for providing therapeutic hypothermia where servo-controlled equipment is unavailable, provided that a rigorous protocol and continuous core-temperature monitoring are in place. The findings do not support replacing servo-controlled systems where they are available on the basis of clinical equivalence. Instead, the results suggest that the principal trade-off is between greater automated temperature precision and the feasibility of providing cooling with a simpler system. Future multicentre studies should use random allocation where ethically and operationally feasible, prespecify equivalence or non-inferiority margins if those are the intended questions, and include longer-term neurodevelopmental outcomes.¹³

The sample was modest and came from a single centre, limiting precision and generalisability. Allocation was non-randomised and determined by device availability, introducing potential selection and confounding bias. Blinding was not feasible. The study assessed neurological status only at discharge and did not evaluate long-term cognitive, motor or behavioural development. The thesis did not separately quantify the frequency, magnitude and duration of individual temperature excursions. Finally, no formal economic analysis was performed; therefore, the study cannot establish cost-effectiveness/economic superiority of PCM cooling.^{14,15}

CONCLUSION

In this prospective comparative cohort, servo-controlled whole-body cooling achieved target temperature more rapidly and maintained the therapeutic range more consistently than PCM cooling. PCM cooling was feasible under continuous core-temperature monitoring and intensive neonatal care, but the study did not establish equivalence of PCM and servo-controlled cooling for clinical or neurological outcomes. Larger, preferably multicentre comparative studies with longer-term neurodevelopmental follow-up are required.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Giri S, Giri P, Jaiswal M, Agarwal P, Bhoyar AC. Temperature control and short-term outcomes of phase-changing material versus servo-controlled whole-body cooling in neonates with hypoxic-ischemic encephalopathy: a prospective comparative cohort study. *Int J Contemp Pediatr* 2026;13:2307-13.