Therapeutic Hypothermia for Birth Asphyxia Using a New Servo-Controlled Device—A Randomised Controlled Trial

Journal of Neonatology
1–8

DOI: 10.1177/09732179251321737
journals.sagepub.com/home/nnt
Sage

Akshaya Govind[1], Chaitali Raghoji[2] and G Guruprasad[2]

Abstract

Introduction: Therapeutic hypothermia (TH) is the standard of care for moderate-to-severe birth asphyxia in high-resource settings, improving the long-term neurodevelopmental outcomes in infants with perinatal asphyxia. While widely adopted in neonatal units nationwide, TH is administered through servo-controlled methods like Tecotherm, CradleCool and manual methods using PCM mattress like Mira Cradle (by Pluss Advanced Technologies Pvt Ltd). Financial challenges in developing nations prompt the evaluation of Revive (Sensivision Health Technologies Pvt Ltd), a low-cost servo thermoregulation device against Mira Cradle in our neonatal unit for thermoregulation and immediate clinical outcomes.
Objective: The aim of this article was to study the thermoregulation achieved (effective cooling time) and immediate clinical outcomes through Revive, servo-controlled device and Mira Cradle, PCM manual device for TH.
Study Design: Randomised controlled trial.
Participants: Seventy neonates admitted to Bapuji Child Health Institute in Davanagere, Karnataka for birth asphyxia with moderate-to-severe hypoxic–ischaemic encephalopathy.
Intervention: TH was initiated via servo-controlled (n = 24) or manual method (n = 28) within 6 hours of birth for 72 hours, followed by passive rewarming.
Outcomes Measures: Thermoregulation parameters like effective cooling time, lowest and highest core temperature, deviations from required temperature, clinico-biological outcomes, dropout reasons and mortality.
Results: Servo-controlled method achieved a higher effective cooling time (91%, P <.05) compared to manual method (68%). It also exhibited enhanced safety, with no deviation of core temperature below 32 °C, in contrast to manual method with 11 patients showing deviations. Neurological outcomes showed no significant differences, but the PCM group (manual method) experienced more complications. Importantly, no death occurred with the servo-controlled method, while three were observed in the manual method group.
Conclusion: The low-cost servo-controlled method proved effective for TH offering good efficacy and safety in resource-constrained settings. It emerges as advantageous for treating TH overall.
Trial Registry Name: Clinical Trial Registry—India.

Keywords

Therapeutic hypothermia, asphyxia, servo controlled, thermoregulation

Received 19 May 2024; **accepted** 03 February 2025

Introduction

Perinatal asphyxia during pregnancy and labour is characterised by impaired gas exchange leading to foetal acidosis, hypoxemia and hypercarbia—eventually hypoxic–ischaemic encephalopathy.[1] Over 20% of neonatal deaths are linked to hypoxic ischemic encephalopathy (HIE), and at least 30% of survivors suffer long-term neurological disabilities. Cerebral palsy is one of the most costly neurologic disabilities because of its frequency (2/1000 births) and persistence over the life span.[2] Asphyxia in newborn can arise due to antepartum causes (70% of cases), intrapartum complications (20%) and 10% due to postnatal events.[3]

The incidence of HIE has not declined even with advances in obstetric care (i.e., foetal monitoring) aimed at preventing the hypoxic–ischaemic event; thus, much of the current neonatal research about HIE focuses on minimising the extent of subsequent brain injury.[4]

[1]Department of Paediatrics, JJM Medical College, Davanagere, Karnataka, India
[2]Department of Neonatology, Bapuji Child Health and Research Centre, Davanagere, Karnataka, India

Corresponding author:
Akshaya Govind, Department of Paediatrics, JJM Medical College, Davanagere, Karnataka 577004, India.
E-mail: akshaya.govind17@gmail.com

Hypoxic–ischaemic encephalopathy progresses through three stages: primary energy failure, latent phase, and secondary energy failure (SEF) which eventually leads to necrotic cell death. This clinical syndrome includes seizures, hypotonia, poor feeding and a depressed level of consciousness that typically lasts from 7 to 14 days. The widely used method to classify this clinical syndrome is Sarnat and Sarnat staging.[5]

Treatment is essential to avoid the devastating complications of HIE spanning from cerebral palsy, seizure disorder, mental retardation to death. However, multiple new neuroprotective agents are being explored to ameliorate these consequences of HIE.[6]

In recent multicenter clinical trials, hypothermia initiated within the first 6 postnatal hours has emerged as the best therapy so far.[7] It is a promising technique that prolongs the therapeutic time window (latent phase).[8]

In high-income setups, cooling is provided in centres with facilities of good intensive care unit (ICU) care, high nursing to patient ratio.[9] They use sophisticated servo-controlled devices like Tecotherm, CradleCool that provide effective cooling by regulated mechanisms with minimal deviations, which avoid harmful side effects of cooling therapy.

This prompted the rise of affordable manual cooling methods like Mira Cradle (by Pluss Advanced Technologies Pvt Ltd). In low- and middle-income countries (LMIC) where utilisation of servo-controlled devices was not feasible, various improvised local solutions including air conditioning, ice packs, phase changing materials were used to manually achieve cooling.[10.] Although widely used in our country with promising results reported in multiple studies, the efficacy of manual methods remains debatable due to concerns about maintaining core temperature, deviations from the mean and suboptimal cooling compared to servo-controlled methods.[11]

Revive, by Sensivision Health Technologies Pvt Ltd, is a low-cost, servo-controlled device designed for whole-body cooling. It features a multi-channel wrap through which coolant circulates, and a rectal probe monitors the patient's temperature. The system automatically adjusts the coolant temperature to maintain the desired range.

Here this randomised controlled trial (RCT) aims at reporting the feasibility, safety and efficacy of this new affordable servo-controlled device for whole body cooling in a tertiary level neonatal intensive care unit (NICU) and its comparison with the widely used manual methods.

Methodology

A total of 70 term babies (aged less than 6 hours with birth weight ≥ 2000 g) who required resuscitation at birth were admitted to the tertiary-level neonatal unit in Bapuji Child Health Institute, Davanagere, Karnataka. Initial blood gas or umbilical arterial blood gas showing pH≤ 7 or base deficit of ≥ 12 mEq/L was included. In case of absence of blood gas, APGAR ≤ 5, assisted ventilation for at least 10 minutes after birth or history of acute perinatal event was used as inclusion criteria. All the neonates were assessed by Modified Sarnat and Sarnat staging for the presence of moderate or severe encephalopathy.

As this is a pilot study, a convenience sample of 70 patients was planned over the period of one year. With this sample size, a 60% difference was to be detected with 90% power and a 5% significance level.

Ethical clearance was obtained and informed parental consent was taken in either local language or English before initiating the treatment. Baseline demographic details collected showed that the average gestational age was 38 weeks with 36 males and 16 females amongst the study population. Majority of these neonates were admitted for clinical diagnosis of HIE stage 2. The medical staff at the NICU were trained in monitoring and maintaining temperatures as per protocol (as mentioned in CONSORT chart in Figure 1).

This study was a RCT approved by the Institutional Review Board and Ethics Committee and registered with the Clinical Trial Registry of India. The procedures followed were in accordance with the Helinski Declaration.

Participants were started on therapeutic cooling on the allocated device within six hours of birth. A rectal probe was connected for temperature monitoring. The range of temperature of 33 °C - 34 °C was the requirement to achieve optimal cooling effects. Temperature recording was done on a Temperature Tracking sheet where:

1. It was monitored every 15 minutes for the first 4 hours, after which every hour for the next 12 hours.
2. It was then recorded every 4 hours in the maintenance phase of cooling and again every hour during the rewarming phase till normothermia was achieved.

The servo controlled device uses a self-regulating method which assesses the rectal temperature of the neonate and alters the coolant temperature accordingly; in order to maintain it within the ideal range. Whereas in the manual device, changing of the PCM mattress had to be done by the staff to maintain the temperature as per requirement.

Other clinical and biological details before and during the treatment were recorded by the treating doctor in the case records. Babies continued to receive regular ICU care like ventilatory support, inotropes, antibiotics, etc., as per need. Electroencephalogram (EEG) monitoring was not done and masking of the intervention was not possible.

Some neonates could not complete 72 hours of cooling due to complications such as hemodynamic instability, cardiac complications and death, hence were excluded from the final analysis.

Statistical Analysis: The data was entered in Microsoft Excel and analysed using SPSS 21 software. Descriptive statistics was used, and categorical data were summarised using frequency (*n*) and percentages. Continuous variables were summarised as mean (standard deviation [SD]). For comparison of data, students T test was applied and a *P* value of <.05 was considered significant.

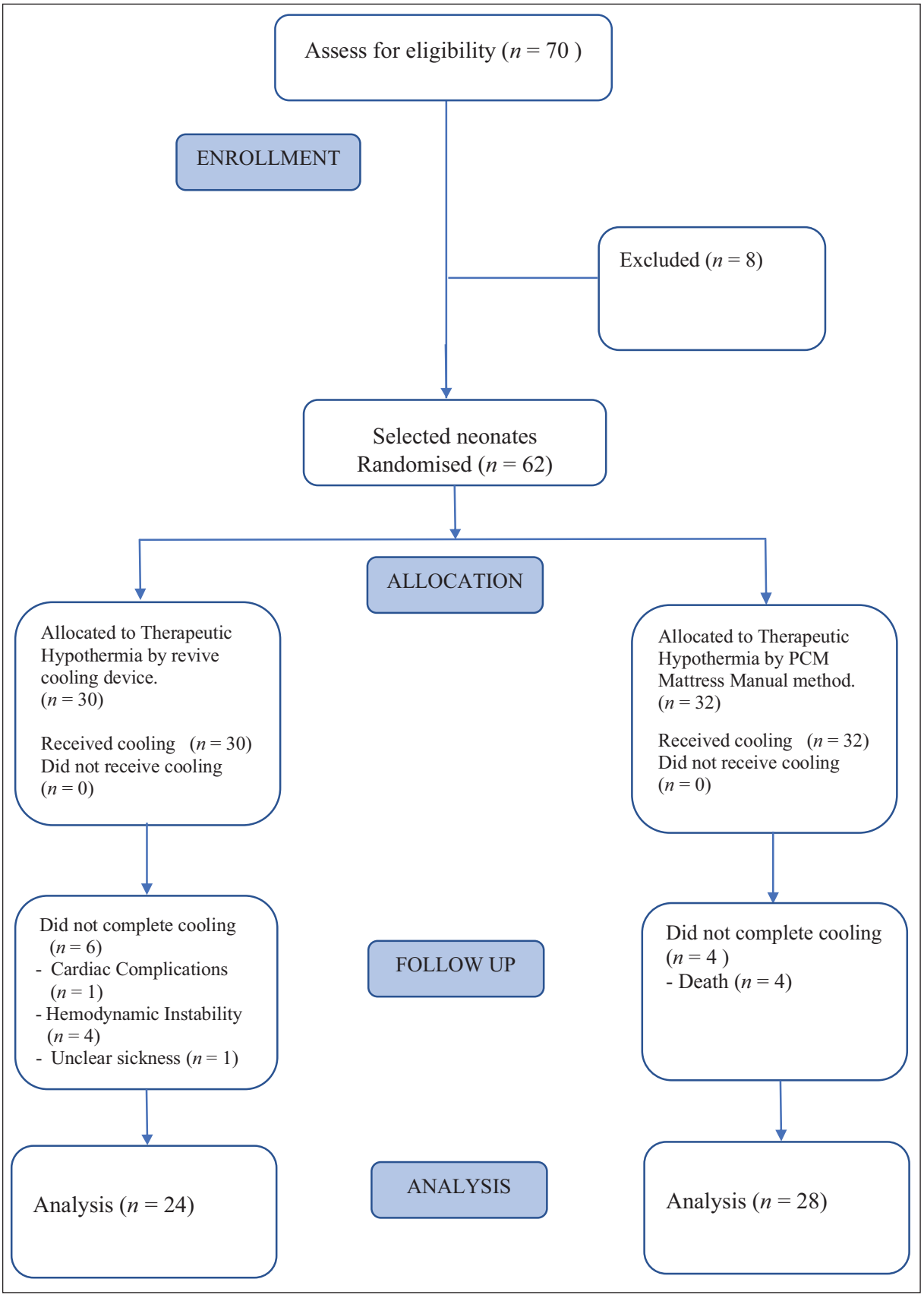


Figure 1. Flow of Participants from Enrolment to Analysis.

Results

Out of the 70 of infants who were included in the study, 62 infants were finally eligible to be a part of it. Baseline characteristics are presented in Table 1.

These characteristics revealed average gestational age of the infants was 38 weeks, comprising 36 males and 16 female, majorly being delivered vaginally. Initial clinical assessments conducted utilising Sarnat and Sarnat staging that categorised the infants into HIE 1,2,3 where majority of 39 (62%) infants exhibited moderate encephalopathy/ HIE stage 2. Nearly all of the infants were admitted within six hours of life, a pivotal inclusion criteria for this study.

These infants were now subjected to therapeutic cooling as a treatment methodology by one of the two above-mentioned devices. Thirty infants were randomly allocated to cooling via servo-controlled device and 32 by manual device. The primary outcome of the study was to analyse the thermoregulation achieved by these two devices.

Thermoregulatory Outcomes

Initial rectal temperature before the commencement of cooling was in close range for both devices with a mean value of 35.51 °C in manual method (Mira Cradle) and 36.55 °C in servo-controlled method (Revive). The optimum temperature set was 33.5 °C, and Mira Cradle achieved this in a shorter time on comparison to the servo method.

Table 1. Demographic Profile of Neonates Included in the Study.

Gestational age *(weeks)*[a]	38
Birth weight *(kg)*[a]	2.94
Gender (*n* = 52)	
Male	36
Female	16
Mode of delivery (*n* = 52)	
Spontaneous vaginal delivery	25
Instrumental vaginal delivery	17
LSCS	5
Assisted breech	1
Not known	4
Age at admission (*n* = 52)	
0–3 h	26
3–6 h	13
6 h	7
Not known	6
HIE stage (*n* = 52)	
I	8
II	39
IIIs	5

Note: Values are expressed as *n* (%) or mean(average)[a] above. LSCS, lower segment caeserean section.

Effective Cooling Time (Table 2)

It is defined as the percentage of data points of time for which the temperature remained between the range of 33 °C to 34°C. This helps in analysing the ability of the device to remain within the required range, to improve efficiency and to reduce the complications. The effective cooling time with manual method was an average of 68% and with servo-controlled method it was 91% indicating that the maximal cooling was achieved with $P < .05$.

Another entity which was analysed was the number of deviations from the mean temperature in each of the devices. This data underscores that all infants who received cooling via the manual device showed multiple deviations up to 20 deviations from the mean temperature (Box Plot 1).

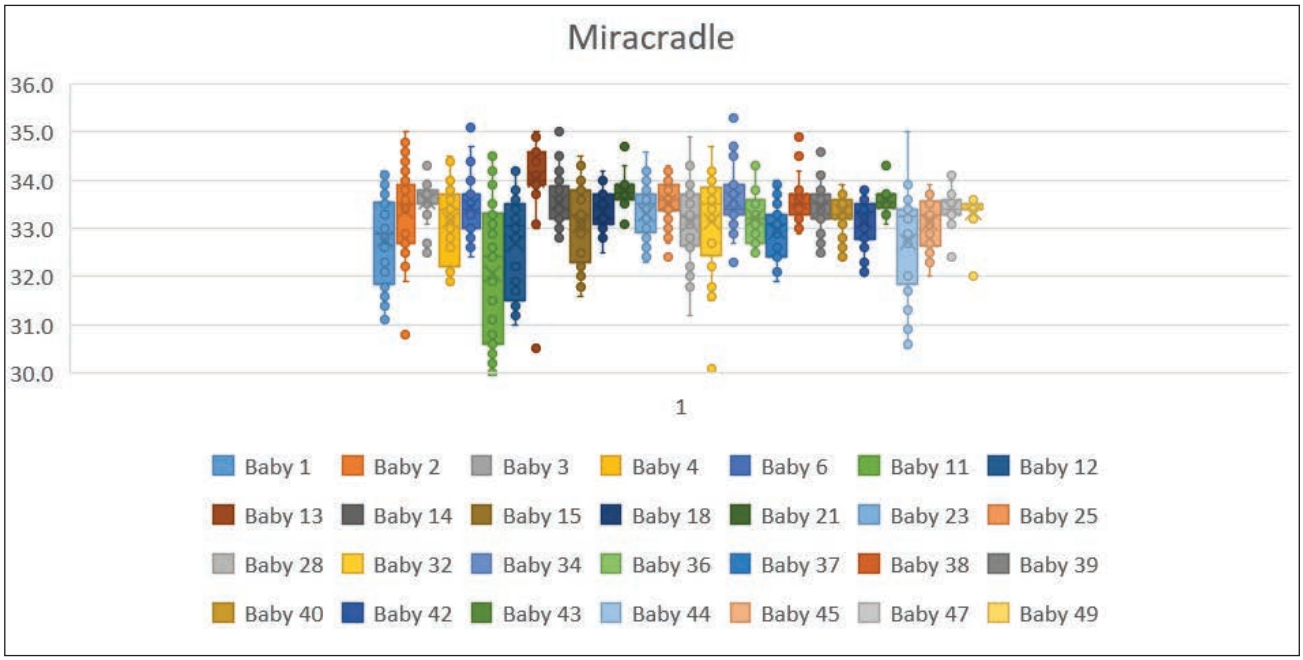
Contrastingly, with the servo-controlled device also deviations were observed, but the numbers were notably fewer with none showing more than 10 deviations. Additionally, four patients maintained the mean temperature with 0 deviations (Box Plot 2). This comparison highlights a more controlled and stable temperature profile with servo-controlled device compared to manual device (Table 2).

As previously mentioned, maintaining the temperature within the prescribed range is crucial for optimal treatment and to prevent significant complications associated with excessive cooling. One parameter analysed was the percentage of time the core body temperature dropped below 32 °C (Table 3). In manual device group, 40% infants experienced a drop during

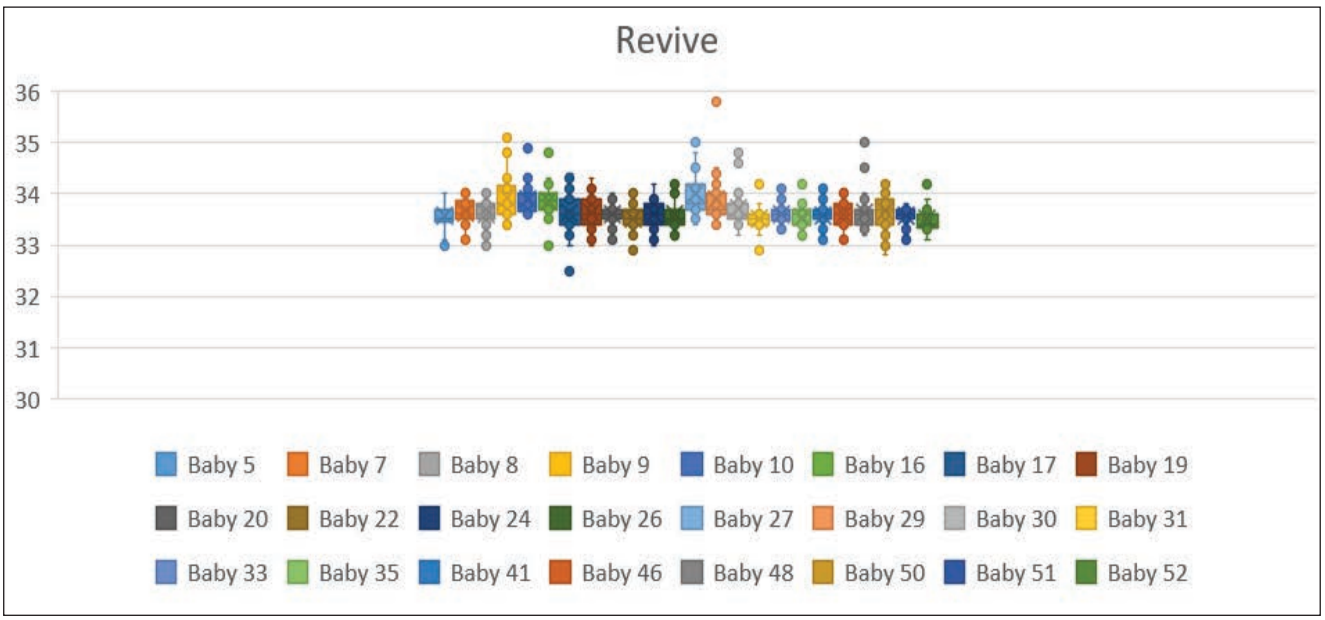
Table 2. Thermoregulatory Parameters Compared Between the Two Cooling Methods.

Thermoregulation Parameters	Manual Device (*n* = 32)	Servo-Controlled Device (*n* = 30)
Rectal temperature before cooling[a]	35.51°C	36.55°C
Cooling completed (*n* = 52)	28	24
Time taken to reach 33.5°C [a]	1 hour, 14 minutes	1 hour, 43 minutes
Effective cooling time	68%	91%*
Number of deviations from mean temperature		
0 deviations	0	4
1–5 deviations	8	15
6–10 deviations	9	5
11–15 deviations	8	0
16–20 deviations	3	0

Note: Values expressed as *n* (%) and mean (Average)[a] with **P* value <.05 for effective cooling time expressed as percentage.



Box Plot 1. Temperature Recording of Mira Cradle Babies.



Box Plot 2. Temperature Recording of Revive Babies.

the 72 hours treatment period, whereas with the servo-controlled device, no occurrences below 32 °C were observed.

All the neonates who were started on cooling could not be completed due to multiple reasons. In the manual device group, 4 out of the 32 could not complete the protocol due to death occurring during the cooling procedure. Six out of the 30 in servo-controlled device group could not complete with reasons for discontinuation being cardiac complications, hemodynamic instability and unclear sickness.

Clinico-biological Outcomes

Apart from the thermoregulatory components, clinico-biological parameters were also assessed. Basic blood workup like haemoglobin, total leukocyte counts and platelets were noted to be normal. Neonatal sepsis was noted in both groups which held not much significance. Five (17%) patients on manual device and three (12%) patients in the servo-controlled device group required ventilatory support; though the

Table 3. Core Body Temperature Compared Between the Two Cooling Methods.

Core Body Temperature	Manual Device (*n* = 28)	Servo-Controlled Device (*n* = 24)
Lowest core body temperature % of time temp <32°C	7% (Average)	0% (Average)
0 occurrence#	17	24
1–5 occurrences	6	-
6–10 occurrences	3	-
11–15 occurrences	1	-
16–20 occurrences	1	-
Highest core body temperature	35.3 °C	35.8 °C

Values expressed as (%) and # indicate the number of times the temperature dropped below 32 °C.

Table 4. Core Body Temperature Compared Between the Two Cooling Methods.

Clinico-biochemical Parameters	Manual Device (*n* = 28)	Servo-Controlled Device (*n* = 24)
Biochemical*a*		
Haemoglobin	17.74	17.91
Total leukocyte count	18,023.3	19,181.9
Platelets	2.03	2.086
Blood culture (if sent, organism isolated)	1—Candida species	1—Candida species 1—Acinetobacter species
Treatment received (*n*)		
Ventilatory support duration	5 (3d, 2d, 3d, 4d, 7d)	3 (4d, 48h, 24h)
Ionotropic support duration	11	11
Blood products	11	14
Anticonvulsants usage	19	16
Complications (*n*)		
Cardiac arrhythmia	0	0
Refractory hypotension	5	0
Bleeding diathesis	3	3
PPHN	0	2
NEC	0	0
Sepsis	1	2
Severe thrombocytopenia	0	0
Renal failure	0	0

Note: Values expressed as mean (average) [a] or *n* (%). PPHN, persistent pulmonary hypertension of newborn; NEC, necrotizing enterocolitis.

numbers were close, it was noticed that the duration of ventilation was longer with the manual method with an average of 3.5 days than servo-controlled method which averaged at two days only. This shows a difference but multiple factors like respiratory distress and cardiac complications could be the cause for prolonged ventilation and cannot be attributed to the device used per say. Other modalities like ionotropic support, blood products usage and anticonvulsants were comparable in both groups (Table 4).

Upon completion of the cooling process, immediate outcomes were assessed. The average hospital stay for Mira Cradle treated infants was nine days, while those treated with Revive was eight days. Mortality was exclusively noted with the manual device group, with one death occurring before initiation of cooling therapy and three additional deaths at 88 hours of life, 4 days of life and at 8 days of life. No deaths were reported in the servo-controlled device treated infants. Immediate neurological assessment was comparable in both groups, with over 50% exhibiting normal outcomes.

Discussion

Multiple studies have been done around the world to study the efficacy and the need for therapeutic hypothermia (TH) for the best outcome in infants with perinatal asphyxia, mostly utilising state-of-the-art expensive cooling devices. The drawback which prevents us from extrapolating those results to countries such as our own is the financial constraint as cooling devices are exclusive and are almost not affordable in majority of the places. Our medical set-ups also have a low doctor/nurses to patient ratio, suboptimal ICU care and higher incidences of obstetric complications that can lead to HIE such as birth asphyxia, MAS and sepsis.

Using innovative manual cooling methods like frozen gel packs and phase changing mattresses significantly reduces mortality and neurodevelopmental morbidity in asphyxiated neonates as per the recent meta-analysis.[12] However, these methods are shown to be associated with wider fluctuations in the target temperature, shivering and subcutaneous fat necrosis (SCFN).

Jacobs et al.[13] concluded that simple manual hypothermia, when applied with strict protocols and proper training, can be used in non-tertiary neonatal settings while awaiting transport to a regional NICU. Similar conclusions were drawn in other studies analysing manual cooling methods.[14–16]

A study done by Hoque et al. is one of the few studies which compares manual and servo methods of cooling showed that manually controlled cooling systems are associated with greater variability in temperature compared with servo-controlled systems and also causes initial overcooling. It is unknown whether large variation in temperature adversely affects the neuroprotection of TH.

Our study compares thermoregulatory patterns between servo-controlled and manual devices. While the manual device achieved target temperatures faster, it showed significantly more temperature fluctuations and a higher proportion of readings outside the target range during the cooling phase. Dangerous drops below the required range were also more frequent with the manual method. These findings highlight the superior ability of servo-controlled devices to maintain stable temperatures within safe limits, underscoring their reliability over the manual approach.

It has been widely studied that ideal temperature has to be maintained for the best neurological outcome and to prevent other iatrogenic side effects of TH. Our study highlights the benefits of the servo method as a smooth and effective cooling technique while introducing an affordable device tailored for low-income countries. This innovation addresses the limitations of manual methods, such as intensive nursing supervision and inconsistent temperature control. In resource-limited settings like India, where staff shortages and higher rates of perinatal asphyxia are challenges, this approach enhances care quality with minimal staff intervention.

The limitation of this study is the lack if long-term follow up of neurodevelopmental outcomes in both groups, which was initially planned but could not be completed due to loss of follow-up of many patients. Our study primarily concentrated on the comparison of the thermoregulation which was achieved. EEG monitoring would have added more value to the results but was not done in our patients. Further studies with larger groups and more robust analysis are required to conclude the efficacy of such new devices. It will help in bringing therapeutic cooling to many more asphyxiated infants which may be the revolution needed.

Key Message

What is already known? TH is the best modality of treatment available for birth asphyxia with HIE in infants.
What does this study add? It introduces an effective and low-cost servo-controlled device for TH by comparing with widely used manual methods.

Acknowledgements

We are thankful to members of Department of Neonatology, Bapuji Child Health Institute and Research Centre for conducting the trial, and team of Sensivision Health Technologies Pvt Ltd for providing the technical support for the trial.

Authors' Contribution

Akshaya Govind helped in analysis of data and drafting of manuscript.
Chaitali Raghoji contributed to collection and analysis of data and review of literature.
G Guruprasad conducted the trial and finalised the manuscript.

CTRI

CTRI/2020/06/025902

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical Approval

Ethical clearance attained from Institutional Ethical Committee of JJM Medical College, Davanagere, Karnataka.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Patient Consent

Written consent taken from patient guardians.

Source

Sensivision Health Technologies Pvt Ltd for providing servo-controlled device, Revive.

ORCID iD

Akshaya Govind https://orcid.org/0009-0000-1607-0220

References

1. Gleason CA, Juul SE, Avery ME. Birth asphyxia. In: Gleason CA, Juul SE, eds. Avery & Mac's Textbook Neonatology. 10th ed. Elsevier; 2018:897–909.
2. Gomella T, Cunningham MD, Eyal F. Birth asphyxia. In: Gomella T, Cunningham MD, Eyal F, eds. Gomella's Neonatology. 8th ed. McGraw-Hill Education; 2020:997–1005.
3. Johnston MV, Hoon AH Jr. Cerebral palsy. *Neuromolecular Med*. 2006;8(4):435–450.
4. Shah PS, Perlman M. Time courses of intrapartum asphyxia: neonatal characteristics and outcomes. *Am J Perinatol*. 2009;26(1):39–44.
5. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch Neurol*. 1976;33:696–705.
6. Volpe J. Perinatal brain injury: from pathogenesis to neuroprotection. *Ment Retard Dev Disabil Res Rev*. 2001;7:56–64.
7. Cotten CM, Shankaran S. Hypothermia for hypoxic-ischemic encephalopathy. *Expert Rev Obstet Gynecol*. 2009;5(2):227–239.
8. Iwata O, Iwata S, Thornton JS, et al. "Therapeutic time window" duration decreases with increasing severity of cerebral hypoxia-ischemia under normothermia and delayed hypothermia in newborn piglets. *Brain Res*. 2007;1154:173–180.
9. Thayyil S, Oliveira V, Lally PJ, et al. Hypothermia for encephalopathy in low and middle-income countries (HELIX): study protocol for a randomised controlled trial. *Trials*. 2017;18:432.

10. Chandrasekaran M, Swamy R, Ramji S, et al. Therapeutic hypothermia for neonatal encephalopathy in Indian neonatal units: a survey of national practices. *Indian Pediatr*. 2017;54:969–970.
11. Robertson NJ, Kendall GS, Thayyil S. Techniques for therapeutic hypothermia during transport and in hospital for perinatal asphyxial encephalopathy. *Semin Fetal Neonatal Med*. 2010;15:276–286.
12. Rossouw G, Irlam J, Horn AR. Therapeutic hypothermia for hypoxic ischaemic encephalopathy using low-technology methods: a systematic review and meta-analysis. *Acta Paediatr*. 2015;104:1217–1228.
13. Jacobs SE, Morley CJ, Inder TE, et al.; Infant Cooling Evaluation Collaboration. 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.
14. Hoque N, Chakkarapani E, Liu X, Thoresen M. A comparison of cooling methods used in therapeutic hypothermia for perinatal asphyxia. *Pediatrics*. 2010;126(1):e124–e130.
15. Thayyil S, Shankaran S, Wade A, et al. Whole-body cooling in neonatal encephalopathy using phase-changing material. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(3):F280–F281.
16. Oliveira V, Kumutha JR, E N, 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 Paediatrics Open*. 2018;2(1):e000245.