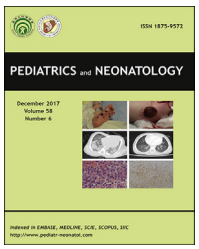
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Review Article

Therapeutic hypothermia for neonates with hypoxic ischemic encephalopathy

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Therapeutic hypothermia (TH) is a recommended regimen for newborn infants who are at or near term with evolving moderate-to-severe hypoxic ischemic encephalopathy (HIE). The Task Force of the Taiwan Child Neurology Society and the Taiwan Society of Neonatology held a joint meeting in 2015 to establish recommendations for using TH on newborn patients with HIE. Based on current evidence and experts' experiences, this review article summarizes the key points and recommendations regarding TH for newborns with HIE, including: (1) selection criteria for TH; (2) choices of method and equipment for TH; (3) TH prior to and during transport; (4) methods for temperature maintenance, monitoring, and rewarming; (5) systemic care of patients during TH, including the care of respiratory and cardiovascular systems, management of fluids, electrolytes, and nutrition, as well as sedation and drug metabolism; (6) monitoring and management of seizures; (7) neuroimaging, prognostic factors, and outcomes; and (8) adjuvant therapy for TH.
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1. Introduction

Perinatal asphyxia and neonatal hypoxic ischemic encephalopathy (HIE) are associated with high morbidity and mortality rates worldwide. Current evidence and guidelines suggest that newborn infants who are at or near term with evolving moderate-to-severe HIE should be treated with therapeutic hypothermia (TH).[1–3] TH was introduced in Taiwan in 2010, and a 2-year follow-up study has recently reported data regarding the results of TH in Taiwan.[4] To achieve consensus and formulate recommendations, a Task Force was organized, and a joint meeting of the Taiwan Child Neurology Society and the Taiwan Society of Neonatology was held in the spring of 2015. The purpose of this panel meeting was to reach a consensus and draw recommendations for neonatologists, pediatric neurologists, and pediatricians who may treat HIE newborn patients with TH.

2. Selection criteria and methods for TH

2.1. Who is eligible for TH?

In 2015, the American Heart Association (AHA) and the International Liaison Committee on Resuscitation updated guidelines for cardiopulmonary resuscitation and emergency cardiovascular care.[5] The criteria for inducing hypothermia in neonates remain the same as in 2010, and TH should be performed in accordance with published protocols based on large clinical trials.[3,5] To date, five large randomized clinical trials have been conducted for neonates with HIE; the enrollment criteria and implementation were similar across the studies (Table 1).[6–10]

In brief, patients born at $\geq$36 weeks of gestation with evolving moderate-to-severe HIE are eligible for TH. TH should be started within 6 hours of birth and continued for 72 hours with a targeted core temperature of about 33.5—34.5°C with slow rewarming back to normal temperature over at least 4 hours. Patients usually present symptoms or signs of acute perinatal brain insults, evidence of significant fetal compromise, and ongoing clinical encephalopathy after birth. Amplitude-integrated electroencephalography (aEEG) was used for 20 minutes in the Cool-Cap trial and 30 minutes in the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial to assist in the diagnosis of moderate-to-severe encephalopathy.[7,8]

The suggested criteria and framework for treating TH in neonates with HIE in Taiwan are shown in Figure 1. All infants must fulfill criteria (A) + (B) + (C) as follows: (A) newborn infants with gestational age $\geq$36 weeks; (B) commencement within 6 hours after birth; (C) evidence of moderate-to-severe encephalopathy *and* one of the following conditions: (1) severe acidosis (pH $\leq$ 7.00 or base deficit $\geq$ 16 mmol/L) within 1 hour after birth, either from the umbilical cord or arterial or venous samples; (2) Apgar score $\leq$ 5 at 10 minutes; or (3) resuscitation $\geq$ 10 minutes after birth.

2.2. Methods and equipment for TH

Based on AHA/International Liaison Committee on Resuscitation guidelines and data from systematic reviews and meta-analyses, either whole-body cooling (WBC) or selective head cooling (SHC) can be used to induce TH.[1,2,11] A recent prospective, randomized, small-scale pilot study compared the differences between SHC and WBC in near-term and term newborns with HIE and showed no significant differences in adverse effects, 12-month neuromotor development, or mortality rates between the two groups.[12] Hence, the Task Force recommended using either WBC or SHC to treat newborn patients with HIE.

Currently, the Cool-Cap system (Olympic Medical Cool Care System; Olympic Medical, Seattle, WA, USA) is used for SHC. It is more complex and expensive than WBC devices and requires manual adjustments of radiant warmers. The aim of SHC is to cool the head by surface cooling and to maintain the core body temperature around 34—35°C.[13]

Fully servo-controlled devices are suggested for WBC because they offer better temperature stability compared with manual or semiautomated devices. The Blanketrol II (Cincinnati Sub-Zero Products, Inc., Cincinnati, OH, USA) cooling mattress was used in the National Institute of Child Health and Human Development (NICHD) trial.[6] It is a microprocessor-controlled system that heats or cools circulating water. Even though it is servo-controlled, marked oscillations occur around the target core temperature, and the patient may require an additional blanket to reduce fluctuations in temperature.[13,14] The new Blanketrol III system does not require the use of an additional blanket and is adapted to neonatal use. However, the system requires water precooling for approximately 15 minutes to a temperature of 5°C prior to use. The rewarming phase is not automated and requires hourly manual adjustment of the set temperature and the radiant warmer output.[13]

The Arctic Sun Temperature Management System (C.R. BARD, Inc., Louisville, CO, USA) consists of two components: a set of pads that cover portions of the patient's skin and a control system that circulates temperature-controlled water. It is a fully servo-controlled device and the temperature control is stable.

3. Implementation issues with TH and outcomes

3.1. TH prior to and during transport

Data from the Vermont Oxford Encephalopathy Registry indicated that >60% of registered neonates were outborn babies,[15] and data from Chang Gung Memorial Hospital demonstrated that three-fourths of enrolled neonates were outborn babies.[4] These data suggest the question: "Should we start TH prior to and during transport?" Fairchild et al[16] showed that one-third of referred patients had rectal temperatures <32°C upon arrival at the referred hospitals. Another study compared active versus passive cooling during transport and showed that 34% of newborn infants were overcooled and 27% of infants did not achieve the target temperature when passive cooling was used.[17] Use of an active cooling device (a servo-controlled system) during transport ensured that 100% of infants were cooled upon arrival at the regional center.[17]

Table 1 Summary of clinical trials.

Clinical trials	Methods		Temperature			Entry criteria				Ref.
	Type	Duration (h)	Targeted (°C)	Route (E or R)	Rewarm (°C/h)	Gestational age (wk)	Age (h)	Evidence of acute perinatal HI events (blood gas taken within 60 min of birth)*	Encephalopathy	
Cool-Cap	SHC	72	34–35	R	≤0.5	≥36	≤6	Apgar score ≤ 5 at 10 min *or* resuscitation ≥ 10 min *or* severe acidosis [pH <7.0 or base deficit (BE) ≥ 16 mmol/L]	Clinical criteria and abnormal background on aEEG	7
NICHD	WBC	72	33.5	E	0.5	≥36	≤6	(1) severe acidosis (pH ≤ 7.0 or BE ≥ 16 mmol/L) *or* (2) an acute event (late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest) *plus* Apgar score ≤ 5 at 10 min *or* assisted ventilation ≥ 10 min	Clinical criteria	6
TOBY	WBC	72	33–34	R	≤0.5	≥36	≤6	Apgar score ≤ 5 at 10 min *or* resuscitation ≥ 10 min *or* severe acidosis (pH < 7.0 or BE ≥ 16 mmol/L)	Clinical criteria and abnormal background on aEEG	8
neo.nEURO. network	WBC	72	33–34	R	≤0.5	≥36	≤6	Apgar score < 5 at 10 min *or* resuscitation ≥ 10 min *or* severe acidosis (pH <7.0 or BE >16 mmol/L)	Clinical criteria and abnormal background on aEEG	9
ICE	WBC	72	33–34	R	0.25	≥35	≤6	≥2 of the following: Apgar score ≤ 5 at 10 min *or* mechanical ventilation ≥ 10 min *or* severe acidosis (pH < 7.0 or BE ≥ 12 mmol/L)	Clinical criteria	10

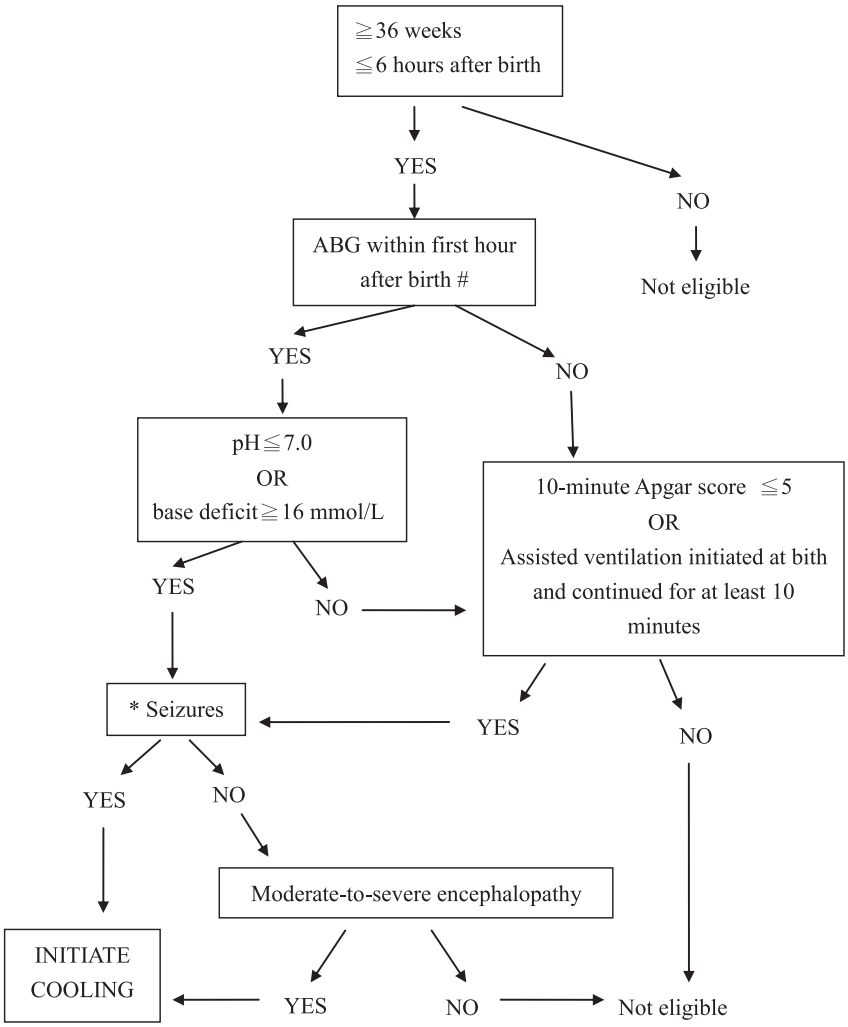
Clinical criteria: presence of one or more signs in at least three of the following six categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck or Moro), and autonomic nervous system (pupils, heart rate, or respiration).
aEEG = amplitude integrated electroencephalography; E = esophageal; HI = hypoxic ischemic; ICE = infant cooling evaluation; NICHD = National Institute of Child Health and Human Development; R = rectal; Ref = reference; SHC = selective head cooling; TOBY = Total Body Hypothermia for Neonatal Encephalopathy; WBC = whole body cooling.
* A sample of umbilical cord blood or any blood during the 1st hour after birth.

Based on the 2010 American Academy of Pediatrics/AHA Guidelines for neonatal resuscitation,[18] the Task Force warns practitioners to avoid unintentional hyperthermia of the newborns while awaiting transport. If they are placed under a radiant warmer, it should be adjusted to the servo-control mode with temperature slightly below the norm of 36.5°C or radiant heater is turned off under the suggestion of the referred hospital. During transport, the Task Force recommends that the incubator can be set at 25°C, and the baby's temperature should be measured regularly to avoid hyperthermia or overcooling. The target core temperature should be maintained around 33–34°C during transport.

3.2. Instructions for TH, rewarming, and systems support

3.2.1. Temperature maintenance, monitoring, and rewarming

Several groups have recommended that for patients undergoing WBC, the target core temperature (esophageal or rectal) should be maintained at 33–34°C for 72 hours,[6,8–10] and that for patients undergoing SHC, the temperature (rectal) should be maintained around 34–35°C for 72 hours.[7] Rewarming should be performed slowly, and the core temperature should rise no more than 0.5°C/h. Rebound



#: Umbilical cord or any arterial or venous blood sample.

*: Seizures indicate that patient has moderate encephalopathy.

Figure 1 Inclusion criteria of the National Health Insurance (Taiwan) for therapeutic hypothermia among neonates with hypoxic ischemic encephalopathy. ABG = arterial blood gas analysis.

seizures have been noted during the rewarming phase.[19] Although the recommendation is not based on strong clinical evidence, adult and animal studies have showed that rapid rewarming may adversely affect outcomes and that slow rewarming may help preserve the benefits of cooling.[13] Some have speculated that rapid rewarming may result in hypotension owing to peripheral vasodilatation or that rapid rewarming may cause electrolyte imbalances (hypoglycemia and hyperkalemia), but these outcomes have not been reported in any randomized controlled trials.[13]

In summary, core body temperature should be measured and recorded frequently and regularly during the period of cooling and rewarming to avoid overcooling or hyperthermia.

3.2.2. Respiration system

During TH, the metabolic rate is reduced by 5—8% when the body temperature drops by 1°C, and the production of CO_2 is decreased as well.[20] With each 1°C decrease in core temperature, pH increases by 0.015, and P_{CO_2} and P_{O_2} decrease by 4% and 7%, respectively.[21] Excessively low P_{CO_2} leads to altered autoregulation of cerebral blood flow and reduced cerebral perfusion. Klinger et al[22] reported that severe hyperoxemia ($P_{O_2} > 200$ mmHg) and severe hypocapnia ($P_{CO_2} < 20$ mmHg) during the 1st 2 hours of life were associated with adverse outcomes in infants with postasphyxial HIE. Analysis of blood gases recorded during clinical studies from birth to 12 hours of age indicated that both minimum P_{CO_2} and cumulative $P_{CO_2} < 35$ mmHg were associated with poor outcomes. Moreover, death or disability at 18—22 months of age increased with greater cumulative duration of exposure to $P_{CO_2} < 35$ mmHg.[23]

The recommendation of the Task Force for ventilation strategies is to avoid hyperoxemia and hypocapnia. Low

inflation pressures (12—14 cmH_2O) and rates (10—20/min) may be quite sufficient to achieve ventilation.[22—25]

3.2.3. Cardiovascular system

Published trials report no difference in the incidence of hypotension between TH infants and normothermic (NT) infants who have the same severity of asphyxia.[26] Treatment principles for hypotension remain the same for TH patients. Researchers have recommended that mean arterial blood pressure should be maintained within the critical range of 40—60 mmHg.[24] The Task Force recommends maintaining mean arterial blood pressure at ≥40—45 mmHg. Echocardiography is a useful guide for therapy because the regimen for treating low blood pressure is different in infants with poor cardiac function versus those with normal cardiac function.[24]

If patients present with hypotension, physicians first should cautiously correct hypovolemia because unnecessary excess fluid may exacerbate cerebral edema. If patients have reduced myocardial contractility, dobutamine is indicated; if they are hypotensive but not hypovolemic or have poor contractility, dopamine is recommended.[25]

In the NICHD trial, the baby's heart rate was usually around 100—110 beats/min.[6] The Task Force recommends that clinicians should be cautious if the baby's heart rate is >110 beats/min and should search for the potential causes that led to tachycardia.

3.2.4. Fluid, electrolytes, and nutrition

Fluid management should be carefully monitored in asphyxiated neonates. Because acute tubular necrosis may develop and fluid overload may lead to cerebral edema, fluid restriction of 60—80 mL/kg/d is recommended. Hypoglycemia may result in brain injury; serum glucose concentrations ≤40 mg/dL may aggravate the severity of perinatal brain injury in neonates with HIE.[27] Clinicians should prevent HIE patients from hypoglycemia during TH.

Hypothermia leads to an intracellular shift of potassium, and hypokalemia may occur and hyperkalemia may develop during rewarming. Even so, a meta-analysis of large trials showed no significant difference in the incidence of hypokalemia between TH and NT patients,[1,24,26] and the Task Force recommends that the patient's potassium level should be monitored during TH. Hypocalcemia and hypomagnesemia are common in asphyxiated neonates and may lower the seizure threshold. Hence, electrolytes should be monitored regularly and maintained in the normal range for HIE patient except that the magnesium level may be maintained within the high normal range.[24—26]

3.2.5. Sedation and drug metabolism

Both TH and asphyxia reduce the clearance of many analgesic, sedative, and anticonvulsant drugs such as phenobarbital, morphine, topiramate, and vecuronium. However, researchers have found no significant differences between TH and NT patients in the clearance rates of inotropic agents and commonly used antibiotics.[26] Because the effects of sedative and analgesic therapies on short- and long-term outcomes in TH and NT patients are unknown, these agents should be used with caution. The current recommendation is not to treat infants receiving hypothermic neuroprotection differently from NT asphyxiated infants.[26]

3.3. Monitoring and management of seizures

Among patients with HIE who were treated with TH, 30—60% experienced electrographic seizures, 10—30% experienced electrographic status epilepticus, and 40% experienced subclinical seizures.[28—31] In a three-center observational cohort study of 90 term HIE neonates treated with hypothermia and monitored with continuous video-EEG, Glass et al[32] found that 43 (48%) had electrographically identified seizures, including nine (10%) with electrographically determined status epilepticus. Whether or not neonatal seizures are accompanied by additional adverse effects in the brains of neonates with underlying encephalopathy remains controversial.

Kwon et al[33] analyzed the data from the NICHD trial and showed that clinical seizures were generally noted during the 1st 4 days of life and rarely afterwards. In addition, when adjustment was made for the treatment and severity of encephalopathy, seizures were not associated with death, moderate or severe disability, or lower Bayley Mental Development Index scores at 18 months of life.[33] In contrast, in the Cool-Cap study, neonates with seizures on aEEG had unfavorable outcomes compared with neonates without seizures.[7] Glass et al[34] also indicated that the Full Scale Intelligence Quotient at 4 years was lower among neonates with HIE who had severe seizures compared with those who experienced mild or moderate seizures or no seizures. Indeed, seizures remain a risk factor for brain injury in the setting of TH, especially in patients who experience status epilepticus or multifocal onset seizures and who require multiple medications. However, 40% of the HIE newborns did not experience brain injury, suggesting that the outcome following seizures is not uniformly poor in children treated with TH.[30]

Because seizures are common in asphyxiated newborn infants, particularly within the 1st 1—2 days of life,[29,35] the Task Force suggests that monitoring seizure activity is important, and using aEEG or continuous video-EEG to monitor seizures is recommended. Phenobarbital remains the first line of treatment for neonatal seizures, but the success rate is <50%;[36] hence, two or more antiepileptic drugs may be needed.[37,38] The Task Force recommends that a pediatric neurologist should be consulted for seizure treatment, particularly if a second or multiple medications are required.

3.4. Neuroimaging, prognostic factors, and outcomes

Biomarkers have been essential topics in HIE research. Biomarkers that define the stage, progression, and improvement of encephalopathy would be valuable.[39] Magnetic resonance imaging (MRI) in NT asphyxiated infants is highly predictive of outcomes; in particular, the presence or absence of findings at the posterior limb of the internal capsule has both a strong positive predictive value (PPV) and a strong negative predictive value for outcomes.[40,41] A nested substudy of the TOBY trial involved

40% of the infants; MRI administered at a median age of 8 days showed that the lesions in the basal ganglia and thalami, in the posterior limb of the internal capsule, and in the white matter were reduced, but not in the cortex, following TH.[42,43] Results also demonstrated that hypothermia does not influence the ability of MRI to predict neurodevelopmental outcomes.[39,43] The accuracy of predictions of death or disability at 18 months of age by MRI was 0.84 in the cooled group and was 0.81 in the noncooled group.[43] In a study that evaluated the NICHD trial participants and used neonatal MRIs as evidence of brain injury, a comprehensive classification of MRI findings was correlated with death and disability at 18 months.[39] Furthermore, the MRI pattern of brain injury may be a biomarker for neurodevelopmental outcomes at 6–7 years of age.[44] However, we should be cautious when predicting outcomes in HIE patients who have normal findings or minor degrees of brain injury on MRI. As many as 26% of those who underwent TH and had normal MRI findings experienced abnormal neurodevelopmental outcomes.[24,45] The timing of scanning is important because the characteristic abnormalities that appear on conventional MRI may occur progressively over several days, and the severity of injuries may be underestimated during the first few days after birth.[42,46–48]

Cranial ultrasound is convenient to evaluate brain injury in both full-term and preterm newborn infants. Pourcelot's resistance index (RI) < 0.55 at 24–62 hours after birth was considered a strong marker for a very poor outcome and death during the period prior to cooling treatments.[49] However, in neonates with HIE treated with TH, RI was a poor predictor of outcomes.[39,50,51] The PPV for poor outcomes with an RI of $\leq$0.55 was 43–60% in cooled infants compared with 84% in NT infants.[50,51] Skranes et al[51] reported that an RI of $\leq$0.55 predicts true poor outcomes in 100% of neonates after rewarming.

In a meta-analysis, magnetic resonance spectroscopy showed that deep gray matter lactate/*N*-acetylaspartate levels had 82% overall pooled sensitivity and 95% specificity for detecting outcomes, exhibiting a better diagnostic accuracy than conventional MRI in the precooling era.[52] The PPV was 100% and the negative predictive value was 93% if the deep gray matter *N*-acetylaspartate/creatine ratio was used as a marker to predict outcomes for neonates with HIE treated with TH.[53] MRI remains by far the most specific way to predict outcomes in cooled asphyxiated newborns.[52,54] Table 2 presents a summary of neuroimaging data and neurodevelopmental outcomes between the precooling and cooling eras.

The ratio of urinary lactate to creatinine has been used for identifying newborn infants at risk of HIE. An RI ratio of $\geq$0.64 within 6 hours after birth had a sensitivity of 94% and a specificity of 100% for predicting the development of HIE.[55] An elevated urinary lactate/creatinine ratio has been associated with adverse outcomes in infants with HIE, and WBC did not affect the decline in the urinary lactate to creatinine ratio.[56] Sustained lactic acidosis has been correlated with so-called seizure burden, but lactate values were not used to predict outcomes.[57] In a subset of patients in a clinical asphyxia database, at least five plasma samples were obtained during the 1st 24 hours of life from each of 33 NT and 21 TH infants; data showed that at all time points the plasma lactate values were similar between NT and HT

Table 2 Relationship between findings of neuroimaging and neurodevelopmental outcomes in the precooling and cooling eras.

Neuroimaging	Precooling era	Cooling era
Cranial ultrasound, RI	RI < 0.55 at 24–62 h after birth is a strong marker for a very poor outcome and death, $N = 34$	RI ≤ 0.55 as a marker to predict poor outcome: PPV 60%, NPV 78%, $N = 125$
	RI ≤ 0.55 as a marker to predict poor outcome: PPV 84%, NPV 76%, $N = 255$	RI > 0.55 predicts good outcomes in 86% during late cooling and in 89% after rewarming, $N = 45$
Conventional MRI	MRI as a marker to predict outcome during neonatal period (Days 1–30): sensitivity 91%, specificity 51%, $N = 860$	The accuracy of prediction by MRI of death or disability: NT 84%, TH 81%, $N = 131$
MRS	Deep gray matter Lac/NAA ratio as a marker to predict poor outcomes (Days 1–30): sensitivity 82%, specificity 95%, $N = 860$	Deep gray matter NAA/Cr ratio as a marker to predict outcomes: PPV 100%, NPV 93%, $N = 20$

Note. From "Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic–ischaemic encephalopathy: a nested substudy of a randomised controlled trial," by M. Rutherford, L.A. Ramenghi, A.D. Edwards, P. Brocklehurst, H. Halliday, M. Levene, et al., 2010, *Lancet Neurol*, *9*, p. 39–45. Copyright 2010, Elsevier Ltd. From "Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic–ischaemic encephalopathy," by P. Eken, M.C. Toet, F. Groenendaal, L.S. de Vries, 1995, *Arch Dis Child Fetal Neonatal Ed*, *73*, p. F75–80. Copyright 1995, BMJ Publishing Group Ltd and the Royal College of Paediatrics and Child Health. From "Cerebral resistance index is less predictive in hypothermic encephalopathic newborns," by M. Elstad, A. Whitelaw, M. Thoresen, 2011, *Acta Paediatr*, *100*, p. 1344–9. Copyright 2011, The Author(s)/Acta Paediatrica and Foundation Acta Paediatrica. From "Hypothermia makes cerebral resistance index a poor prognostic tool in encephalopathic newborns," by J.H. Skranes, M. Elstad, M. Thoresen, F.M. Cowan, T. Stiris, D. Fugelseth, 2014, *Neonatology*, *106*, 17–23. 2014, S. Karger AG, Base. From "Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis," by S. Thayyil, M. Chandrasekaran, A. Taylor, A. Bainbridge, E.B. Cady, W.K.K. Chong WKK, et al., 2010, *Pediatrics*, *125*, p. e382–95. Copyright 2010, the American Academy of Pediatrics. From "Prognostic value of brain proton MR spectroscopy and diffusion tensor imaging in newborns with hypoxic–ischemic encephalopathy treated by brain cooling," by G. Ancora, C. Testa, S. Grandi, C. Tonon, F. Sbravati, S. Savini S, et al., 2013, *Neuroradiology*, *55*, p. 1017–25. Copyright 2013, Springer-Verlag Berlin Heidelberg. With permission.

Cr = creatinine; Lac = lactate; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; NAA = *N*-acetylaspartate; NPV = negative predictive value; NT = normothermia; PPV = positive predictive value; RI = resistance index; TH = therapeutic hypothermia.

infants.[41] A small study found that higher serum levels of lactate following TH were associated with poor neurodevelopmental outcomes in neonates with HIE.[4]

4. Adjuvant therapy for TH

The mechanisms of neonatal HIE are complex.[24,58,59] TH improves the survival and decreases the rate of disability of neonates with HIE, yet death or disability remains high (40—50%) according to data from large clinical trials.[6—11] Hence, there is an urgent need for additional therapies to improve the outcomes of HIE.[59,60] Adjuvant therapies for use with TH are undergoing investigation and include erythropoietin, topiramate, xenon, melatonin, and stem cell therapy.[59,60] A phase II study (NEATO) of erythropoietin (1000 U/kg/dose) intravenous injections among patients with HIE treated with TH is ongoing (NCT01913340). Another phase I/II trial (DANCE) investigating the dosage safety and pharmacokinetic data of darbepoetin-α administered concurrently with TH in newborn infants with HIE has been completed. The results have not been released yet (NCT01471015). A phase II trial of topiramate (NeoNATI) has been completed (NCT01241019), and another phase I/II study is currently recruiting participants (NCT01765218). A phase I/II study of xenon (TOBYXe) has been completed (NCT00934700), and a phase I/II trial (CoolXenon2) is ongoing but is not recruiting participants (NCT01545271). A phase I/II trial of melatonin has been completed, but no data are available (NCT02071160).

5. Conclusion

Newborn infants born at $\geq$36 weeks of gestation with evolving moderate to severe HIE should be treated with TH. It should be performed within 6 hours of birth and should maintain a core body temperature of about 33.5—34.5°C for 72 hours, followed by rewarming at a rate of $\leq$0.5°C/h. Multidisciplinary team care is essential, and all treated patients should be followed longitudinally.

Conflicts of interest

The authors have no conflicts of interest or personal financial relationships relevant to this article.

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