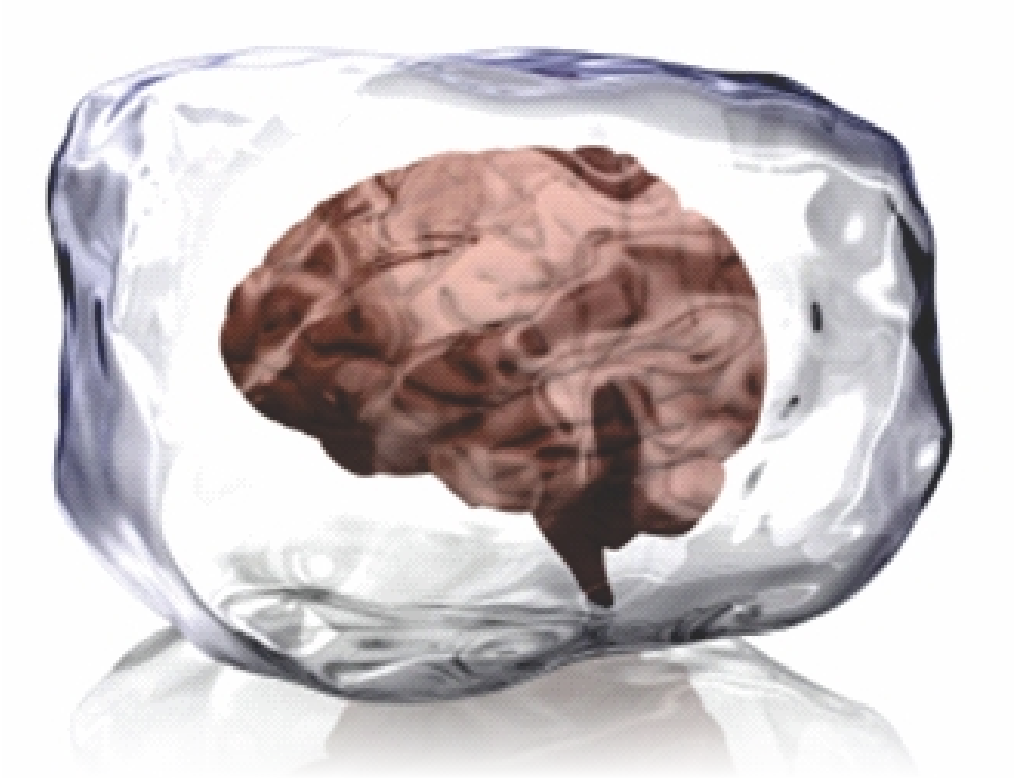
MANUAL ON THERAPEUTIC HYPOTHERMIA FOR PERINATAL ASPHYXIA

An NNF Publication



NATIONAL NEONATOLOGY FORUM

NATIONAL NEONATOLOGY FORUM OF INDIA

803, 8th Floor, A-9, GDITL Tower, Netaji Subhash Place, Pitampura, Delhi-110034
Phone: 27353535, Mobile: 8527453535, E-mail: secnnf@nnfi.org, Website: www.nnfi.org

NNF Office Bearers

Dr. B.D. Bhatia
President, NNF

Dr. Ajay Gambhir
Past President, NNF

Dr. Alok Bhandari
Hony. Secretary, NNF

Dr. Lalan Kr. Bharti
Jt. Secy.
cum Treasurer, NNF

NNF Governing Body Members

Dr. Utpal Kant Singh
Member

Dr. Anurag Singh
Member

Dr. Mohit Sahni
Member

Dr. Vishnu Bhat
Member

Dr. Himanshu Kelkar
Member

EDITORS:

Dr. VISHNU BHAT. B

Dr. ADHISIVAM. B

FOREWORD

Cooling is standard of care in perinatal asphyxia for term and late preterms in developed countries. In India therapeutic hypothermia (TH) in perinatal asphyxia with HIE management has started picking up and most of level 3 neonatal units either in private or medical college set up have started practicing it with good results. The National Neonatology Forum in its accreditation programme has made it mandatory for level 3 B accreditation. It is now appropriate time for NNF to bring out a manual on "Therapeutic hypothermia for perinatal asphyxia" so that it can help the new units to start cooling therapy and also provide standardized care. The NNF at its annual convention every year conducts workshops on Therapeutic hypothermia. Hence, it was further necessary to have a manual on the same. The NNF is thankful to Prof. B Vishnu Bhatt and Dr. Adhisivam B and all the other contributors to have accepted the request and complete the project in the record short time of couple of weeks. We are also thankful to the Miracradle® team (Pluss Advanced Technologies Pvt. Ltd.) for sponsoring the printing of this manual to be distributed to all the delegates attending the 37th annual convention of NNF-2017 at Gurgaon.

Dr. Alok Bhandari
Secretary NNF

Dr. B. D. Bhatia
President NNF

MiraCradle®
Neonate Cooler

GIVING EVERY CHILD A CHANCE TO BEAT BIRTH ASPHYXIA

Miracradle® Neonate Cooler is an affordable passive cooling device which uses the advanced sav*E*® Phase Change Material technology to induce therapeutic hypothermia among newborns suffering from birth asphyxia.

Tried and tested by credible hospitals and doctors, Miracradle® hopes to give every baby in the developing world, a fair chance to survive.

THE MIRACRADLE® ADVANTAGE

EASY TO USE
Minimal manual supervision required. PCMs can be charged in a normal refrigerator.

SAFE
Passive cooling system; does not have any electrical supply near the baby.

EFFICIENT
Gives precise temperature control.

ECONOMICAL
Less than 1/5th of the cost of the available electronic devices.

LONG LASTING
The PCMs are designed for repetitive use.

PLUSS | TECHNOLOGY FOR A BETTER WORLD

www.pluss.co.in | info@pluss.co.in

PREFACE

DR. B. VISHNU BHAT

Dean (Research)
Professor & HOD
Department of Neonatology,
JIPMER Pondicherry

There is ample evidence for the benefit of therapeutic hypothermia for term and late preterm neonates with perinatal asphyxia. Though it is the standard of care practiced in most of the developed countries, it is yet to gain momentum in India. We are happy that National Neonatology Forum (NNF), India is bringing out a manual on therapeutic hypothermia for perinatal asphyxia. The chapters in this manual have been contributed by clinicians with expertise in the field. Both theory and practical aspects of therapeutic hypothermia with special relevance to the Indian context have been covered. We are sure that this manual will be of great help to Neonatology fellows and Pediatric postgraduates in understanding the principles of therapeutic hypothermia and the nuances of practical application of this intervention.

Dr. B. Vishnu Bhat

CONTRIBUTING AUTHORS

S. No.	AUTHORS
1	Dr. VISHNU BHAT B Senior Professor and Head, Dept. of Neonatology, JIPMER, Pondicherry
2	Dr. ADHISIVAM B Additional Professor, Dept. of Neonatology, JIPMER, Pondicherry
3	Dr. NIVEDITA M Associate Professor, Dept. of Neonatology, JIPMER, Pondicherry
4	Dr. NISHAD P Assistant Professor, Dept. of Neonatology, JIPMER, Pondicherry
5	Dr. SRIDHAR SANTHANAM Professor and Head, Dept. of Neonatology, CMC, Vellore
6	Dr. NIRANJAN THOMAS Professor, Dept. of Neonatology, CMC, Vellore
7	Dr. MANISH KUMAR Associate Professor, Dept. of Neonatology, CMC, Vellore
8	Dr. SUMITHA ARUN Assistant Professor, Dept. of Neonatology,CMC, Vellore
9	Dr. KUMUTHA J Professor and Head, Dept. of Neonatology, Saveetha Medical College, Chennai
10	Dr. PRAKASH AMBOIRAM Professor and Head, Dept. of Neonatology, SRMC, Chennai
11	Dr. UMAMAHESWARI B Associate Professor, Dept. of Neonatology, SRMC, Chennai
12	Dr. MANIGANDAN CHANDRASEKARAN Consultant Neonatologist, Cloudnine Hospital, Chennai
13	Dr. MINTOO TERGESTINA Senior Resident, Dept. of Neonatology, CMC, Vellore
14	Dr. NITHYA J PONMUDI Senior Resident, Dept. of Neonatology, CMC, Vellore
15	Dr. VASANTHAN T Neonatology Fellow, JIPMER, Pondicherry

TABLE OF CONTENTS

CHAPTER

1

HYPOXIC ISCHEMIC ENCEPHALOPATHY

PATHOPHYSIOLOGY & CLINICAL FEATURES

Dr. Adhisivam B

INTRODUCTION

The WHO definition of perinatal asphyxia is "failure to initiate and sustain breathing at birth". Perinatal asphyxia leads to multi-organ dysfunction in the neonate and the neurological dysfunction inherent to this clinical condition is referred as Hypoxic Ischemic Encephalopathy (HIE). HIE is characterized by clinical and laboratory evidence of acute or sub-acute brain injury secondary to asphyxia. The primary causes of HIE are systemic hypoxemia and/or reduced cerebral blood flow. Every year, around 4 million babies die in the neonatal period (first 28 days of life) globally and asphyxia is one of the major causes accounting for 23% of these neonatal deaths. Among the survivors of asphyxia, cerebral palsy is a dreaded complication associated with loss of potential productive member for the society and direct burden lasting for the entire life on the individual and family and social institutions. Hence every effort should be made to prevent perinatal asphyxia and pediatricians should be well versed with the management of this important clinical condition.

Every year, around 4 million babies die in the neonatal period (first 28 days of life) globally and asphyxia is one of the major causes accounting for 23% of these neonatal deaths.

EPIDEMIOLOGY

It is a sad fact that most of the neonatal deaths due to asphyxia (99%) occur in developing countries. HIE occurs in 1.5 per1000 full term births. While 15 - 20% of neonates with HIE die early, 25% will survive with disabilities. Moreover HIE is a major problem at all levels - individual, family and society, contributing to 15-28% of children with cerebral palsy and 25% of all children with developmental delay. Despite significant advances in perinatal care, cerebral palsy among term infants continues to occur. The long term neuro-developmental outcome depends on the severity of the neonatal encephalopathy.

According to NNPD 2003 data, Apgar score <7 at 1 minute (including moderate and severe asphyxia) was noted in 9% of all intramural deliveries while 2.5% babies continued to have Apgar scores <7 at 5 minutes of age. Bag and mask ventilation was required in 4.5% infants while less than 1% infants required cardiac compressions and/ or medications as part of resuscitation at birth. Clinical features of HIE were noted in 1.5% of all babies and it accounted for 20% of neonatal deaths.

ETIOLOGY

It is practically impossible to ascertain the exact time of the hypoxic insult sustained by a newborn unless some convincing evidence is available. Some of the common etiology for HIE are listed in Table 1. The clinical presentation of neonatal encephalopathy due to varied etiologies can overlap and hence it is difficult for the clinician to identify the etiology using neurological examination alone. It is always prudent to exclude other causes of neonatal encephalopathy when the perinatal risk factors are not clear.

PATHOPHYSIOLOGY

HIE does not refer to a single event but rather refers to a continuing process beginning from the time of hypoxic insult. There are two different episodes of neuronal impairment which are known to occur during HIE. The immediate hypoxic insult is called the primary phase and this is followed by a short period of recovery (latent phase) lasting for approximately six hours. Subsequently there is a longer phase during which there is a release of chemical mediators causing secondary neuronal damage. Neurons may die during the actual ischemic or primary phase itself. Several neurons however recover at least partially in the 'latent' phase but die hours or even days later (secondary or delayed cell death) (Fig.1).

Based on the cerebral energy state, HIE involves two phases of energy failure - primary and secondary. The blood flow and oxygen substrates in the brain are decreased in primary energy failure. Reduction in ATP and other phosphorylated compounds like phosphocreatine and significant tissue acidosis are important features during this phase. An "excito toxic - oxidative cascade" characterized by excessive stimulation of neurotransmitter receptors and membrane depolarization causing increased intracellular calcium is also observed. Increased levels of intracellular calcium activate nitric oxide synthase to perpetuate the release of nitric oxide, which in turn affects mitochondrial respiration (Fig.2). Signals from damaged mitochondria lead to apoptosis or programmed cell death till energy stores are available. However cessation of these energy supply results in cell necrosis. Activation of caspase enzyme system can also trigger apoptosis. Resolution of hypoxia can reverse the decrease in ATP and intracellular pH and enhances recycling of

neurotransmitters. In case of prolonged and severe insult, the initial cascade of events will cause a second phase of energy failure in the mitochondria. This secondary energy failure differs from the primary in that the decline in the levels of ATP and other phosphorylated compounds are not associated with brain acidosis. The secondary energy failure is characterized by continuing excite toxic-oxidation cascade, apoptosis, inflammation and altered growth factor levels and protein synthesis (Table 2). The interval between the primary and secondary energy failure is called the latent phase, an important therapeutic window (approximately 6 hours). When neuronal tissue sustains a hypoxic insult, cell death may be either delayed or remain progressive depending on the region and severity of the injury. Gestational age has a role in the susceptibility of the brain to hypoxic damage. In term neonates, the gray matter is primarily affected (selective neuronal necrosis) while in the preterm it is the white matter leading to periventricular leucomalacia. The other factors which contribute to the degree of damage include cellular susceptibility, watershed areas, regional metabolic rates and degree of asphyxia.

OXIDATIVE STRESS AND DNA DAMAGE IN ASPHYXIA

There are three important pathways that lead to free radical production. First one is Fenton reaction. During hypoxic ischemia, protein-bound iron is liberated from its binding proteins in the neuronal and microglial cells. Non protein bound iron (NPBI) or free iron usually accumulates during hypoxic ischemia. When the damaged brain is reperfused and re-oxygenated, toxic hydroxyl free radical will be formed as NPBI react with hydrogen peroxide. Thus NPBI is related to excessive neuronal damage immediately following the insult. Second, the activation of neuronal and inducible nitric oxide synthase leads to the generation of the nitric oxide radical (NO), which reacts with superoxide to form the toxic peroxynitrite (ONOO). Peroxynitrite and reactive oxygen species cause DNA damage and cell death. Finally, hypoxanthine, accumulated during the hypoxic-ischemic episode as a degradation product of ATP, is metabolized to uric acid by xanthine oxidase (XO). This reaction gives rise to further formation of superoxide radicals (Fig.3). The toxicity of these free radicals contribute substantially to reperfusion injury of the neuronal tissue after the hypoxic insult. Neonatal brain is more susceptible to oxidative stress because of low concentrations of antioxidants, a high consumption of oxygen and presence of high concentrations of unsaturated fatty acids that break down to form more oxygen free radicals.

CLINICAL FEATURES

The important CNS clinical features of HIE include altered level of sensorium, seizures and tone abnormalities. Their appearance is variable depending on the progression of energy failure and severity of insult and the usual time frame of these clinical features is depicted in Fig. 4. For quantifying the severity of HIE, Sarnat and Sarnat classification is commonly used while Levene's classification is also helpful (Tables 3 and 4). Though the CNS features are sine qua non of HIE all other organ systems including the kidney and heart are also affected in variable proportions depending on the disease severity and quality of care (Table 5). When

the neonate sustains a hypoxic insult, almost all organs are at risk of cell injury and death. However, certain organs are more vulnerable to injury than others despite inbuilt physiological reflexes trying to protect these vital organs.

Acute kidney injury (AKI) is a common occurrence in infants with neonatal encephalopathy (NE), with a reported incidence of 50–72 %. Most of these studies are small and employ varying definitions for AKI based on elevation of serum creatinine, oliguria, decreased glomerular filtration rate and presence of haematuria and proteinuria. Nevertheless, these studies emphasize the frequency of AKI complicating NE and underline the uncertainty surrounding the precise and early diagnosis of AKI in critically ill neonates. The majority of AKI following perinatal hypoxia-ischemia is prerenal in origin and often non oliguric.

Cardiac dysfunction is part of the clinical spectrum of multi organ dysfunction in term infants with HIE. In children with HIE, the reported incidence of cardiovascular dysfunction ranges from 29 - 78%. Oxygen deprivation secondary to a hypoxic and /or ischaemic insult causes myocardial damage. This eventually leads to decreased cardiac output, impaired myocardial contractility, systemic hypotension and pulmonary hypertension.

DIFFERENTIAL DIAGNOSES

History of prolonged and difficult labor coupled with need for significant resuscitation, low apgar scores, altered sensorium and early onset seizures will usually point towards HIE. However, other differential diagnoses likes inborn errors of metabolism, neuromuscular disorders, developmental defects of brain and sepsis should be kept in mind as their clinical features my overlap with HIE. It is not uncommon to find meconium aspiration syndrome and sepsis associated with HIE in term and preterm babies respectively.

APPROACH TO DIAGNOSIS

A detailed history including antenatal and delivery details reflecting events leading to compromised blood supply and/or oxygenation of the fetus should be obtained. History of placental abruption, cord around neck, cord prolapse, maternal hemorrhage, trauma, cardiorespiratory arrest, uterine rupture or significant fetal decelerations if present should be recorded. There is increased risk of neonatal encephalopathy if the mother has fever during antepartum or intrapartum period. A careful neurologic examination needs to be performed to diagnose encephalopathy.

BIBLIOGRAPHY

1. Shankaran S. Hypoxic-ischemic encephalopathy and novel strategies for neuroprotection. Clin Perinatol. 2012; 39:919-29.
2. Wachtel EV, Hendricks-Muñoz KD. Current management of the infant who presents with neonatal encephalopathy. CurrProbl Pediatr Adolesc Health Care. 2011; 41:132-53.
3. Bhat BV, Adhisivam B. Therapeutic cooling for perinatal asphyxia-Indian experience. Indian J Pediatr. 2014; 81:585-91
4. Bharadwaj SK, Bhat BV. Therapeutic hypothermia using gel packs for term neonates with hypoxic ischaemic encephalopathy in resource-limited settings: A randomized controlled trial. J Trop Pediatr. 2012; 58:382-8.
5. Perrone S, Stazzoni G, Tataranno ML, Buonocore G. New pharmacologic and therapeutic approaches for hypoxic-ischemic encephalopathy in the newborn. J Matern Fetal Neonatal Med. 2012; 25Suppl 1:83-8.
6. Galvao TF, Silva MT, Marques MC, de Oliveira ND, Pereira MG. Hypothermia for perinatal brain hypoxia-ischemia in different resource settings: a systematic review. J Trop Pediatr. 2013; 59:453-9.
7. Thayyil S, Shankaran S, Wade A, Cowan FM, Ayer M, Satheesan K, et al. Whole-body cooling in neonatal encephalopathy using phase changing material. Arch Dis Child Fetal Neonatal Ed. 2013; 98(3):F280-1
8. Joy R, Pournami F, Bethou A, Bhat VB, Bobby Z. Effect of therapeutic hypothermia on oxidative stress and outcome interm neonates with perinatal asphyxia: a randomized controlled trial. J Trop Pediatr 2013; 59:17–22
9. Aggarwal R, Deorari AK, Paul VK. Post-resuscitation management of asphyxiated neonates. Indian J Pediatr. 2001; 68:1149-53
10. AIIMS protocol 2014 - Post-resuscitation management of asphyxiated neonate. Available from: URL: http://www.newbornwhocc.org/clinical_proto.html. Accessed May6, 2014.
11. Pauliah SS, Shankaran S, Wade A, Cady EB, Thayyil S. Therapeutic Hypothermia for Neonatal Encephalopathy in Low and Middle Income Countries: A Systematic Review and Meta-Analysis. PLoS ONE 2013; 8: e58834.
12. Gane BD, Bhat V, Rao R, Nandhakumar S, Harichandrakumar KT, Adhisivam B. Effect of therapeutic hypothermia on DNA damage and neuro-developmental outcome among term neonates with perinatal asphyxia: A randomized controlled trial. J Trop Pediatr. 2014 ; 60(2): 134-40.
13. Thomas N, Chakrapani Y, Rebekah G, Kareti K, Devasahayam S. Phase changing material: An alternative method for cooling babies with hypoxic ischaemic encephalopathy. Neonatology. 2015; 107(4):266-70.
14. Tanigasalam V, Bhat V, Adhisivam B, Sridhar MG. Does therapeutic hypothermia reduce acute kidney injury among term neonates with perinatal asphyxia? – a randomized controlled trial. J MaternFetal Neonatal Med. 2016; 29(15):2544-7

BOX 1: DEFINITIONS

Hypoxia or Anoxia: A partial (hypoxia) or complete (anoxia) lack of oxygen in the brain or blood.

Asphyxia: The state in which placental or pulmonary gas exchange is compromised or ceases altogether.

Ischemia: The reduction or cessation of blood flow to an organ which compromises both oxygen and substrate delivery to the tissue.

Hypoxic-Ischemic Encephalopathy: Abnormal neurologic behavior in the neonatal period arising as a result of a hypoxic-ischemic event.

Neonatal Encephalopathy: A clinical syndrome of "disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often seizures."

Definition of Perinatal Asphyxia (PA)

- World Health Organization: Failure to initiate and sustain breathing.
- NNPD Network:
  - Moderate PA: Slow/gasping breathing or an Apgar score of 4 to 6 at 1 minute.
  - Severe PA: No breathing or an Apgar score of 0-3 at 1 minute of age.
- American Academy of Pediatrics and American College of Obstetrics and Gynecology: Presence of all of following criteria-
  - Profound metabolic or mixed acidemia (pH< 7.00) in umbilical cord blood.
  - Persistence of low Apgar scores less than 3 for more than 5 minutes
  - Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities).
  - Evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart and intestine).

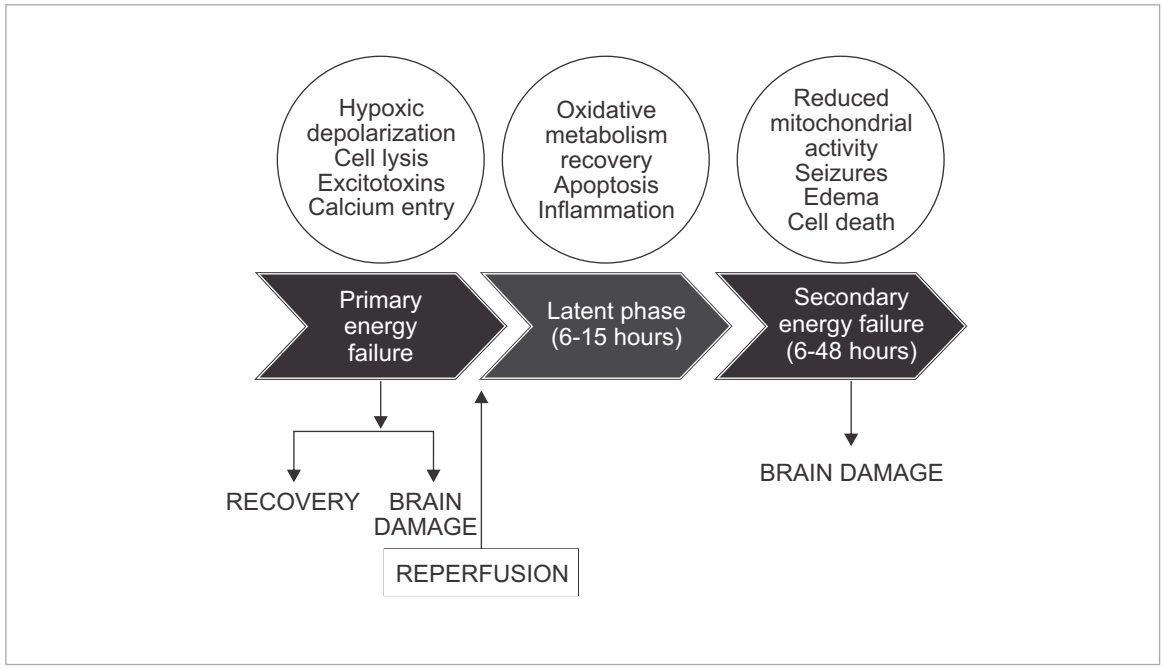


Fig.1: Pathophysiology of HIE - Overview

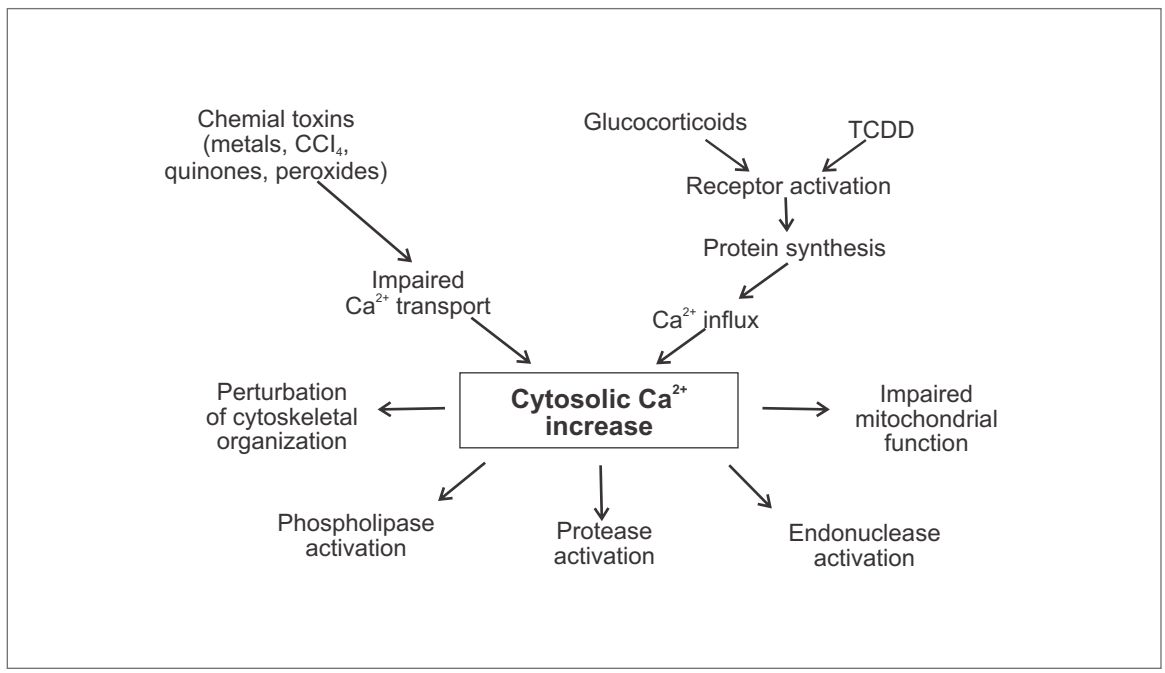


Fig. 2: Pathophysiology of HIE - Key Events

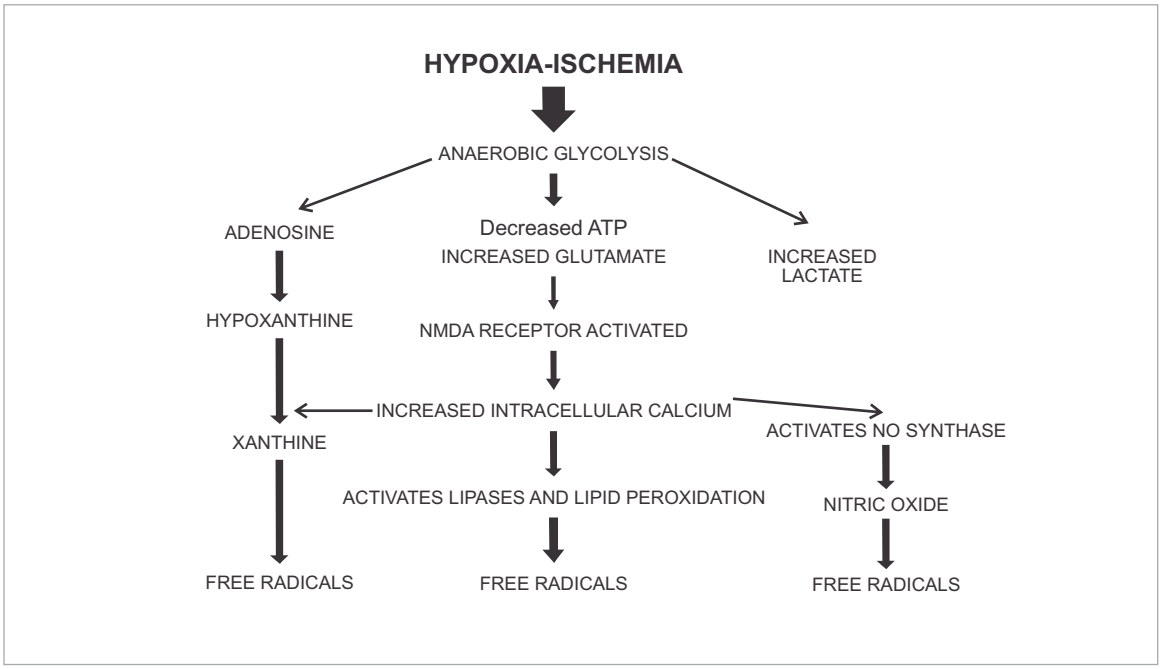


Fig. 3: Free radicals production in HIE

Birth -12 hours	Depressed level of alertness, periodic breathing or respiratory failure, intact pupillary and occulomotor responses, hypotonia, seizures
12 - 24 hours	Change in level of alertness, seizures, apnoeic spells, jitteriness, weakness in proximal limbs, upper > lower (term), lower > upper (preterm)
24 -72 hours	Stupor or coma, respiratory arrest, brain stem pupillary and occulomotor disturbances, catastrophic deteoriation with severe intraventricular hemorrhage and periventricular hemorrhagic infarction (premature)
> 72 hours	Persistent yet diminishing stupor, disturbed sucking, swallowing, gag and tongue movements, hypotonia / hypertonia, limb weakness

Fig.4: HIE - Clinical Features

Table 1: Etiology of HIE

Maternal	Uteroplacental	Fetal
Cardiac arrest	Placental abruption	Feto maternal hemorrhage
Asphyxiation	Cordprolapse	Twin to twin transfusion
Severe anaphylaxis	Uterine rupture	Severe iso immune hemolytic disease
Status epilepticus Hypovolemic shock	Hyper stimulation with oxytocic agents	Cardiac arrhythmia

Table 2: Characteristics of energy failures related to HIE

Primary energy failure	Secondary energy failure
Decrease in cerebral blood flow, oxygen substrates and ATP	Continuing of excite toxic-oxidative cascade
Excito toxic-oxidative cascade	Activation of microglia-inflammatory response
Loss of ionic homeostasis across membranes	Activation of caspase proteins
Entry of intracellular calcium	Reduction in levels of growth factors, protein synthesis
Mitochondrial disruption	Continuing Apoptosis and necrosis
Brain acidosis	

Table 3: Sarnat and Sarnat classification of HIE

	STAGE 1	STAGE 2	STAGE 3
Level of consciousness Neuromuscular control	Hyperalert	Lethargic or obtunded	Stuporous
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong: low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic fuction	Generalized sympathetic	Generalized parasympathetic	Both systems decreased

Continued on next page...

Autonomic fuction	Generalized sympathetic	Generalized parasympathetic	Both systems decreased
Pupils	Mydriasis	Miosis	Variable: often unequal; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Spars	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased: diarrhea	Variable
Seizures	None	Common: focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram findings	Normal (awake)	Early low-voltage continuous delta and theta	Early: periodic pattern with isopotential phases.
		Later, periodic pattern (awake), Seizures: focal 1- to 1.5-Hz spike-and-wave	Later: totally isopotential
Duration	Less than 24 hours	2-14 days	Hours to week

Table 4: Levene's classification of HIE

Feature	Mild	Moderate	Severe
Consciousness	Irritable	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe hypotonia
Seizures	No	Yes	Prolonged
Sucking/respiration	Poor suck	Unable to suck	Unable to sustain spontaneous respiration

Table 5: Organ system dysfunction in perinatal asphyxia

CNS	Hypoxic ischemic encephalopathy, intracranial hemorrhage, seizures, long-term neurological sequelae
Cardiac	Myocardial dysfunction, valvular dysfunction, rhythm abnormalities, congestive cardiac failure
Renal	Hematuria, acute tubular necrosis, renal vein thrombosis
Pulmonary	Delayed adaptation, respiratory failure, meconium aspiration, surfactant depletion, primary pulmonary hypertension
GI tract	Necrotizing enterocolitis, hepatic dysfunction
Hematological	Thrombocytopenia, coagulation abnormalities
Metabolic	Acidosis, hypoglycemia, hypocalcemia, hyponatremia

CHAPTER

2

THERAPEUTIC HYPOTHERMIA

MECHANISMS OF ACTION

Dr. Vishnu Bhat B

Therapeutic Hypothermia (TH) has been proven to be effective in reducing morbidity associated with HIE and has become the standard of care for HIE in developed countries.

Therapeutic Hypothermia (TH) has been proven to be effective in reducing morbidity associated with HIE and has become the standard of care for HIE in developed countries. However in underdeveloped and transitional countries where the problem is more common, therapeutic cooling is still in the nascent phase. There are several reasons for this in resource restricted settings. Similarly, despite availability of compelling clinical evidence that TH initiated within a few hours after hypoxic insult can improve neurological outcome in term infants, implementing the same in resource restricted settings of India is not that easy mainly because of the non-availability of expensive devices used for providing TH in developed countries. Recently, two systematic reviews on the efficacy and safety of TH in low and middle income resource settings have been published. The systematic review by Pauliah et al did not find any statistically significant reduction in neonatal mortality in underdeveloped countries although the confidence intervals were wide. Galvao et al observed that there is ample evidence for designating hypothermia as the standard of care for HIE but more evidence from low income countries is required.

TH is neuroprotective by inhibiting several steps in the excito toxic oxidative cascade which include inhibiting the increase in the concentration of lactic acid, glutamate and nitric oxide in the brain (Fig. 1 and Box 1). Moreover, TH inhibits protease activation, mitochondrial failure, free radical damage, lipid peroxidation and inflammation. TH has been shown to decrease brain energy use, prolong the latent phase, reduce infarct size, decrease neuronal cell loss, retain sensory motor function, and preserve hippocampal structures. Early application of TH preferably within 6 hours i.e. before the onset of the secondary phase of energy failure is likely to be effective and improve neurodevelopmental outcome. Usually it is

continued for a period of 72 hours for better neuro protection. Applying TH immediately or within a few hours after reperfusion and continued for 72 hours has been shown to favorably affect outcome in newborn and adult animals.

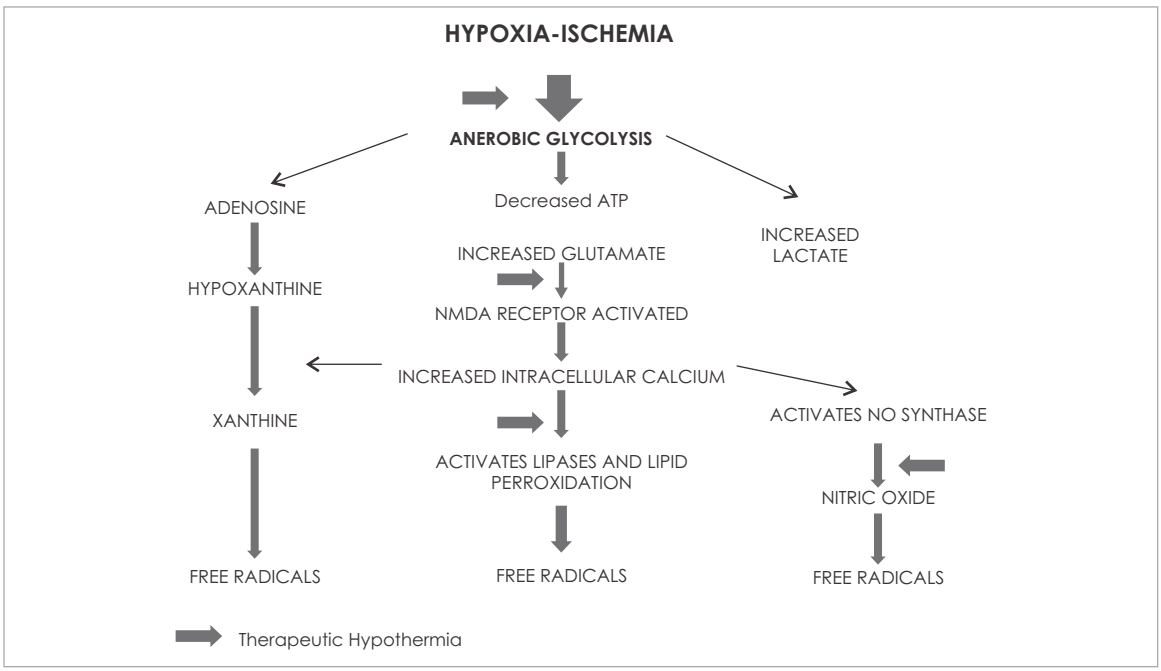


Fig.1: Pathophysiology of HIE - Key Events

Box 1: Summary – Mechanisms of action of Therapeutic Hypothermia

- Reduction of cerebral metabolism and prevention of edema
- Decrease in energy utilization
- Reduction of cytotoxic amino acid accumulation and nitric oxide
- Inhibition of platelet-activating factor and inflammatory cascade
- Suppression of free radical activity
- Attenuation of secondary energy failure
- Inhibition of apoptosis (cell death)
- Reduction of the extent of brain injury

CHAPTER

3

THERAPEUTIC HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY

EVIDENCE

Dr. Nishad P

SUMMARY OF EVIDENCE OF BENEFIT

There is now unequivocal and high-quality evidence from multiple large RCTs that neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE) following a perinatal event benefit from hypothermia under tightly controlled conditions. The trials used either head cooling devices (with mild systemic hypothermia),[1-5] or whole-body cooling alone.[6-12] A recent Cochrane review included 11 RCTs, comprising a total of 1,505 infants, and concluded that TH resulted in a reduction in the combined outcome of death or neurodevelopmental disability (to 18 months of age).[13]

Cooling appears to reduce DNA damage induced by oxidative stress and improve neurodevelopmental outcome.

Cooling resulted in an absolute risk reduction (risk difference, RD) of 15% in the composite outcome. Put another way, the number needed to treat for one additional beneficial outcome (NNTB) was 7 (95% CI: 5 to 10). The RD for mortality with cooling was -9% (95% CI: -13% to -4%); NNTB 11 (95% CI: 8 to 25) and for neurodevelopmental disability in survivors was -13% (95% CI: -19% to -7%); NNTB 8 (95% CI: 5 to 14). The most influential RCTs are listed in Table 1.

Cooling appears to reduce DNA damage induced by oxidative stress and improve neurodevelopmental outcome.[14] There is also evidence that therapeutic hypothermia limits myocardial and renal injury in term infants with HIE.[15, 16]

METHOD OF COOLING

A metaanalysis of the trials that used selective head cooling did not show a statistically significant difference in mortality (RR 0.78, 95% CI 0.59 to 1.04) or major neurodevelopmental disability (all participants,

RR 0.72, 95% CI 0.50 to 1.05).[13] But it is worth noting that the trend toward benefit was strong and consistent, the magnitude of benefit was comparable to the trials that used whole body cooling, and the intervention in the head-cooling trials also included mild systemic hypothermia. In addition, there was a statistically significant reduction in the hypothermia groups when neurodevelopmental disability was assessed in survivors as opposed to all participants (RR 0.66, 95% CI 0.47 to 0.94).

Metaanalysis of the trials that used whole body cooling showed a significant reduction in mortality (RR 0.73, 95% CI 0.61 to 0.89) and a trend towards reduction in neurodevelopmental disability (all participants, RR 0.79, 95% CI 0.62 to 1.01). There was also a significant reduction in neurodevelopmental disability among survivors (RR 0.67, 95% CI 0.53 to 0.83).[13] Apart from concerns about selective head cooling being less effective in cooling deeper brain structures, this method offers no advantages in cost or convenience over whole body hypothermia. Whole body hypothermia can also be delivered using inexpensive devices (discussed next) in low and middle income countries, hence should be the preferred method of cooling.

COOLING DEVICES

While most western centers currently prefer systemic hypothermia delivered using servo-controlled mattresses, these devices are expensive. Other techniques have been used to cool infants, ranging from passive hypothermia to fans, ice/gel packs and phase-changing materials. Of the large RCTs, the ICE trial notably used gel packs to cool infants.[11] The use of gel packs to cool infants has been studied in more resource-limited settings and appears to reduce the risk of death or developmental delay.[17, 18] In practice, ice packs are associated with wider fluctuations in temperature and are labor intensive, because of the need to rearrange the number and position of the gel packs based on infant temperature.

Passive cooling is a very practical and inexpensive option, especially for transporting outborn infants who may not arrive in an NICU within the 6-hour window for initiating hypothermia. But some infants do not cool enough with passive cooling, while others may overshoot the target temperature. In a retrospective observational study, only 39% of passively cooled transported infants were within the target temperature range upon arrival at the regional unit,compared to 100% of actively cooled infants.[19]

The use of phase changing material for cooling is increasingly popular in India because of the availability of a relatively inexpensive device. This has been studied as an alternative to servo-controlled cooling and appears to perform reasonably well, with one study reporting that the target temperature was maintained during 96.2% of the cooling phase.[20] As the study authors noted, however, careful monitoring is required, especially during the

induction phase and the rewarming phase. This has also been our experience, and overcooling appears to be a more common problem than failure to induce hypothermia.

DURATION OF COOLING

The duration of hypothermia in most trials was 72 hours. One trial cooled infants for 48 hours[8] and another for 48 to 72 hours depending on the neurological status of the infant.[1] In the ICE study, infants were re-warmed by 0.5°C every 2 hours[11] and in two other studies, infants were allowed to re-warm spontaneously at room temperature.[4,5] All the other studies rewarmed infants by 0.5°C per hour.[1-3, 6-8, 10, 12]

In 2014, NICHD investigators reported the initial results of a 2X2 factorial RCT which aimed to determine if cooling infants for a longer duration (for 120 hours), or to a lower temperature (to 32°C), or both are better than cooling at 33.5°C for 72 hours in term infants with moderate to severe HIE.[21]They reported an adjusted risk ratio for NICU deaths of 1.37 (95% CI: 0.92 to 2.04) for the 120 hours group Vs. the 72 hours group. Safety outcomes were similar. The trial was stopped early for safety and futility after enrolling 364 instead of the planned 726 infants. Follow up data were available for 95% (n=347) of these infants at 18-22 months, and showed that death or moderate to severe disability occurred in 56 of 176 infants (31.8%) cooled for 72 hours and in 54 of 171 infants (31.6%) cooled for 120 hours (adjusted RR 0.92, 95% CI 0.68 to 1.25). The adjusted RD was -1.0% (95% CI -10.2% to 8.1%), indicating an NNTB of around 100.[22] It is interesting to note that infants who were cooled for 120 hours at 32°C had the lowest disability rates but the highest mortality rates. Although the authors noted an interaction between longer and deeper cooling, the study was not powered to examine this interaction. Current evidence therefore suggests that cooling for a duration longer than 72 hours is not beneficial.

DEPTH OF COOLING

In the NICHD trial discussed above, death or disability occurred in 59 of 185 infants (31.9%) cooled to 33.5°C and in 51 of 162 infants (31.5%) cooled to 32.0°C (adjusted RR 0.92, 95%CI 0.68 to 1.26); adjusted RD was −3.1% (95%CI, −12.3% to 6.1%).[22] Deeper cooling did not appear to be beneficial. The authors observed a significant interaction between longer and deeper cooling (P = .048); the primary outcome rates were 34.5% at 32.0°C for 72 hours, 29.3% at 33.5°C for 72 hours, 28.2% at 32.0°C for 120 hours, and 34.4% at 33.5°C for 120 hours. There is currently no evidence to cool below the commonly used target temperature of 33.5°C (range of 33°C-34°C).

REWARMING

There is concern about decrease in systemic blood pressure during rewarming.[23] Rebound seizures can occur during rewarming,[24, 25] and in at least one case, the infant had to be recooled for another 24 hours to control the seizures.[25] Rewarming has also been reported to affect the EEG background.[26] However, it is not clear if another regime for rewarming will be better than the ones used in the RCTs. With current evidence, it appears prudent to rewarm slowly, at a rate of no more than 0.5°C per hour.

COOLING PRETERM INFANTS

As can be seen from Table 1, most RCTs have been done in term and late preterm infants, with a gestational age of 35 weeks or higher. The vast majority of enrolled infants in these trials were born at term. Preterm animal models of asphyxia indicate that hypothermia may offer short-term neuroprotection.[27] This would appear to support the idea of offering therapeutic hypothermia to preterm neonates with HIE, but there are serious obstacles to overcome.

In term infants, encephalopathy is more easily attributable to an acute peripartum event, and hence indicates a clinically significant hypoxic-ischemic event. In preterm infants, attributing an abnormal neurologic status to an intrapartum event is harder, because acute pulmonary and cardiac problems are common after birth, as is sepsis. EEG or aEEG, used in some RCTs of hypothermia, is harder to interpret in preterm infants, owing to maturational changes.[28, 29]

Initial reports of cooling preterm infants indicate that caution is warranted.[30, 31] An RCT of whole body hypothermia in preterm infants between 33 and 35 weeks gestational age and weighing $\geqslant$ 1500g, with neonatal encephalopathy within 6 hours of birth, is currently recruiting infants (Clinicaltrials.gov identifier: NCT01793129). This is a multicentric trial conducted by the NICHD Neonatal Research Network, and the primary outcome is death or moderate or severe disability assessed at 18 to 22 months corrected age. Until more evidence is generated by this and other trials, hypothermia should not be offered to infants below 35 weeks of gestation.

Table 1: Etiology of HIE

NAME OF TRIAL	COOLING METHOD	PARTICIPANTS	TARGET TEMP. AND DURATION	INCLUSION CRITERIA	PRIMARY OUTCOME	PRIMARY OUTCOME INCIDENCE	COMMENTS
Gunn et al, 2001 (18-month outcomes published later: Battin 2001)	Head cooling	22 term infants. Battin 2001: data on more infants (n= 40)	Minimal (rectal 36.3 ± 0.2°C) or mild (35.7 ± 0.2°C)	Encephalopathy	Mortality or major disability at 18 months	44% in normothermic, 26% in combined cooled groups	First RCT (safety study). 15 normothermic controls, 6 minimal cooling, 19 mild cooling.
Gluckman et al, 2005. CoolCap trial	Head cooling	235 term infants	34°C-35°C rectal for 72 hours	Moderate to severe encephalopathy + abnormal EEG	Death or severe disability at 18 months	66% in conventional, 55% in cooled. aOR 0.61 (0.34-1.09), p=0.10	Selective head cooling.
Zhou et al, 2010. Chinese RCT	Head cooling	256 infants	34°C nasopharyngeal and 34.5°C -35°C rectal for 72 hours	Encephalopathy	Death or severe disability at 18 months	49% in controls, 31% in cooled. OR 0.47 (0.26-0.84) P=0.01	21 post-randomization exclusions; ~20% had mild encephalopathy. Data unavailable for 41 infants.
Shankaran et al, 2005. NICHD trial	Whole body cooling	208 term infants	33.5°C esophageal for 72 hours	Moderate or severe encephalopathy	Death or moderate/severe disability at 18 months	62% in usual care, 44% in cooled. RR 0.72 (0.54-0.95), p=0.01	Data unavailable for 3 infants.
Azzopardi et al, 2009. Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial	Whole body cooling	325 infants ⩾36 weeks	33°C to 34°C rectal for 72 hours	Moderate or severe encephalopathy and abnormal EEG	Death or severe neurodevelopmental disability at 18 months	53% in usual care, 45% in cooled. RR 0.86 (0.68-1.07), p=0.17	Data unavailable for 2 infants. Survival without disabilities higher and rate of CP lower in cooled group.
Simbruner et al, 2010. neo.nEURO network RCT	Whole body cooling	129 infants	33°C to 34°C rectal for 72 hours	Moderate or severe encephalopathy and abnormal EEG	Death or disability at 18 months	83% in usual care, 51% in cooled. RR 0.21 (0.09-0.54), p=0.001	Data on 18 infants not available. All infants received morphine infusions.
Jacobs et al, 2011. Infant cooling evaluation trial (ICE trial)	Whole body cooling	221 infants ⩾35 weeks	33°C to 34°C rectal for 72 hours	Moderate or severe encephalopathy and abnormal EEG.	Death or major disability at 24 months	66% in controls, 51% in cooled. RR 0.77 (0.62-0.98), p=0.001	Data on 13 infants not available. Cooling initiated at referral hospital. Mild encephalopathy in 15% of hypothermia group and 23% of controls.

BIBLIOGRAPHY

1. Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. Pediatrics. 1998 Oct;102(4 Pt 1):885-92.

2. Akisu M, Huseyinov A, Yalaz M, Cetin H, Kultursay N. Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia. Prostaglandins LeukotEssent Fatty Acids. 2003 Jul;69(1):45-50.

3. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentrerandomised trial. Lancet. 2005 Feb 19-25;365(9460):663-70.

4. Zhou WH, Cheng GQ, Shao XM, Liu XZ, Shan RB, Zhuang DY, et al. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: a multicenter randomized controlled trial in China. J Pediatr. 2010 Sep;157(3):367-72, 72 e1-3.

5. Lin ZL, Yu HM, Lin J, Chen SQ, Liang ZQ, Zhang ZY. Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: an experience from a single neonatal intensive care unit. J Perinatol. 2006 Mar;26(3):180-4.

6. Shankaran S, Laptook A, Wright LL, Ehrenkranz RA, Donovan EF, Fanaroff AA, et al. Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants. Pediatrics. 2002 Aug;110(2 Pt 1):377-85.

7. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005 Oct 13;353(15):1574-84.

8. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: safety outcomes. Pediatr Neurol. 2005 Jan; 32(1):18-24.

9. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. Pediatr Neurol. 2005 Jan; 32(1):11-7.

10. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009 Oct 01;361(14):1349-58.

11. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. Arch Pediatr Adolesc Med. 2011 Aug;165(8):692-700.

12. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. Pediatrics. 2010 Oct;126(4):e771-8.

13. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013 Jan 31(1):CD003311.

14. Joy R, Pournami F, Bethou A, Bhat VB, Bobby Z. Effect of therapeutic hypothermia on oxidative stress and outcome in term neonates with perinatal asphyxia: a randomized controlled trial. J Trop Pediatr. 2013 Feb;59(1):17-22.

15. Rakesh K, Vishnu Bhat B, Adhisivam B, Ajith P. Effect of therapeutic hypothermia on myocardial

dysfunction in term neonates with perinatal asphyxia - a randomized controlled trial. J Matern Fetal Neonatal Med. 2017 Jul 06:1-6.

16. Tanigasalam V, Bhat V, Adhisivam B, Sridhar MG. Does therapeutic hypothermia reduce acute kidney injury among term neonates with perinatal asphyxia?--a randomized controlled trial. J Matern Fetal Neonatal Med. 2016;29(15):2545-8.

17. Bharadwaj SK, Bhat BV. Therapeutic hypothermia using gel packs for term neonates with hypoxic ischaemic encephalopathy in resource-limited settings: a randomized controlled trial. J Trop Pediatr. 2012 Oct;58(5):382-8.

18. Bhat BV, Adhisivam B. Therapeutic cooling for perinatal asphyxia-Indian experience. Indian J Pediatr. 2014 Jun;81(6):585-91.

19. Chaudhary R, Farrer K, Broster S, McRitchie L, Austin T. Active versus passive cooling during neonatal transport. Pediatrics. 2013 Nov;132(5):841-6.

20. Thomas N, Chakrapani Y, Rebekah G, Kareti K, Devasahayam S. Phase changing material: an alternative method for cooling babies with hypoxic ischaemic encephalopathy. Neonatology. 2015;107(4):266-70.

21. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. JAMA. 2014 Dec 24-31;312(24):2629-39.

22. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, et al. Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2017 Jul 04;318(1):57-67.

23. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics. 2000 Jul;106(1 Pt 1):92-9.

24. Battin M, Bennet L, Gunn AJ. Rebound seizures during rewarming. Pediatrics. 2004 Nov;114(5):1369.

25. Kendall GS, Mathieson S, Meek J, Rennie JM. Recooling for rebound seizures after rewarming in neonatal encephalopathy. Pediatrics. 2012 Aug;130(2):e451-5.

26. Birca A, Lortie A, Birca V, Decarie JC, Veilleux A, Gallagher A, et al. Rewarming affects EEG background in term newborns with hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia. Clin Neurophysiol. 2016 Apr;127(4):2087-94.

27. Laptook AR. Birth Asphyxia and Hypoxic-Ischemic Brain Injury in the Preterm Infant. Clin Perinatol. 2016 Sep;43(3):529-45.

28. Sisman J, Campbell DE, Brion LP. Amplitude-integrated EEG in preterm infants: maturation of background pattern and amplitude voltage with postmenstrual age and gestational age. J Perinatol. 2005 Jun;25(6):391-6.

29. Sommers R, Tucker R, Harini C, Laptook AR. Neurological maturation of late preterm infants at 34 wk assessed by amplitude integrated electroencephalogram. Pediatr Res. 2013 Dec;74(6):705-11.

30. Smit E, Liu X, Jary S, Cowan F, Thoresen M. Cooling neonates who do not fulfil the standard cooling criteria - short- and long-term outcomes. Acta Paediatr. 2015 Feb;104(2):138-45.

31. Walsh W. Report of a pilot study of Cooling four preterm infants 32-35 weeks gestation with HIE. J Neonatal Perinatal Med. 2015 Mar 10.

32. Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, Thoresen M, et al. The TOBY Study. Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: a randomised controlled trial. BMC Pediatr. 2008 Apr 30;8:17.

33. Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. Lancet Neurol. 2010 Jan;9(1):39-45.

34. Shankaran S, Barnes PD, Hintz SR, Laptook AR, Zaterka-Baxter KM, McDonald SA, et al. Brain injury following trial of hypothermia for neonatal hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed. 2012 Nov;97(6):F398-404.

35. Cheong JL, Coleman L, Hunt RW, Lee KJ, Doyle LW, Inder TE, et al. Prognostic utility of magnetic resonance imaging in neonatal hypoxic-ischemic encephalopathy: substudy of a randomized trial. Arch Pediatr Adolesc Med. 2012 Jul 01;166(7):634-40.

36. Weeke LC, Boylan GB, Pressler RM, Hallberg B, Blennow M, Toet MC, et al. Role of EEG background activity, seizure burden and MRI in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischaemic encephalopathy in the era of therapeutic hypothermia. Eur J Paediatr Neurol. 2016 Nov;20(6):855-64.

CHAPTER

4

THERAPEUTIC HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY

EVIDENCE ASPHYXIA AND THERAPEUTIC HYPOTHERMIA IN INDIA-AN OVERVIEW

Dr. Niranjan Thomas, Dr. Mintoo Tergestina

An estimated 4 million babies die every year in the neonatal period.

According to the Lancet Global Series on Neonatal survival, an estimated 4 million babies die every year in the neonatal period.[1] Ninety nine percentage of these deaths are in low to middle income countries. India contributes to one-fifth of global live births and more than a quarter of neonatal deaths. The neonatal mortality rate (NMR) as of 2013 is 28 per 1000 live births, of which the NMR for rural and urban is 31 and 15 per 100 live births respectively.[2] Intrapartum complications and birth asphyxia account for 23% of neonatal deaths globally and 19.2% of neonatal deaths in India, of which 97.8% of deaths due to asphyxia occur in the first week of life and 70% within the first 24 hours. The reported incidence of deaths due to hypoxia varies from 2 to 16.2% in community-based studies, with case fatality rates ranging from 38.5 to 74%.[3] Survivors of Hypoxic ischemia encephalopathy carry an additional burden of long term morbidity, neurological disability and functional impairment. As of today, the only modality for treatment and a means to decrease long term morbidity in babies with perinatal asphyxia is the initiation of therapeutic hypothermia within the first 6 hours of life.

COOLING IN LOW AND MIDDLE INCOME COUNTRIES

There has been considerable debate regarding the use of cooling in low and middle income countries. Increased rates of maternal malnutrition, inadequate maternal pelvis size, poor antenatal

obstetric care, late referral of complicated pregnancies, lack of trained birth attendants for and basic equipment for neonatal resuscitation, lack of referral centers that can manage neonates that require ventilation, increased rates of HIV, malaria and puerperal sepsis are factors that increase the risk of perinatal asphyxia.[6]

While the perinatal services offered in high income-low neonatal mortality countries are either institutional deliveries or home deliveries with rapid transport to a tertiary level neonatal unit, 25% of deliveries in India are home deliveries with minimal care thereafter.[3] Lack of access to transport, large distances and costs that are required to be borne for transport, coupled with weak communication systems and deliveries in resource poor settings can lead to delay in care that can be offered to a sick neonate. Even in cases of institutional delivery, delay in transport and referral can lead to loss of the window for initiation of therapeutic hypothermia.

An increased rate of perinatal infections has also raised concern when cooling in India. Data from animal studies suggest that hypothermia may not be neuroprotective after bacterial lipopolysaccharide-sensitized brain injury as compared to hypothermia without bacterial lipopolysaccharide.[7] There has also been concern that hypothermia can lead to decreased neutrophil function and chemotaxis and increased or worsening sepsis. However, reported rates of culture proven sepsis in a trial of cooling with gel packs done in India was 6.5%, with similar rates reported from the National Institute of Child Health and Human Development (NICHD) trial.[8] In a case series of 40 babies from a tertiary level NICU, of 40 babies who received therapeutic hypothermia, only one had a positive blood culture result and 11 had results that were positive for C-reactive protein.[9]

Other concerns that have been expressed are that the population has increased rates of intrauterine growth retarded babies, and an increased incidence of meconium aspiration syndrome. Temperature fluctuations and shivering have been pointed out as drawbacks to cooling with low-tech methods. However, when done under close monitoring, the fluctuations seen with manual cooling devices are no different from those seen in the NICHD and Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trials.

A constant criticism of therapeutic hypothermia by hypothermia-sceptics is that hypothermia decreases mortality but leads to an increase in survival of neonates with neuro-developmental morbidities. In India, there is a lack of institutionalized developmental follow up and support for children with developmental delay and disability is limited from governmental organizations and the society at large. This situation, however, has the potential to change and improve. While the economics of cooling in low to middle income countries has not yet been worked out, data from the TOBY trials show a clear benefit to cooling.

EQUIPMENT USED AND TRIALS FROM INDIA

Cooling equipment used in the high-income countries is expensive and unsuitable for wider use in low and middle-income countries. Studies have looked at passive cooling (keeping the baby without clothes, and without the use of a radiant warmer) during transport and the induction phase of therapeutic hypothermia. This was found to lead to over cooling, with temperatures < 32°C noted. It was also thought to be unlikely to be able to sustain temperatures within the target range for the 72 hour duration of cooling that is required.[11]

Whole body cooling has been described from other countries using water bottles, gloves filled with water, a laminar flow device and a servo controlled fan. The first trial of whole body cooling in India was reported from the Christian Medical College, Vellore, and was a study done to determine the feasibility and safety of whole body cooling in newborn infants with perinatal encephalopathy in a low resource setting. This described hypothermia using ice gel packs. This study involved neonates >35 weeks gestation who were cooled to a rectal temperature of 33±0.5°C for 72 hours. Twenty infants were included in this study that used reusable ice gel packs obtained from the immunization clinic at no added expense. While this low cost alternative required frequent changes of packs, more nursing input and constant monitoring, the target temperature was achieved and maintained with ease. The study concluded that whole body cooling in term infants with perinatal asphyxia was achievable, safe and inexpensive in a low-resource setting. However, the swings of temperature, and shivering of the cooled infant lead to the beginning of a search for a better low cost solution.[12]

The second published trial in India came from the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, a year later, which cooled babies with cloth covered gel packs and followed them up to an age of 6 months. These infants were assessed at 6 months using Baroda Developmental Screening Test, and the group that received therapeutic hypothermia showed a significant reduction in the combined rate of death or developmental delay at 6 months of age by 21% (8.1% in the TH group vs. 29% in the control, RR 0.28, 95% CI: 0.11-0.70; p = 0.003).[13] The same researchers from JIPMER also showed that therapeutic hypothermia reduced oxidative stress as measured by total antioxidant status and malondialdehyde,[14] and reduced oxidative stress-induced DNA damage.[15]

In 2009, Iwata et al published their report of the successful use of phase changing material (PCM) for cooling newborn piglets that had been exposed to hypoxia. The use of the PCM mattress was found to give more stable cooling, and a longer period within the target range of temperature.[16] The first randomized controlled trial of whole body cooling using phase changing material was conducted in Calicut in south India in 2013. Thirty three infants with Thompsons encephalopathy score >5 were cooled. However, the study found that cooling with PCM was effective only when the ambient temperature was <28°C, and required close temperature monitoring by the nursing staff.[17]

In 2014, a study was conducted on 28 newborns in the neonatal unit of the Madras Medical College, Tamil Nadu, which assessed the feasibility of the use of the Tecotherm-HELIX cooling mattress. This was a servo-controlled cooling device developed for low to middle income countries, with an estimated cost of US$1000.[18] It worked on the basis of re-circulating water mixed with alcohol through a re-usable cooling mattress to achieve a set temperature of 33.5°C. The advantage of the Tecotherm-HELIX cooling mattress was that refilling the machine with water every 6 – 8 hours was the only additional nursing input required. However, the cooling mattress required replacement once in the 6 month study period.

During the years from 2011 to 2014, a wholly indigenous passive cooling mattress that was based on phase changing material was in development at the Christian Medical College, Vellore. Multiple attempts were made to find the ideal PCM that was easy to use, safe, lightweight, portable and gave precise temperature control of 33-34°C for 72 hours with minimal manual supervision and no requirement of constant electricity. The feasibility of the technology was reported in 2015, on a retrospective series of 41 babies with HIE who had been cooled with PCM (OM 32™ or HS 29™) to a target rectal temperature of 33-34°C. This was successful in maintaining the target temperature range 96.2% of the time in the cooling phase.[19]

The final product was the CMC PCM Mattress- Patent-3184/DEL/2013. This used a cascaded system of PCMs that were incorporated in a polymer matrix that provided form stability and ensured that the PCM retained its shape and form, preventing leakage. The melting points, thicknesses, conductivities and placement of the involved layers were such that a "quasi-automated" cooling system was created, which functioned similar to a servo controlled system. Pluss Advanced Technologies, who supplied the phase change material worked closely with the research team from Christian Medical College Vellore, and later marketed it as the MiraCradle®. Over the years, from 2011, more than 200 babies have been cooled successfully, with minimal complications and successful maintenance of temperature within the target ranges. More than 150 commercial PCM mattresses are currently in use in India and data of 103 babies cooled in 10 different hospitals in India with good results has been sent for publication. They are also used across the world, in South Africa, Turkey and in Kenya.

SYSTEMATIC REVIEW AND META-ANALYSIS

A systematic review by Pauliah et al,[20] did not show any significant improvement in mortality and concluded that cooling cannot be recommended in both low and middle income countries until further data suggest benefit. However, the confidence intervals in this review were wide, and it was speculated by the authors that the reasons for the lack of treatment effect observed were poor quality of the included studies; lack of efficiency of low technology cooling devices; lack of optimal neonatal intensive care, sedation and ventilation support; intrauterine growth restriction; and maternal malnutrition.

The review concluded that therapeutic hypothermia using low technology methods was achievable, safe and inexpensive. When combined with intensive care, this is proven to significantly reduce the mortality and neurological morbidity in survivors at discharge. The Meta-Analysis by Rossouw et al shows that low technology cooling devices are effective, and make a difference in the mortality and morbidity of the babies when used in an intensive care setting where mechanical ventilation is available, and when it is possible to provide more intensive nursing. The initial feasibility study from India had shown that cooling with manual application of cloth-covered gel packs was feasible with a nurse-to-infant ratio of 1:3.[12]

A meta-analysis by Galvao et al.[23] of 16 studies and a total of 1889 neonates (of which 8 of the studies included were conducted in lower income countries) showed that hypothermia significantly reduced mortality (RR = 0.77; 95% CI: 0.65-0.92). Meta-regression analysis also revealed that hypothermia efficacy does not increase as the gross domestic product per capita of the country in which it is done rises, and they concluded that there is enough evidence to support therapeutic hypothermia as the standard of care for hypoxic-ischemic encephalopathy.

CONCLUSION

India, with diverse patient profiles, has centers that have facilities that equal those in high income countries. A trial of cooling can no longer be done in a high income country due to the loss of equipoise. To do so in our country – to offer cooling versus normothermia in babies with perinatal asphyxia should raise ethical questions. In areas that lack basic facilities, the focus should remain on improving antenatal and neonatal care to prevent asphyxia. Training of personnel, following standard protocols for cooling, setting up and maintaining a national registry to monitor neurodevelopmental outcome (similar to the TOBY registry) is what we should achieve. While the equipment used in high income countries cannot be sustainably used in low and middle income countries, therapeutic hypothermia using low cost technology can provide sustainable, efficient and effective treatment with minimal costs and maximal benefits, and should be implemented as a standard of care for infants with moderate or severe HIE and refusal cannot be justified where facilities exist.

BIBLIOGRAPHY

1. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? Lancet Lond Engl. 2005 Mar 5;365(9462):891–900.
2. Neo Natal Mortality Rate (NMR) (per 1000 live births) | NITI Aayog, (National Institution for Transforming India), Government of India [Internet]. [cited 2017 Oct 6]. Available from: http://niti.gov.in/content/neo-natal-mortality-rate-nmr-1000-live-births
3. National Family Health Survey [Internet]. [cited 2017 Oct 6]. Available from: http://rchiips.org/NFHS/factsheet_NFHS-4.shtml
4. Edwards AD. The discovery of hypothermic neural rescue therapy for perinatal hypoxic-ischemic encephalopathy. Semin Pediatr Neurol. 2009 Dec;16(4):200–6.
5. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013 Jan 31;(1):CD003311.
6. Montaldo P, Pauliah SS, Lally PJ, Olson L, Thayyil S. Cooling in a low-resource environment: lost in translation. Semin Fetal Neonatal Med. 2015 Apr;20(2):72–9.
7. Osredkar D, Thoresen M, Maes E, Flatebø T, Elstad M, Sabir H. Hypothermia is not neuroprotective after infection-sensitized neonatal hypoxic-ischemic brain injury. Resuscitation. 2014 Apr;85(4):567–72.
8. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005 Oct 13;353(15):1574–84.
9. Aker K. Birth asphyxia and whole body cooling: a descriptive study of newborns admitted with perinatal asphyxia in a tertiary care Perinatal center in south India. Masters thesis. Trondheim, Norway: Norweigian University of Science and Technology; 2009.
10. Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, Thoresen M, et al. The TOBY Study. Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: a randomised controlled trial. BMC Pediatr. 2008 Apr 30;8:17.
11. Akula VP, Gould JB, Davis AS, Hackel A, Oehlert J, Van Meurs KP. Therapeutic hypothermia during neonatal transport: data from the California Perinatal quality care collaborative (CPQCC) and California perinatal transport system(CPeTS) for 2010. J Perinatol 2013;33(3):194e7.
12. Thomas N, George KC, Sridhar S, Kumar M, Kuruvilla KA, Jana AK. Whole body cooling in newborn infants with perinatal asphyxial encephalopathy in a low resource setting: a feasibility trial. Indian Pediatr. 2011 Jun;48(6):445–51.
13. Bharadwaj SK, Bhat BV. Therapeutic hypothermia using gel packs for term neonates with hypoxic ischaemic encephalopathy in resource-limited settings: a randomized controlled trial. J Trop Pediatr. 2012 Oct;58(5):382–8.
14. Joy R, Pournami F, Bethou A, Bhat VB, Bobby Z. Effect of therapeutic hypothermia on oxidative stress and outcome in term neonates with perinatal asphyxia: a randomized controlled trial. J Trop Pediatr. 2013 Feb;59(1):17–22.

15. Effect of Therapeutic Hypothermia on DNA Damage and Neurodevelopmental Outcome Among Term Neonates With Perinatal Asphyxia: A Randomized Controlled Trial [Internet]. PubMed Journals. Available from: https://ncbi.nlm.nih.gov/labs/articles/24343823/

16. Iwata S, Iwata O, Olson L, Kapetanakis A, Kato T, Evans S, et al. Therapeutic hypothermia can be induced and maintained using either commercial water bottles or a "phase changing material" mattress in a newborn piglet model. Arch Dis Child. 2009 May;94(5):387–91.

17. Thayyil S, Shankaran S, Wade A, Cowan FM, Ayer M, Satheesan K, et al. Whole-body cooling in neonatal encephalopathy using phase changing material. Arch Dis Child Fetal Neonatal Ed. 2013 May;98(3):F280-281.

18. Pauliah S, Narayanan E, Kumutha K, Vijayakumar M, Nair M, Shankaran S. Hypothermia for Encephalopathy in Low and Middle-income Countries (HELIX): a feasibility study. Archs Dis Child Fetal Neonatal Ed 2014;99. A74.

19. Thomas N, Chakrapani Y, Rebekah G, Kareti K, Devasahayam S. Phase Changing Material: An Alternative Method for Cooling Babies with Hypoxic Ischaemic Encephalopathy. Neonatology. 2015 Feb 26;107(4):266–70.

20. Pauliah SS, Shankaran S, Wade A, Cady EB, Thayyil S. Therapeutic hypothermia for neonatal encephalopathy in low- and middle-income countries: a systematic review and meta-analysis. PloS One. 2013;8(3):e58834.

21. Rossouw G, Irlam J, Horn AR. Therapeutic hypothermia for hypoxic ischaemic encephalopathy using low-technology methods: a systematic review and meta-analysis. Acta Paediatr Oslo Nor 1992. 2015 Dec;104(12):1217–28.

22. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. Arch Pediatr Adolesc Med. 2011 Aug;165(8):692–700.

23. Galvao TF, Silva MT, Marques MC, de Oliveira ND, Pereira MG. Hypothermia for perinatal brain hypoxia-ischemia in different resource settings: a systematic review. J Trop Pediatr. 2013 Dec;59(6):453–9.

CHAPTER

5

COOLING DEVICES FOR THERAPEUTIC HYPOTHERMIA IN NEWBORN BABIES

Dr. Sumitha Arun, Dr. Manish Kumar

Many tertiary level hospitals in India have started providing therapeutic hypothermia as standard of care to newborn with moderate to severe degree of hypoxic ischemic encephalopathy. One of the limiting factors to provide therapeutic hypothermia in India is availability of cooling device. Therapeutic hypothermia can be provided as selective head cooling or whole body cooling. In this article, we will discuss what would constitute an ideal cooling device, what are the devices available and a description on how they function.

One of the limiting factors to provide therapeutic hypothermia in India is availability of cooling device.

THE CHARACTERISTICS OF AN IDEAL COOLING DEVICE

- It should induce cooling rapidly to the desired core temperature
- It should maintain the core temperature tightly within the target range
- It should allow re-warming in a slow and controlled manner
- It should be easy to use
- It should require minimal nursing input
- It should not interfere with access to the baby
- Environmental temperature should not affect cooling efficacy
- Safety systems in case of accidental probe displacement

Since the early 2000's, therapeutic hypothermia has been tried either as selective head cooling or as whole body cooling. Many of these devices are cost-prohibitive. Hence alternate low cost cooling systems have been developed for use in resource limited settings. The various high technology devices with their cooling methods are summarized in Table 1.

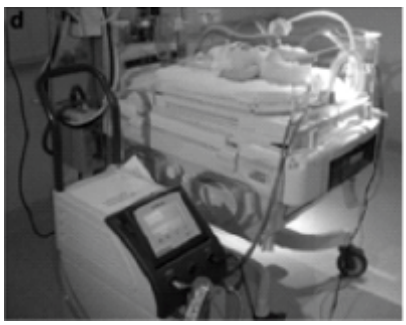
Cooling Equipment- High technology devices

1.**BLANKETROL 2** (Cincinnatti subzero products Inc, USA) was used in the NICHD trial.[1] It is a microprocessor controlled device based on conductive water therapy. Target temperature is achieved by heating and cooling water circulated through mattress and wraps. Due to fluctuations in temperature, additional blankets were used around the baby. The rewarming process is manually done in the device.

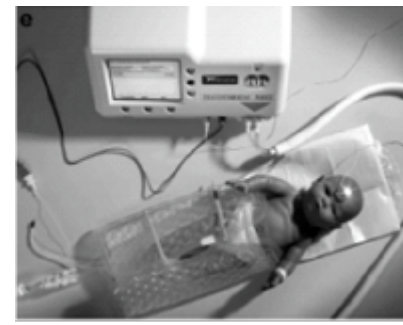
Blanketrol 2 used in NICHD

BLANKETROL 3 used gradient programme technology to minimize fluctuations in water temperature. It did not require use of additional blankets. It involved precooling to 5°C 15 minutes prior to starting. Oesophageal probes were used for temperature recording. Data export software was incorporated.

2. **Criticool from MTRE,** Charter Kontron, Milton Keynes, UK, is a microprocessor controlled servo device. It has a large basal unit and disposable cure wraps through which water is circulated. Access to baby is restricted due to wraps covering the baby. The rewarming phase can be set in manual or controlled mode. Controlled rewarming is set at 0.2°C per 30 minutes. It takes 7.5 hours to rewarm.

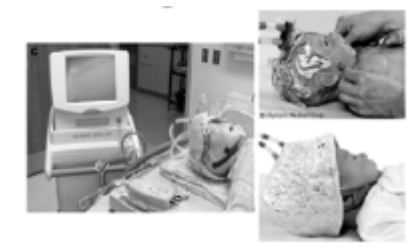


3. **Tecotherm TS med 200** from Tec-com, Halle Germany: Is a manual cooling device which was used in the TOBY trial.[2]



4. **Tecotherm Servo** from Tec-com, Halle Germany: This consists of a mattress that is wrapped around baby's trunk and legs. The device is fully automated and requires no further input after initiation. The baby's temperature is cooled to 33.5°C within 30 minutes. This temperature is maintained for 72 hours and a fully automated rewarming process starts. The rewarming occurs to 37°C at 0.2-0.5°C/hour (requiring around 7 hours for rewarming). The monitor displays rectal and skin temperature. Data can be transported out of the machine and analyzed. Default temperature settings on the machine can be altered according to individual needs.

5. **Cool cap** (Olympic Medical Cool Care System, Olympic Medical, Seattle, WA, USA): This was used for selective head cooling. Olympic cool cap system maintains the water in the fitted cap at an operator specified temperature. The rest of the body is exposed to radiant warmer. It requires lot of nursing input. Rectal temperature is used to guide the set temperature. Target temperature is 34-35°C. Rewarming is manual in cool cap.



There is a statistically significant reduction in the composite outcome of death or major neurodevelopmental disability in both selective head cooling and whole body cooling as per Cochrane meta-analysis.[3] During selective head cooling there is a temperature gradient between the surface and deeper structures of the brain. Even when we effectively cool the surface of brain to desired temperature, the deep brain structures may not be adequately cooled. This is a significant concern as profound hypoxic injury particularly affects the deep brain structures. In a comparative study there were lesser lesions on MRI after whole body cooling in comparison to selective head cooling.[4]

Table 1:

NAME OF DEVICE	DESIGN	FEATURES	ISSUES	RECURRENT EXPENSES
Blanketrol 2	Mattress Wraps	Coolant- water Wraps	1. Temperature fluctuation 2. Rewarming –manual 3. Not portable	Cooling wraps
Blanketrol 3	Mattress Wraps	Coolant –water Less fluctuations in temperature Less fluctuations in temperature Wraps	1. Pre-cooling required.	Cooling wraps
Criticool	Wraps	1. Coolant- water Rewarming –automated 2. Portable 3. Alcohol based coolant	1. Rewarming –manual/controlled 2. Not portable	Cooling wraps
Tecotherm Servo	Mattress	1. Fully automated Rewarming –automated 2. Portable 3. Alcohol based coolant		Coolant top ups and mattress
Cool cap	Cap	1. Selective head cooling	Manual rewarming More nursing input	Cooling cap

COOLING EQUIPMENT-LOW COST DEVICES

Various low technologies methods like passive cooling, ice gel pack, cooling fan, etc.; have been tried to achieve therapeutic hypothermia because of the high cost and unavailability of servo controlled equipment. There have been concerns of overcooling, fluctuations in temperature, cold injury like subcutaneous fat necrosis, increased shivering and need of more nursing input. Increase in awareness, intensive monitoring, refinement of technology (e.g., use of phase changing material) and appropriate intervention (e.g., use of analgesia, frequent change in position) have helped to achieve therapeutic hypothermia without overcooling and minimal fluctuations of temperature. We have shown the efficacy and safety of low technologies devices like frozen gel pack and phase changing materials which is comparable to standard servo-controlledcooling equipment.[5] A recent systematic analysis has shown that low technology device in tertiary level settings has improved survival and neurological outcome in HIE babies with moderate to severe encephalopathy.[6]

PASSIVE COOLING

Babies are kept naked with radiant warmer switched off. This has been mainly tried during transportation for induction phase of cooling. It is feasible to achieve cooling passively but there has been concern of overcooling. Several studies have reported significant overcooling (<32°C) in approximately one third of the babies.[7] There is no published data regarding use of passive cooling for maintenance and rewarming phase.

FROZEN/ICE GEL PACK

ICE trial, a multi-center randomized controlled trial, showed improved disability free survival in babies with moderate to severe HIE after achieving therapeutic hypothermia with frozen gel pack.[8] In India, the feasibility trial from Christian Medical College, Vellore showed safety and effectiveness of frozen gel pack (FGP) for therapeutic hypothermia.[9]

Method: Insert rectal probe 5 cm inside and fix to thigh. Switch off the radiant warmer. For induction phase, distribute 4-5 packs over the head, both axillae, back and abdomen. Once the temperature reaches 34°C, remove packs one by one, targeting the temperature of 33.5± 0.3°C. The packs on the head and back are to be removed last.

Gel packs should be stored in deep freezer. Wrap the FGPs with cloth and avoid direct skin contact for longer duration. This minimizes cold injury to skin. Always have rectal probes for temperature monitoring. Skin probes are NOT an acceptable alternative.[10] Leave only one FGP at the temperature of 33.5°C. Set the alarm limit at 33.2°C and 33.8°C on monitor during maintenance phase. At the end of 72 hours of induced hypothermia, remove cool packs and turn on the radiant warmer to raise the body temperature by 0.3°C/hour to reach a target temperature of 36.5°C. (This should take 12-15 hours). The temperature probe should

be removed after monitoring the temperature for a further 12 hours (72 + 12 hours after initiation of cooling).

If the infant's rectal temperature increases to 33.8°C, more cloth covered cooling-gel packs should be placed and then subsequently removed when the rectal temperature reaches 33.5°C.

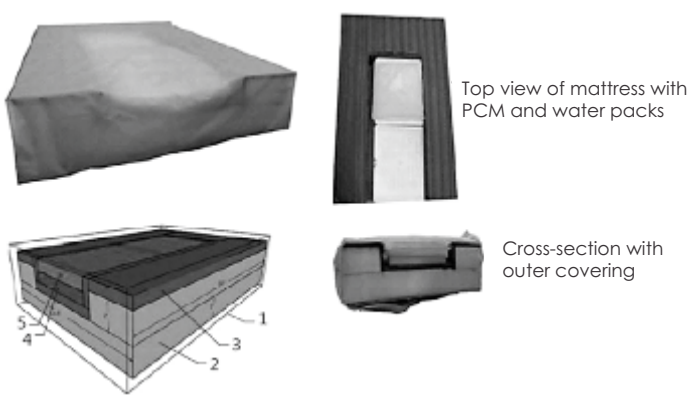
If the temperature decreases to 33°C, remove cooling gel packs/turn warmer on till temperature reaches 33.5°C

PHASE CHANGING MATERIALS

Phase changing materials (PCM) are made of salt hydride, fatty acid and esters or paraffin, melting at a set point. PCMs absorb and release heat at a nearly constant temperature and can store 5–14 times more heat per unit volume compared to material like water or masonry. When a baby is placed on a bed made of PCM, heat from the baby is transferred to the PCM which absorbs the heat till it melts. Hence, PCM has the potential to provide a mechanism of heat removal which will be easier and safer to use than ice packs. Keeping the melting point of the PCM at the target temperature will ensure that the baby's temperature will not fall below this temperature. The device designed by our unit has used PCM with 2 different melting point: PCM 21 with melting point at 21°C for induction phase and PCM 29 with the melting point at 29°C for maintenance phase. The theory and methodology has been described in detail.[11] PCM should not be frozen. It should be stored in the lower compartment of refrigerator.

In our study with PCM, induction time was 45 minutes, only 3.8% of temperature readings were outside the target range and fluctuation of core body temperature was 0.28°C.[5]

Equipment description



1. Outer covering layer - good conductor (only lines)
2. Foam layer (orange-yellow)
3. Insulating layer (green)
4. PCM layer (red)
5. Water pack layer (blue)

METHODS

Switch off radiant warmer. Fix the rectal probe.

Remove the PCM from refrigerator and keep it in room temperature for 30 minutes before commencing cooling. Use PCM 21 for induction and PCM 29 for maintenance phase if nursery temperature is 27°C or above. If nursery temperature is 26°C or less, use 29 PCM for both the phases.

If you are using 21 PCM for induction, remove it once rectal temperature is 34°C.

If the infant's rectal temperature increases to 33.8°C, change 29 PCM if it is melted. If 29 PCM is good, add a 21 PCM and then subsequently remove when the rectal temperature reaches 33.5°C.

If the temperature decreases to 33.2°C, introduce a bed sheet between baby and PCM. If temperature remains low, turn warmer on till temperature reaches 33.5°C.

PCM based devices have been successfully used in CMCH, JIPMER and various other hospitals in India over the past few years with documented evidence of safety and efficacy.

OTHERS

Laminar flow device, cooling fans, clay pots have been used for therapeutic hypothermia in various studies.

Table 2: Comparison of different cooling device

	Frozen gel pack	Phase changing material	Servo controlled device
Time taken to reach target temperature, minutes; median (IQR)	45 (10, 100)	90 (25, 150)	90 minutes (NICHD) 30 minutes (TOBY)
Temperature fluctuation during cooling phase, °C; mean (SD)	0.4	0.28	0.4 (TOBY) 0.5 (NICHD) (semi-automated)
Temperature readings outside the target range	9.8 %	3.8 %	
Subcutaneous Fat Necrosis	13 %	2.2 %	2.8 %
Laborious nursing input	More	Less	Least

Fully automated servo controlled Cooling devices are ideal for providing therapeutic hypothermia to newborn with asphyxia. Affordability is the main issue. Low technology cooling devices like frozen gel packs and Phase change materials are effective, safe and an affordable alternative in intensive care settings.

BIBLIOGRAPHY

1. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. N Engl J Med. 2005;353(15):1574–1584.
2. The TOBY Study Group, Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, et al. The TOBY Study. Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: A randomised controlled trial. BMC Pediatr [Internet]. 2008 Dec [cited 2017 Oct 2];8(1). Available from: http://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-8-17
3. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic is chaemic encephalopathy. Cochrane Database Syst Rev. 2013 Jan 31;(1):CD003311.
4. Sarkar S, Donn SM, Bapuraj JR, Bhagat I, Barks JD. Distribution and severity of hypoxic-ischaemic lesions on brain MRI following therapeutic cooling: selective head versus whole body cooling. Arch Dis Child Fetal Neonatal Ed. 2012 Sep;97(5):F335-339.
5. Shabeer MP, Abiramalatha T, Smith A, Shrestha P, Rebekah G, Meghala A, et al. Comparison of Two Low-cost Methods of Cooling Neonates with Hypoxic Ischemic Encephalopathy. J Trop Pediatr. 2016 Oct 6;fmw067.
6. 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 Dec;104(12):1217–28.
7. Fairchild K, Sokora D, Scott J, Zanelli S. Therapeutic hypothermia on neonatal transport: 4-year experience in a single NICU. J Perinatol Off J CalifPerinat Assoc. 2010 May;30(5):324–9.
8. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. Arch Pediatr Adolesc Med. 2011 Aug;165(8):692–700.
9. Thomas N, George KC, Sridhar S, Kumar M, Kuruvilla KA, Jana AK. Whole body cooling in newborn infants with perinatal asphyxial encephalopathy in a low resource setting: a feasibility trial. Indian Pediatr. 2011 Jun;48(6):445–51.
10. Thomas N, Rebekah G, Sridhar S, Kumar M, Kuruvilla KA, Jana AK. Can skin temperature replace rectal temperature monitoring in babies undergoing therapeutic hypothermia in low-resource settings?: Temperature monitoring during therapeutic hypothermia. Acta Paediatr. 2012 Dec;101(12):e564–7.
11. Thomas N, Chakrapani Y, Rebekah G, Kareti K, Devasahayam S. Phase Changing Material: An Alternative Method for Cooling Babies with Hypoxic Ischaemic Encephalopathy. Neonatology. 2015 Feb 26;107(4):266–70.

CHAPTER

6

PROCEDURE FOR WHOLE BODY COOLING

Dr. Sumitha Arun, Dr. Manish Kumar

WHICH NEONATES TO COOL?

Neonates can be considered for cooling if the following criteria are met (NICHD criteria):

1. Gestational age ⩾ 36 weeks
2. Less than 6 hours old
3. A pH of 7.0 or less or a base deficit of 16 mmol per liter or more in a sample of umbilical cord blood or any blood during the first hour after birth. If the pH is between 7.01 and 7.15, a base deficit is between 10 and 15.9 mmol per liter, or a blood gas is not available, additional criteria are required. These include an acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest) and either a 10-minute Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 minutes.
4. Moderate to severe encephalopathy on clinical examination.

Neonates can be considered for cooling if the following criteria are met (NICHD criteria)

TYPES OF COOLING

Two different types of hypothermia were practiced:

a) Selective head cooling

b) Whole body cooling

Though selective head cooling appears to be attractive, it does not correlate well with core body temperature. There is also differential cooling between the superficial and deeper parts of the brain causing differential perfusion. In contrast, whole body cooling correlates well with core body temperature but associated with more adverse effects.

PREREQUISITES TO PRACTICE THERAPEUTIC HYPOTHERMIA

The minimum prerequisites to start the practice of therapeutic hypothermia have been depicted in Table.1:

Table 1: Minimum requirements to practice therapeutic hypothermia.

Place	Personnel	Paraphernalia	Protocols
Well established level-3 NICU care.	Trained doctors & Staff nurse	Radiant warmer, Cooling device, ABG machine, Multi-parametric parameters, Ventilators	Evidence based standard protocol. Neuro-development follow up.

DIFFERENT PHASES OF COOLING THERAPY

The different phases of therapeutic hypothermia are depicted in the Table 2.

Table 2: Phases of therapeutic hypothermia.

Hypothermia phases	Strategies
INDUCTION	Rapid cooling to 33-34°C. Duration: 45 minutes-1 hour. Monitor temperature and vitals. Treatment of shock and seizures. Avoid shivering and overcooling. Rectal probe inserted 5 cm into the rectum and skin probe over the abdomen are connected to the monitor for continuous monitoring. The radiant warmer is switched off.
MAINTENANCE	The target temperature is monitored every 15 minutes for the first four hours and later hourly for 72 hours. Vital parameters like heart rate, capillary filling time and blood pressure are recorded hourly. Close monitoring of temperature and vitals. Maintain temperature: 33-34°C. Total Duration: 72 hours. Monitor urine output and adjust total fluid intake. Monitor for multi-organ damage. Adjust drug dosages. Look for bed sores and skin damage.
REWARMING PHASE	Slow rewarming initiated. Duration: 6-10 hours. Temperature raise: 0.5°C/hour. Look for seizures. Avoid fluid shifts. Careful vitals monitoring. After rewarming feeding is started gradually.

CHAPTER

7

MONITORING OF NEONATES DURING THERAPEUTIC HYPOTHERMIA

Dr. KumuthaJ, Dr. Manigandan Chandrasekaran

INTRODUCTION

As cooling is used more widely and has been newly introduced in neonatal units, continued surveillance of its use in clinical practice is mandatory. The initial management of infants with HIE following admission to the neonatal unit consists of standard neonatal intensive care measures, continuous core temperature monitoring using a rectal probe and initiation of therapeutic hypothermia. Monitoring of such infants is critical to the neurological outcome. We describe here the systematic approach to monitor these infants.

As cooling is used more widely and has been newly introduced in neonatal units, continued surveillance of its use in clinical practice is mandatory.

TEMPERATURE MONITORING

Both the core temperature and skin temperature are monitored continuously. The core temperature is usually monitored by rectal or oesophageal probe. The rectal probe should be inserted 3-6 cm and secured to the thigh. The oesophageal probe is inserted to a length of measured distance (Angle of mouth to tragus and up to a point 2 cm above Xiphisternum). The temperature is recorded every 15 minutes till a core temperature of 33.5°C is achieved and thereafter every hour till rewarming is completed. The core temperature should be maintained between 33.5°C to 34°C. The fluctuation of temperature during the maintenance phase should be very minimal as it can adversely affect the neurological outcome.

CARDIORESPIRATORY CARE

Hypothermia is consistently associated with sinus bradycardia as it slows the atrial pacemaker and intracardiac conduction. The QT

interval also can be prolonged. The heart rate can be even lower than 100. Heart rate drops by nearly 14 beats per one degree drop in temperature. HR up to 70 can be tolerated as long as it is normal sinus rhythm and normal SPO2 and BP are observed. Therefore, it is vital to observe these neonates with continuous cardiac monitoring preferably with multi-channel monitoring. Sinus bradycardia usually does not need intervention. Close monitoring of blood pressure is very essential to identify shock since CRT will be not a reliable indicator of hypo perfusion in babies receiving cooling therapy. All infants should be monitored closely with invasive blood pressure monitoring (if possible) and treated with inotropes accordingly.

MECHANICAL VENTILATION

Ventilation may not be needed for all neonates during cooling, however, it is important to maintain normal pCO_2, pO_2, pH and respiratory effort. Decreasing body temperature lowers metabolic rate by about 5-8% per °C. Furthermore, partial pressure of blood gases and pH are also affected because of altered gas solubility during hypothermia. With each degree Celsius decrease in core temperature, pH increases by 0.015, pCO_2 and pO_2 decrease by 4% and 7% respectively. Excessively low pCO_2 during therapeutic hypothermia may result in altered cerebral blood flow auto regulation, and reduced cerebral perfusion, and may lower the seizure threshold. Hence, blood gas values should be corrected for core body temperature. The corrected blood gas values should be maintained within the normal range by appropriate ventilator adjustments.

CARDIO-RESPIRATORY MANAGEMENT

- Correct respiratory acidosis by manipulating ventilator support
- Start mechanical ventilation if repeated desaturations associated with seizures or incipient respiratory failure with rising oxygen requirements and increasing respiratory acidosis are observed.
- Avoid hypocapnia. Aim for pCO2 around 45 - 50 mm during cooling
- Maintain SaO2 ⩾92%to lessen risk of pulmonary hypertension
- Obtain arterial access to monitor blood pressure if mechanical ventilation is required
- Monitor regional perfusion using capillary refill scores and core-peripheral temperature gap as guides to peripheral blood distribution
- Aim for mean blood pressure (BP) ⩾ 40 mm Hg. A low BP requires assessment. Perform echocardiographic assessment (if available) of cardiac contractility and stroke volume to guide fluid/inotrope administration

SKIN MONITORING

Poor skin perfusion occurs during cooling. The skin has to be inspected periodically and the back to be inspected at least 12 hourly. The position has to be changed 6 to 12 hourly from flat to slightly tilted in the supine position. Cyanosis of the hands and feet is common and usually transient.

FLUID BALANCE

Disturbances in electrolytes and glucose homeostasis are common in infants with HIE, including those receiving therapeutic hypothermia. Fluid balance is essential in cooling neonates as the metabolic rate is low, and they may not need large volume of fluids. It is challenging to restrict fluids and supplement adequately. Fluid boluses should be avoided as it can lead to exacerbation of oedema which is due to capillary leak. The cooled babies may need more volume during rewarming phase due to redistribution of fluid into the tissues and increased diuresis.

It is recommended that serum electrolytes and plasma glucose should be kept within the normal range during hypothermia treatment. Hypocalcemia, hypomagnesemia, and hypoglycemia are common in asphyxiated newborn infants. Hence close monitoring of electolytes and blood gas should be performed as per needs of the baby.

FLUID BALANCE

- Hypoglycemia can be a serious complicating factor in HIE. Monitor plasma glucose closely (4 hourly) and adjust glucose intake accordingly.
- Oliguria/anuria is common following HIE; Monitor urinary output and aim for urine output $\geqslant$ 1ml/kg/hour. Observe for bladder retention. Urinary catheterization may be useful.
- Daily weight monitoring should be carried out.
- Initial intravenous fluid requirements are approximately 40 ml/kg/day 10% Dextrose solution. Monitor blood electrolyte levels 8 hourly for first 24–48 hours.
- Grade up fluid depending on the weight gain and presence of oedema. as these babies tend to retain lot of fluid.
- Consider electrolyte additives or parenteral nutrition after 24 - 48 hours when electrolytes/ renal function stable.
- Give maintenance potassium supplementation if renal function is adequate (2 mmol/ kg/day). Avoid potassium supplementation during cooling, as hyperkalemia may occur on rewarming.

HEMATOLOGICAL MONITORING

It is preferable to monitor lab parameters during cooling as mentioned below.

INVESTIGATIONS	TIMINGS
CBC	0, 24, 48, 72 hours
Electrolytes /RFT	12, 24, 48, 72 hours
Coagulation profile	0, 24, 72 hours
LFT	0, 24, 72 hours
ABG	0, 12, 24, 48, 72 hours

NEUROLOGICAL MONITORING

Details are elaborated in chapters 10, 11 and 12.

CONCLUSION

Meticulous neonatal care provided by multi disciplinary team is critical for ensuring better outcomes for infants with HIE on therapeutic hypothermia.

BIBLIOGRAPHY

1. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. N Engl J Med. 2005;353(15): 1574–1584.
2. Sarkar S, Barks JD. Systemic complications and hypothermia. Semin Fetal Neonatal Med. 2010 Oct; 15(5):270-5.
3. Bhat BV, Adhisivam B. Therapeutic cooling for perinatal asphyxia-Indian experience. Indian J Pediatr. 2014; 81:585-91

CHAPTER

8

PREVENTION & MANAGEMENT OF COMPLICATIONS OF THERAPEUTIC HYPOTHERMIA

Dr. Vishnu Bhat B, Dr. Adhisivam B

Inadvertent excessive cooling (cold-injury syndrome) may occur during therapeutic hypothermia and may be due to inadequate monitoring.

Inadvertent excessive cooling (cold-injury syndrome) may occur during therapeutic hypothermia and may be due to inadequate monitoring, inexperienced staff or non-servocontrolled cooling systems. Asphyxiated newborns with HIE per se are known to have impaired thermo-regulation. The effects of excessive cooling, especially pulmonary and cardiac dysfunction, are expected to be more serious in asphyxiated infants who already have multiorgan dysfunction, or the multi-organ dysfunction initially triggered by the HIE may be exaggerated by superimposed cold-injury syndrome.

Excessive cooling can cause cardiovascular instability and re-emergence of seizures. Some of the problems associated with cold-injury syndrome include increased mortality; development of sclerema, skin erythema, and acrocyanosis; pulmonary hemorrhage; renal failure; increased blood viscosity and disseminated intravascular coagulation; hypoglycemia; acid base and electrolyte disturbances; increased risk ofinfections (secondary to decreased leukocytemobility and phagocytosis); significant cardiovascular disturbances including sudden cardiac arrest and ventricular tachyarrhythmia. Sinus bradycardia and thrombocytopenia have been reported to be the only significant adverse effects of hypothermia in all of the current meta-analysis of the cooling trials. Advances in intensive care including continuous cardio-respiratory monitoring, mechanical ventilation, and better understanding of pathophysiology of hypothermia have reduced many of the adverse effects previously reported with therapeutic hypothermia.

CARDIOVASCULAR

Therapeutic hypothermia is consistently associated with sinus bradycardia as it slows the a trial pacemaker and intra-cardiac conduction. The QT interval can also be prolonged, and hypotension can occur.

HEMATOLOGICAL

Hypothermia-induced coagulation abnormalities include platelet dysfunction, increased fibrinolytic activity and prolongation of prothrombin time and partial thromboplastin time. However, no increase in bleeding complications is reported in any of the three large randomized cooling trials.

RENAL

Therapeutic hypothermia can suppress antidiuretic hormone, and in experimental animal models cooling was associated with decrease in renal perfusion and glomerular filtration rate. However, according to a recent meta-analysis, there was no statistically significant difference in the rate of oliguria in cooled infants.

DRUG METABOLISM

Drugs including anti convulsants, sedatives, neuromuscular paralyzing agents, antibiotics, and inotropic agents are commonly used in asphyxiated infants while receiving therapeutic hypothermia. Metabolism and excretion of these drugs and their metabolites may be modified by cooling, as well as by the frequent presence of hypoxic ischemic hepatocellular and renal injury complicating HIE. Close monitoring of anti convulsant levels and clinical level of sedation and paralysis while morphine and paralyzing agents are used, is warranted during treatment with hypothermia. Typical adjustment of gentamicin dosing for impaired renal function based on trough serum concentrations is recommended when treating actual or suspected infection during therapeutic hypothermia.

The common complications noted with therapeutic hypothermia from JIPMER, Pondicherry are listed in Table 1.

Table 1: Complications of Therapeutic hypothermia

- Bradycardia (25%) and other cardiac arrhythmia (1%)
- Thrombocytopenia (13% - 25%)
- Hypoglycemia (10%)
- Hypocalcemia (6%)
- Shock (8%)
- Sclerema and Subcutaneous fat necrosis (6%)
- Acid-base and electrolyte disturbances
- DIC (5%)
- Pulmonary hemorrhage
- Increased blood viscosity- hemoconcentration

Though therapeutic hypothermia is generally safe, it is important to cool neonates using strict protocols and often at centers with considerable experience with cooling.

BIBLIOGRAPHY

1. Sarkar S, Barks JD. Systemic complications and hypothermia. Semin Fetal Neonatal Med. 2010 Oct; 15(5):270-5.

CHAPTER

9

ADJUVANT THERAPIES FOR THERAPEUTIC HYPOTHERMIA

Dr. Nishad P

For every infant with HIE that benefits from hypothermia, many more do not. Hence, there is an urgent need to focus on adjuvant therapies that may be neuro protective in this condition. Enhancing the endogenous neuro protective responses of the body using melatonin, endogenous endocannabinoids, or erythropoietin may also be more physiologic, and less likely to cause adverse effects.[2]

For every infant with HIE that benefits from hypothermia, many more do not.

XENON

Xenon is one of the leading adjuvant therapies being investigated in neonatal HIE. Xenon is a potent NMDA receptor antagonist and can decrease neuronal apoptosis, and also inhibits AMPA and kainate receptors.[3]

The multicenter Total Body hypothermia plus Xenon trial (TOBY-Xe) enrolled 92 infants (36–43 weeks, 46 randomly assigned to hypothermia alone and 46 to xenon plus hypothermia.[4] The primary outcomes were reduced thalamic lactate to N-acetyl aspartate (NAA) ratios (on magnetic resonance spectroscopy) and preserved fractional anisotropy (FA) in the posterior limb of the internal capsule on MRI within 15 days of birth. Lactate to NAA ratios can predict neurodevelopmental outcomes. Changes in FA also correlate well with outcomes in infants with HIE. No significant differences on MRI were detected between the groups. Based on these results, the authors concluded that combined treatment with hypothermia and 30% xenon for 24 hours may not improve clinical outcomes compared to hypothermia alone. The CoolXenon3 trial (ClinicalTrials.gov Identifier: NCT02071394) is currently underway, and is likely to be

completed by August 2019. Xenon is, however, very expensive. The need for special ventilation circuits that can reuse the gas implies that even if it is shown to be effective, xenon is unlikely to be a favored adjuvant therapy in more resource-limited countries including India.

ERYTHROPOIETIN/DARBEPOIETIN

Although originally identified as an erythropoietic factor, Erythropoietin (Epo) plays many roles in the human body. It has myriad effects on immunomodulation, inflammation, angiogenesis, and neurodevelopment. Many cell types in the central nervous system express EPO receptors during different stages of development, suggesting a role for Epo. It has been shown to be neuroprotective in a variety of experimental settings in animal models, using a wide range of doses (1000 to 30,000 U/kg). Recombinant human Epohas also been shown to improve neurological outcomes in preterm infant.[5-7]

The use of Epo in term infants with hypoxic-ischemic encephalopathy is relatively more recent. When compared to hypothermia, a potential advantage is that Epo may be effective even when started more than 6 hours (but <48 hours) after birth. In a randomized trial of Epo (without hypothermia) involving 167 infants in China, those receiving Epo had significantly lower Thompson scores by day 7.[8] The composite outcome of death or moderate-severe disability at 18 months was lower (24.6%) in the Epo group compared to controls (43.8%). On subgroup analysis, benefits were limited to infants with moderate hypothermia. In this study, the Epo dose used was 300 (52 infants) or 500 U/kg (31 infants) on alternate days for 2 weeks. There was no obvious toxicity or hematopoietic effect in the Epo group.

A small, prospective non-randomized study of Epo in infants with HIE found fewer neurologic and developmental abnormalities at 6 months in infants administered a 5-day course of Epo at a dose of 2500 IU/kg, when compared to control groups.[9] Another phase II placebo-controlled trial of Epo used an Epo dose of 1000 U/kg (n = 24) or placebo (n = 26) at 1, 2, 3, 5, and 7 days and found improved motor function at 1 year and less MRI brain injury in the Epo group.[10] This group had earlier conducted a phase I trial of Epo with hypothermia and shown that Epo at 1000 U/kg given intravenously resulted in plasma Epo levels similar to animal studies of neuro protection. Some adult studies have reported an increased risk of adverse outcomes with the use of Epo. In addition, questions about dose and duration of therapy remain. A recent pharmacokinetic analysis of 47 infants who previously received Epo in 2 trials suggested that in infants receiving hypothermia, a dose of 1000 U/kg every 24 hours for the first 2 days resulted in achievement of target levels.[11]

MELATONIN

Melatonin, like erythropoietin, is endogenously produced and serves normal functions in the human body, but is also available in a synthetic form. The pineal gland synthesizes melatonin from tryptophan, with secretion peaking at around 3-4 am in normal adults. In

adults, melatonin secretion follows a circadian rhythm (one cycle per 24 hours). In neonates, the rhythm is ultradian (many cycles per 24 hours).[12]

Melatonin has antioxidant and anti-inflammatory properties and can reduce apoptosis. In mouse models of excitotoxic brain injury, melatonin has a dose-dependant neuro protective effect.[12] It also has no known adverse effects, making it an attractive candidate for adjuvant therapy.

In a small study, 10 asphyxiated infants were given oral melatonin (8 doses of 10 mg each at 2-hour intervals) and were noted to have reductions in the levels of malondialdehyde and nitrite/nitrate at 12 and 24 hours.[15] The study used 10 asphyxiated infants and 10 healthy infants as controls. There were no deaths in the melatonin group, and 3 deaths among the asphyxiated controls. A randomized controlled trial of melatonin in infants with HIE reported that infants who received melatonin in addition to hypothermia had fewer seizures and less white matter abnormalities on MRI.[16] Controls included a group of infants who received hypothermia alone, and a group of healthy infants. Survival without neurological abnormalities to 6 months of age was higher in the melatonin/hypothermia group.

An advantage of melatonin is that it crosses the placenta and the blood-brain barrier and appears to be safe, and can potentially serve as a neuro protectant when administered antenatally.[3]

MAGNESIUM

The role of magnesium sulfate in neuro protection in the preterm fetus at risk of imminent delivery is now well established. Magnesium salts modulate NMDA-mediated neuronal injury and may be neuro protective in infants being cooled for HIE. An RCT of magnesium sulfate infusion involving 50 neonates in Bangladesh reported better neurologic status at discharge in the experimental group.[17] While others have also reported better outcomes with the use of magnesium sulfate, these studies did not include infants undergoing hypothermia.[18-20] A multicenter RCT of hypothermia plus magnesium sulfate versus hypothermia plus placebo in 60 term and near-term infants with moderate to severe HIE reported no differences in neonatal death, seizures, hypotension or other adverse outcomes but long-term outcomes are not reported.[21]

ANTIEPILEPTIC DRUGS

Antiepileptic drugs are commonly used in neonates with HIE to control seizures. In theory, control of seizures itself may protect neurons from the effects of repetitive firing and energy depletion. However, some of the newer anticonvulsants have been proposed to have other neuroprotective effects that may be beneficial in HIE.

Topiramate (TPM) is a well-known anticonvulsant that modulates AMPA and kainite receptors and other ion channels.[22] In neonatal rats, topiramate helps to limit damage from oxygen-glucose deprivation. Topiramate may reduce excitotoxic injury and limit neuronal

cell loss in neonatal HIE, and this effect is probably independent of its anticonvulsant effect. However, hypothermia has been shown to prolong the half-life of TPM, hence more pharmacokinetic data may be required. The NeoNATI trial was a pilot randomized multicentric trial designed to assess the safety and efficacy of TPM in neonates undergoing hypothermia for HIE.[23] The trial involved 44 term infants, 23 in the hypothermia group and 21 in the hypothermia + TPM group. There were no significant differences in mortality, severe neurological disability, MRI changes or safety outcomes between the groups, but the combined treatment group had a lower prevalence of epilepsy.

Levetiracetam is increasingly used for neonatal seizure control. Besides its anticonvulsant effect, levetiracetam regulates AMPA and NMDA receptor mediated transmission, and reduces reducing glutamate release.[24] Since levetiracetam also has reasonable efficacy in controlling neonatal seizures and a low toxicity, it is an attractive candidate for adjuvant treatment. However, evidence from RCTs is yet to be generated.

2-IMINOBIOTIN

2-Iminobiotin (2-IB) is a biotin analogue which inhibits inducible nitric oxide synthase, and may prevent NO-mediated mitochondrial injury. 2-IB was shown to hypoxia-mediated neurotoxicity in an in-vitro human neuronal cell model.[25]

N-ACETYL CYSTEINE

N-Acetylcysteine (NAC) scavenges oxygen radicals and decreases inflammation and nitric oxide (NO) production in experimental stroke models.[26] In rat models of stroke, NAC reduces infarct volume and improves neurologic scores. In newborn piglets with hypoxic brain injury, NAC helps maintain normal cerebral amino acid chemistry.[27] A large RCT of NAC to evaluate its effect on broncho pulmonary dysplasia (BPD) in extremely low birth infants found no reduction in BPD, but there was less periventricular leukomalacia in the NAC group.[28] Studies of NAC in term infants with asphyxia are yet to be done.

CANNABINOIDS

Cannabinoids may be neuro protective by inducing hypothermia or through other specific mechanisms. However, since the only reported benefit of cannabinoids is in animal models and cannabis use during pregnancy has been linked to cognitive defects in infants, it is likely that more experimental data will be required before human trials can be conducted.[2]

HUMAN CORD BLOOD

Stem cell therapy appears to be neuro protective in animal models of hypoxic-ischemic injury. Since umbilical cord blood (UCB) is an easily accessible and ethically acceptable source of stem cells, this therapy would be attractive, if proven to be effective in human infants with HIE. In an open-label feasibility trial in 23 infants cooled for HIE, non-cyropreserved autologous UCB cells were administered.[29] 74% of cell recipients survived to 1 year with BSID scores >85, compared to 41% of concurrent cooled infants.

REMOTE ISCHEMIC POST CONDITIONING

In clinical studies of transient ischemic attack and angina, brief non-lethal episodes of ischemia have been shown to be protective. This is called ischemic preconditioning. When this technique is used after the major ischemic episode, we call it ischemic post conditioning. In remote ischemic post conditioning (RIPC), the brief ischemic stimulus is applied to a non-vital organ (e.g. a limb) away from the affected organ (e.g. the brain).[2] While the exact mechanisms by which RIPC confers protection are yet to be described, a neuronal pathway (involving the autonomic nervous system), a humoral pathway (involving, as the name suggests, mediators transported through the bloodstream) and a systemic response (including reduced neutrophil activation and decreased expression of genes involved in inflammation and apoptosis) are believed to be involved.[2] Studies in animal models of HIE indicate that RIPC may be beneficial.[30] Clinical trials in neonates with HIE are yet to be conducted.

CONCLUSION

While a number of adjunct therapies are being studied, many are currently not ready for wide spread adoption due to reasons of limited evidence, cost, or convenience. However, it appears likely that this situation will change very soon, given the number of trials that are in progress.

BIBLIOGRAPHY

1. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013 Jan 31(1):CD003311.

2. Hassell KJ, Ezzati M, Alonso-Alconada D, Hausenloy DJ, Robertson NJ. New horizons for newborn brain protection: enhancing endogenous neuroprotection. Archives of Disease in Childhood Fetal and Neonatal Edition. 2015;100(6):F541-F52.

3. McAdams RM, Juul SE. Neonatal Encephalopathy: Update on Therapeutic Hypothermia and Other Novel Therapeutics. Clin Perinatol. 2016 Sep;43(3):485-500.

4. Azzopardi D, Robertson NJ, Bainbridge A, Cady E, Charles-Edwards G, Deierl A, et al. Moderate hypothermia within 6 h of birth plus inhaled xenon versus moderate hypothermia alone after birth asphyxia (TOBY-Xe): a proof-of-concept, open-label, randomised controlled trial. Lancet Neurol. 2016 Feb;15(2):145-53.

5. Song J, Sun H, Xu F, Kang W, Gao L, Guo J, et al. Recombinant human erythropoietin improves neurological outcomes in very preterm infants. Ann Neurol. 2016 Jul;80(1):24-34.

6. Ohls RK, Cannon DC, Phillips J, Caprihan A, Patel S, Winter S, et al. Preschool Assessment of Preterm Infants Treated With Darbepoetin and Erythropoietin. Pediatrics. 2016 Mar;137(3):e20153859.

7. Ohls RK, Kamath-Rayne BD, Christensen RD, Wiedmeier SE, Rosenberg A, Fuller J, et al. Cognitive outcomes of preterm infants randomized to darbepoetin, erythropoietin, or placebo. Pediatrics. 2014 Jun;133(6):1023-30.

8. Zhu C, Kang W, Xu F, Cheng X, Zhang Z, Jia L, et al. Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. Pediatrics. 2009 Aug;124(2):e218-26.

9. Elmahdy H, El-Mashad AR, El-Bahrawy H, El-Gohary T, El-Barbary A, Aly H. Human recombinant erythropoietin in asphyxia neonatorum: pilot trial. Pediatrics. 2010 May;125(5):e1135-42.

10. Wu YW, Mathur AM, Chang T, McKinstry RC, Mulkey SB, Mayock DE, et al. High-Dose Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy: A Phase II Trial. Pediatrics. 2016 Jun;137(6).

11. Frymoyer A, Juul SE, Massaro AN, Bammler TK, Wu YW. High-dose erythropoietin population pharmacokinetics in neonates with hypoxic-ischemic encephalopathy receiving hypothermia. Pediatr Res. 2017 Jun;81(6):865-72.

12. Biran V, Phan Duy A, Decobert F, Bednarek N, Alberti C, Baud O. Is melatonin ready to be used in preterm infants as a neuroprotectant? Dev Med Child Neurol. 2014 Aug;56(8):717-23.

13. Welin AK, Svedin P, Lapatto R, Sultan B, Hagberg H, Gressens P, et al. Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. Pediatr Res. 2007 Feb;61(2):153-8.

14. Robertson NJ, Faulkner S, Fleiss B, Bainbridge A, Andorka C, Price D, et al. Melatonin augments hypothermic neuroprotection in a perinatal asphyxia model. Brain. 2013 Jan;136(Pt 1):90-105.

15. Fulia F, Gitto E, Cuzzocrea S, Reiter RJ, Dugo L, Gitto P, et al. Increased levels of malondialdehyde and nitrite/nitrate in the blood of asphyxiated newborns: reduction by melatonin. J Pineal Res. 2001 Nov;31(4):343-9.

16. Aly H, Elmahdy H, El-Dib M, Rowisha M, Awny M, El-Gohary T, et al. Melatonin use for

neuroprotection in perinatal asphyxia: a randomized controlled pilot study. J Perinatol. 2015 Mar;35(3):186-91.

17. Hossain MM, Mannan MA, Yeasmin F, Shaha CK, Rahman MH, Shahidullah M. Short-term outcome of magnesium sulfate infusion in perinatal asphyxia. Mymensingh Med J. 2013 Oct;22(4):727-35.

18. Ichiba H, Tamai H, Negishi H, Ueda T, Kim TJ, Sumida Y, et al. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. Pediatr Int. 2002 Oct;44(5):505-9.

19. Ichiba H, Yokoi T, Tamai H, Ueda T, Kim TJ, Yamano T. Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate. Pediatr Int. 2006 Feb;48(1):70-5.

20. Bhat MA, Charoo BA, Bhat JI, Ahmad SM, Ali SW, Mufti MU. Magnesium sulfate in severe perinatal asphyxia: a randomized, placebo-controlled trial. Pediatrics. 2009 May;123(5):e764-9.

21. Rahman S, Canpolat F, Oncel M, Evli A, Dilmen U, Parappil H, et al. Multicenter randomized controlled trial of therapeutic hypothermia plus magnesium sulfate versus therapeutic hypothermia plus placebo in the management of term and near-term infants with hypoxic ischemic encephalopathy (The Mag Cool study): A pilot study. Journal of Clinical Neonatology. [Original Article]. 2015 July 1, 2015;4(3):158-63.

22. Noh MR, Kim SK, Sun W, Park SK, Choi HC, Lim JH, et al. Neuroprotective effect of topiramate on hypoxic ischemic brain injury in neonatal rats. Exp Neurol. 2006 Oct;201(2):470-8.

23. Filippi L, Fiorini P, Catarzi S, Berti E, Padrini L, Landucci E, et al. Safety and efficacy of topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia (NeoNATI): a feasibility study. J Matern Fetal Neonatal Med. 2017 Mar 28:1-8.

24. Lee CY, Chen CC, Liou HH. Levetiracetam inhibits glutamate transmission through presynaptic P/Q-type calcium channels on the granule cells of the dentate gyrus. Br J Pharmacol. 2009 Dec;158(7):1753-62.

25. Zitta K, Peeters-Scholte C, Sommer L, Parczany K, Steinfath M, Albrecht M. Insights into the neuroprotective mechanisms of 2-iminobiotin employing an in-vitro model of hypoxic-ischemic cell injury. Eur J Pharmacol. 2016 Dec 05;792:63-9.

26. Khan M, Sekhon B, Jatana M, Giri S, Gilg AG, Sekhon C, et al. Administration of N-acetylcysteine after focal cerebral ischemia protects brain and reduces inflammation in a rat model of experimental stroke. J Neurosci Res. 2004 May 15;76(4):519-27.

27. Jantzie LL, Cheung PY, Johnson ST, Bigam DL, Todd KG. Cerebral amino acid profiles after hypoxia-reoxygenation and N-acetylcysteine treatment in the newborn piglet. Neonatology. 2010;97(3):195-203.

28. Ahola T, Lapatto R, Raivio KO, Selander B, Stigson L, Jonsson B, et al. N-acetylcysteine does not prevent bronchopulmonary dysplasia in immature infants: a randomized controlled trial. J Pediatr. 2003 Dec;143(6):713-9.

29. Cotten CM, Murtha AP, Goldberg RN, Grotegut CA, Smith PB, Goldstein RF, et al. Feasibility of autologous cord blood cells for infants with hypoxic-ischemic encephalopathy. J Pediatr. 2014 May;164(5):973-9 e1.

30. Drunalini Perera PN, Hu Q, Tang J, Li L, Barnhart M, Doycheva DM, et al. Delayed remote ischemic postconditioning improves long term sensory motor deficits in a neonatal hypoxic ischemic rat model. PLoS One. 2014;9(2):e90258.

CHAPTER
10

AMPLITUDE INTEGRATED EEG IN ASPHYXIA AND THERAPEUTIC HYPOTHERMIA

Dr. Sridhar Santhanam, Dr. Nithya J Ponmudi

INTRODUCTION

Amplitude integrated electro-encephalography (aEEG) is a method of continuous tracing of EEG which evaluates long term changes and trends in electro cortical background activity. In the 1960s, Dr. Maynard and Prior introduced aEEG as an adjunct to continuous EEG (cEEG) to monitor cerebral function during surgical anaesthesia. Full array electro-encephalography uses about 16 electrodes and requires the expertise of a neurophysicist who is trained to interpret EEG. The advantage of aEEG over continuous EEG include limited number of electrodes, ease of operation with shorter training of personnel to interpret, immediate interpretation at the bedside itself and condensed output. The equipment is more cost effective than cEEG. With advent of therapeutic hypothermia in asphyxiated babies, aEEG is increasingly being used as eligibility to start cooling, to detect subclinical seizure activity and to assess as a long term prognosticator.

In the 1960s, Dr. Maynard and Prior introduced aEEG as an adjunct to continuous EEG (cEEG) to monitor cerebral function during surgical anaesthesia.

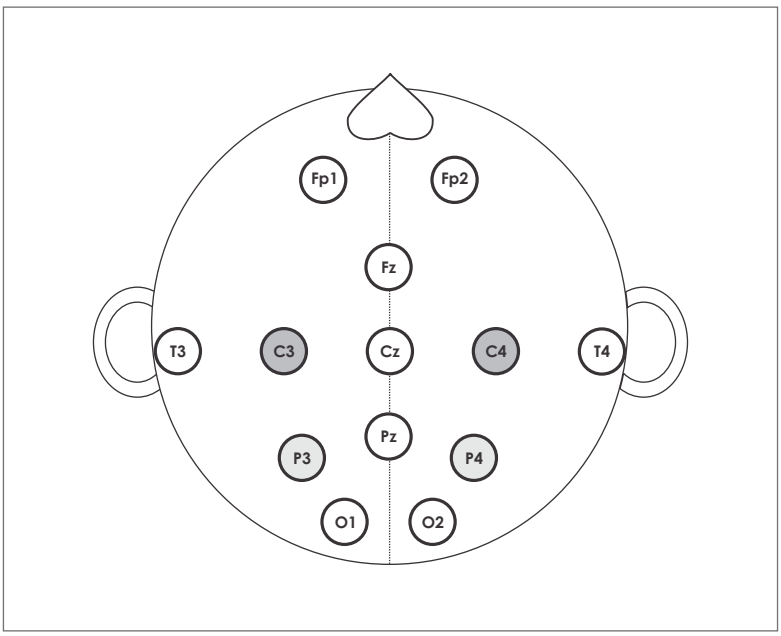
HOW DOES aEEG WORK ?

All aEEG machines will give a trace of raw EEG as well as either bilateral or cross-cerebral aEEG traces. In aEEG, the signals from continuous EEG are amplified, filtered, rectified and compressed using a piecewise semi-logarithmic transformation and is portrayed as a slow trend display. It is useful for continuous monitoring of brain function.

PLACEMENT OF ELECTRODES

The recording measures differences in electrical potential and displays the changes in electrical activity over time. Unlike cEEG, a minimum of 3 electrodes are required in aEEG (single channel monitoring). Of these two are biparietal (P3 and P4) and the third is the ground electrode. It can use two channel monitoring (Brainz Monitor and Olympic Brainz Monitor) where two additional electrodes are used in the central (C3 and C4) or frontal (F3 and F4) regions which improves the sensitivity of detecting seizures and also detecting laterality of lesions. The number of electrodes can be increased on witnessing seizures. The logic behind parietal placement of electrodes is that this overlies the cerebral cortex at the junction of the anterior, middle and posterior cerebral circulations and thus might be most affected in is chaemia. The electrode placement is shown in Fig. 1.

Fig. 1: Electrode placement



WHAT TO LOOK FOR IN AN aEEG TRACE?

While analyzing an aEEG trace, it is necessary to comment on the following:

A. Background activity

B. Seizure activity

C. Sleep wake cycle

A. BACKGROUND ACTIVITY

This is a representation of the background electro-cortical activity of the underlying brain. The monitor displays both the EEG and aEEG traces. X- axis represents time and Y-axis represents EEG amplitude on a semi-logarithmic scale. Background pattern refers to the dominant pattern of electrical activity. This varies depending on gestational age, medications and state of arousal. There are different patterns of background activity which are classified as either normal or abnormal.

Normal patterns include

Continuous Normal Voltage (CNV) or background

Discontinuous background (normal in preterm or moderately abnormal in term babies) (DC)

Abnormal patterns include

Burst Suppression pattern (BS)

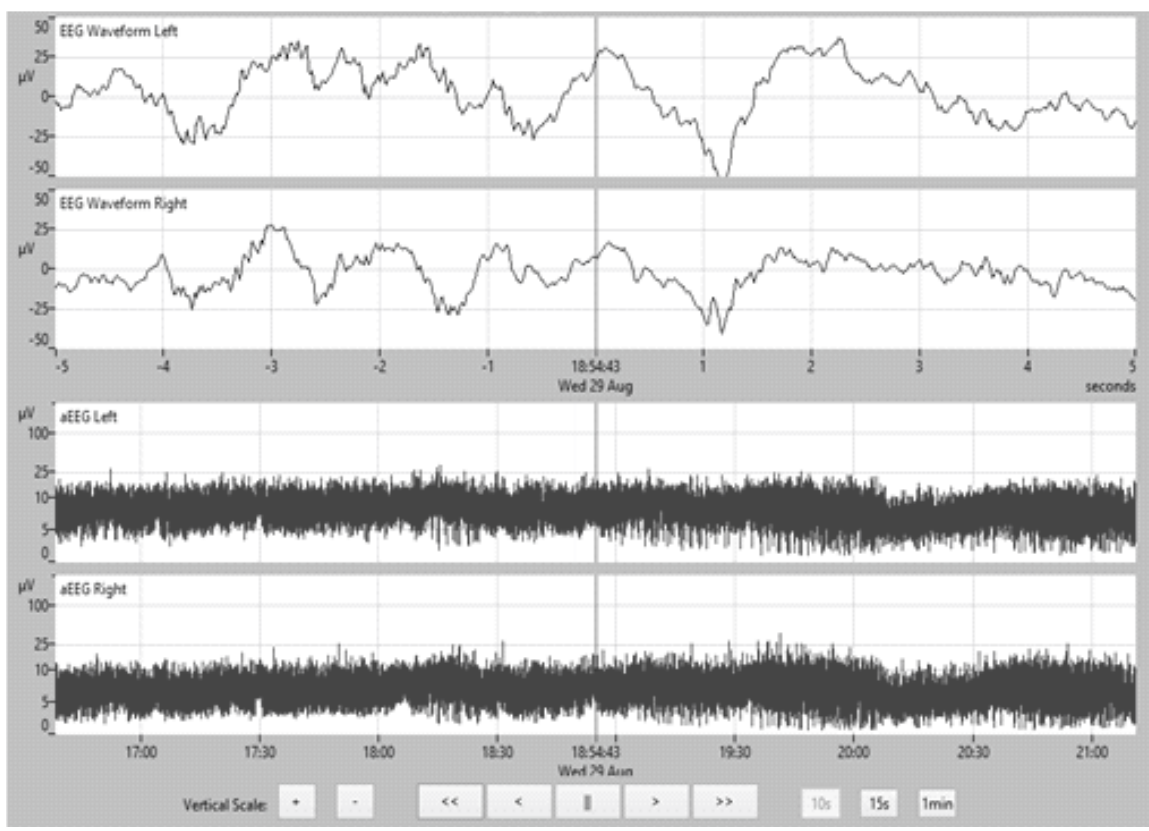
Continuous Low Voltage (CLV)

Iso-electric or Flat Trace (FT)

CONTINUOUS BACKGROUND

Here, the lower margin of the aEEG trace is above 5 µV and the upper margin is above 10 µV. This pattern is commonly seen in full term infants. (Fig. 2.)

Fig. 2:

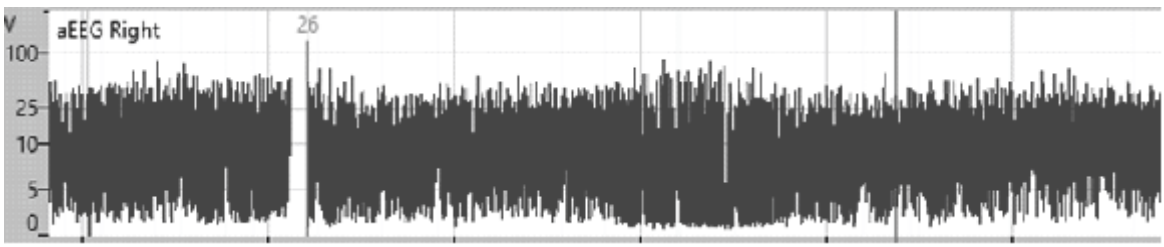


DISCONTINUOUS PATTERN

EEG: In discontinuous pattern, there are periods of lower amplitude interspersed with periods of higher amplitude.

aEEG: There is a wide depressed trace with a lower voltage of <5μV and upper voltage of >10μV. (Fig. 3.)

Fig. 3:



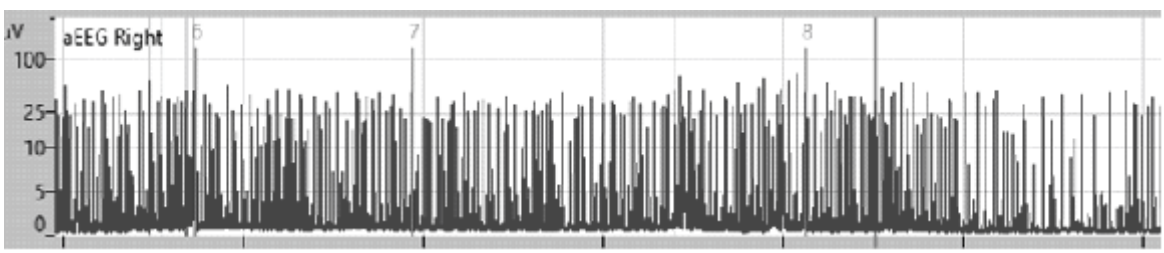
INTERPRETATION: Discontinuous pattern may be normally seen in prematurity. However, it is sometimes encountered after cerebral injury in term babies and after anti-convulsant therapy. In very preterm babies, the discontinuous pattern mimics burst suppression and is called "tracédiscontinu". As the premature infant approaches term, the pattern changes to a continuous pattern.

BURST SUPPRESSION PATTERN

EEG: There are periods of abnormally high amplitude activity (bursts) interspersed with periods of markedly suppressed amplitude (suppression).

aEEG: There are burst spikes (with amplitudes of >25μV) interspersed with iso electric suppression where there is no or minimal electrical activity with flat lower margins having voltage 0-1μV. (Fig.4.)

Fig. 4:



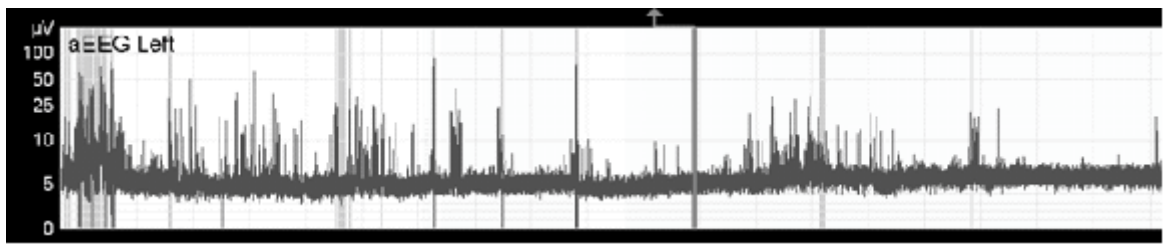
INTERPRETATION: Prolonged burst suppression pattern is highly suggestive of severe brain injury and is often seen in asphyxiated babies with severe encephalopathy. Since EEG inactivity is associated with damage to non-specific but widespread regions of the brain, the time of interburst interval (IBI) (the period of suppressed activity between bursts) may correlate with long term outcome. It is thought that there is high probability of adverse neurological outcome if IBI exceeds 30 seconds.

CONTINUOUS LOW VOLTAGE PATTERN

EEG: There is continuous low amplitude

aEEG: There is narrowing of EEG trace with both the upper and lower margins having and amplitude of <5µV. (Fig. 5.)

Fig. 5:



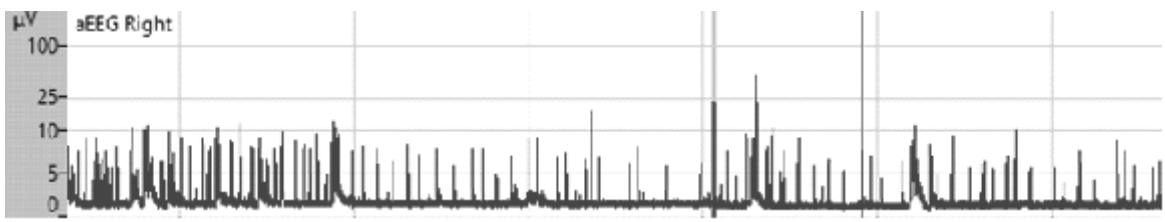
INTERPRETATION: A prolonged continuous low voltage pattern is highly suggestive of severe brain injury. This is often seen in asphyxiated babies with severe encephalopathy.

FLAT TRACE

EEG: In this pattern, the amplitude is very low (close to zero)

aEEG: aEEG shows low amplitude with a narrow trace , upper and lower margins are <5µV and almost close to zero µV (Fig. 6.)

Fig. 6:



INTERPRETATION: Prolonged flat trace is an ominous sign indicative of severe brain injury. This pattern is often associated with poor neuro developmental outcome as well as death.

B. SEIZURES

HOW TO DETECT SEIZURES ON aEEG?

Seizures may be appreciated as solitary or repetitive seizures (Fig. 7.) or status epilepticus (Fig. 8.). Solitary seizure refers to a single episode where there is a spike or sharp wave with elevation of the lower margin. It is seen as an abrupt rise in the minimum amplitude and simultaneous rise in maximum amplitude. This is often followed by a short period of decreased amplitude. On continuous EEG, seizure activity is seen as repetitive sharp waves or spikes. The duration is at least 5 to 10 seconds.

Fig. 7:

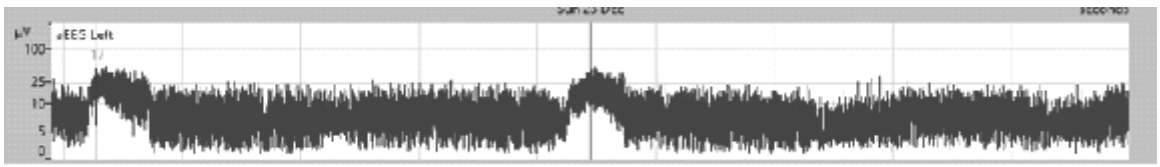
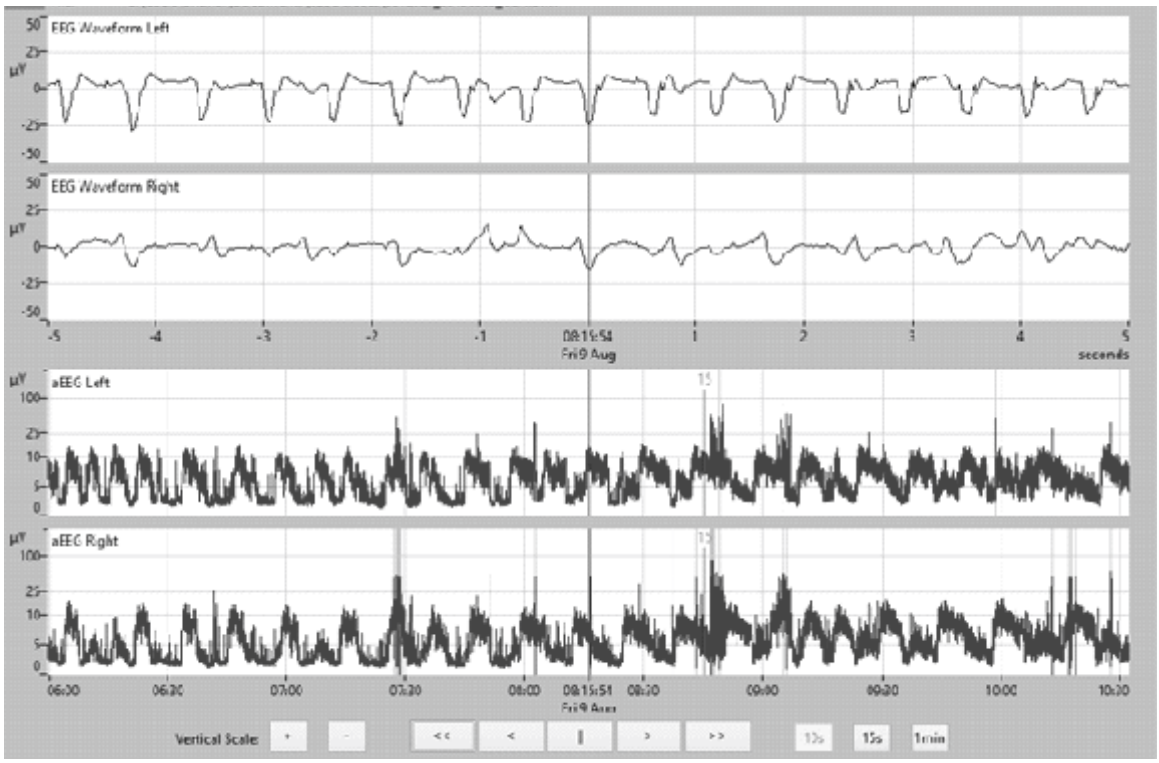


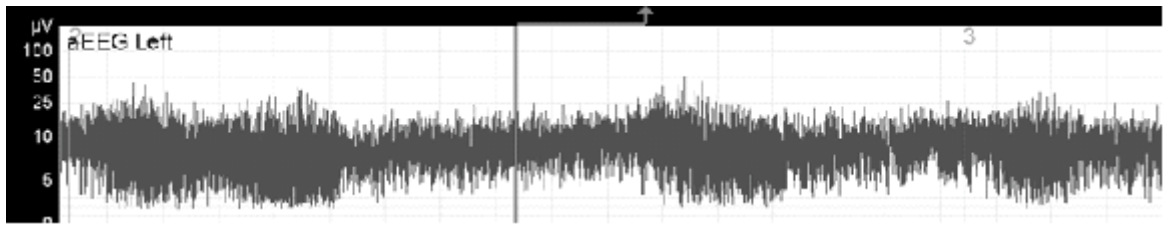
Fig. 8:



C. SLEEP WAKE CYCLE (SWC)

Normal sleep wake cycle is seen as smooth sinusoidal variations, mostly in the minimum amplitude. Continuous pattern with good variability and no repetitive waveform (like spike or sharp waves) is witnessed while the newborn is awake or in active sleep. This is seen as narrowing of the wave on aEEG. This alternates with widening that represents discontinuous pattern seen when a baby is in quiet sleep. A mature or developed cycle lasts about 20 minutes. Therefore, sleep wake cycles are seen as alternating widening and narrowing of the aEEG trace.(Fig. 9.)

Fig. 9:



ASPHYXIA AND aEEG

Hypoxia or ischemia is associated with suppression of the EEG waveform. The duration and amplitude of suppression can correlate with the severity of the hypoxic event. Thus, early aEEG background pattern may be used as an adjunct in selecting newborn who may benefit by therapeutic hypothermia. Various researchers have also tried to use the aEEG trace either with or without hypothermia as a prognosticator.

aEEG AS CRITERIA TO INITIATE HYPOTHERMIA

The TOBY trial in the UK used three criteria to cool newborn:

1. Evidence of asphyxia
2. Evidence of moderate or severe encephalopathy
3. aEEG evidence of hypoxic injury. This included a 30 minute aEEG with any of the following:
    a. normal background with some seizure activity
    b. moderately abnormal activity
    c. suppressed activity
    d. continuous seizure activity

Similarly, the Cool cap trial and the European trials on hypothermia used aEEG as a criteria for recruitment. However, the NICHD trial and the ICE trial did not have aEEG as entry criteria to initiate cooling. Though we have been using aEEG in asphyxiated newborn since 2009 and have practised therapeutic hypothermia since 2007, we do not use aEEG abnormality as essential criteria for cooling newborn.

A study by Skranes et al from Norway assessed if aEEG as an entry criteria improved selection of infants for cooling. They compared the trace at 6 hours of life with MRI lesion load and 24 months outcome. They found that babies most babies with continuous normal background at entry were normal at 24 months. Babies with severe EEG voltage criteria (BS,CNV or FT) were more likely to have adverse outcome with time to normal trace in these babies being the best predictor of outcome. Hence they suggested that recruitment for cooling should be only in babies who had abnormal aEEG background.

aEEG AS A PROGNOSTICATOR

Researchers have looked at the prognostic value of early aEEG (at <6 hours or prior to initiation of cooling) as well as changes in aEEG over time to assess if it would prognosticate on long term neurological outcome. The results when comparing early aEEG to outcome have been variable.

In a follow up analysis of the TOBY trial data, the value of early aEEG to accurately predict death or disability at 18 months was studied. In a cohort of 315 babies, it was seen that the positive predictive value (PPV) of a severely abnormal aEEG by voltage and pattern was 0.63 and 0.59 respectively in non-cooled infants and 0.55 and 0.51 in cooled infants ($p>0.05$). The authors attributed the lower PPV in cooled babies to the neuro protective effect of cooling.

Similarly, Marianne Thoresen et al studied the value of early as well as changes in pattern and voltage over 72 hours in cooled and non-cooled babies. They recruited seventy-four infants whose outcome was assessed at 18 months. The positive predictive value of an abnormal aEEG pattern at <6 hours was 84% in non-cooled babies vs 59% for cooled infants. The recovery time to normal background pattern was the best predictor of poor outcome in both cooled and non-cooled babies (96.2% and 90.9% respectively). Never developing sleep wake cycling over 72-96 hours always predicted poor outcome. Infants treated with hypothermia had good outcome if the background became continuous by 48 hours.

Thus, early aEEG abnormalities are more likely to predict adverse outcome in babies who do not receive hypothermia. Both these studies show that early aEEG may not accurately predict outcome in cooled infants. Change in pattern from abnormal (BS. CNV or FT) to continuous normal voltage by 48 hours predicted good outcome and never achieving sleep wake cycle by 96 hours uniformly predicted poor outcome.

Chandrasekharan et al published a meta-anlysis of all studies using aEEG for prognostication. This looked at aEEG criteria at various time periods (6, 24, 48 and 72 hours). They considered only continuous background as normal pattern and all other patterns (DC, BS, CLV and FT) as abnormal and used death or disability at 1 year as adverse outcome measure. Nine studies involving 520 infants were used in the meta-analysis. The pooled sensitivity and specificity for an abnormal trace at 6 hours of age in predicting adverse were 96% and 39%. The diagnostic odds ratio of an abnormal trace was highest (66.9%). They also showed that a normal background at 6 hours predicted good outcome.

Similarly, a systematic review of prognostic tests in term infants with HIE showed that aEEG had the highest sensitivity and specificity in predicting outcome (0.93 and 0.9 respectively) followed by EEG, visual evoked potential. Diffusion weighted MRI had higher specificity whereas T1, T2 weighted MRI had better sensitivity.

WHAT IS THE EFFECT OF COOLING ON aEEG?

In most infants with asphyxia, the aEEG background will eventually become normal over few days. As seen in the few studies quoted, aEEG may normalize earlier in cooled infants because of the neuro protective role of hypothermia. A study was done to see if the amplitude of the aEEG trace would change with cooling but no change was found. However, it is possible that the amplitude of seizures can decrease with cooling and hence it may be more difficult to diagnose electrical seizures in cooled infants. An EEG is always necessary to diagnose seizures in hypothermis infants. Studies also show that the frequency and duration of seizures is less in hypothermic infants. Hence aEEG may be a poor to diagnose electrical seizures in cooled babies.

Therefore, aEEG may be used as an adjunct to clinical criteria to select babies for cooling. Babies with continuous normal background at 6 hours may not benefit much with cooling. Babies with persistently abnormal trace are most likely to have death or adverse long term neurological outcome. Seizures may not be adequately detected by aEEG especially in cooled babies and hence it may useful to study the raw EEG to identify seizures. Hence aEEG may be a useful adjunct in babies who are offered therapeutic hypothermia.

TAKE HOME POINTS

- Though not essential, amplitude integrated EEG may be a useful tool to identify babies who would most benefit by hypothermia.
- Continuous normal background at initiation of hypothermia is a good prognosticator.
- Persistence of abnormal trace at 48 or 72 hours may indicate poor prognosis.
- Never achieving sleep wake cycle by 96 hours always denotes poor long term prognosis.
- Seizures cannot be adequately diagnosed by aEEG especially in babies undergoing therapeutic hypothermia.

BIBLIOGRAPHY

1. Hellström-Westas L, De Vries LS, Rosén I. An atlas of amplitude-integrated EEGs in the newborn. Parthenon Publishing; 2003.
2. Shah NA, Wusthoff CJ. How to use: amplitude-integrated eeg (aeeg). Archives of Disease in Childhood-Education and Practice. 2015 Apr 1;100(2):75-81.
3. Azzopardi D. Predictive value of the amplitude integrated EEG in infants with hypoxic ischaemic encephalopathy: data from a randomised trial of therapeutic hypothermia. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2013 Jun 22:fetalneonatal-2013.
4. Thoresen M, Hellström-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010 Jul 1;126(1):e131-9.
5. Chandrasekaran M, Chaban B, Montaldo P, Thayyil S. Predictive value of amplitude-integrated EEG (aEEG) after rescue hypothermic neuro protection for hypoxic ischemic encephalopathy: a meta-analysis. Journal of Perinatology. 2017 Jun 1;37(6):684-9.

CHAPTER

11

CRANIAL ULTRASONOGRAPHY IN PERINATAL ASPHYXIA

Dr. Prakash Amboiram

Cranial ultrasonography (CUG) is the first choice for initial radiological evaluation as it is very convenient, portable and non-invasive.

Technique: Brain is usually visualized through anterior fontanelle in two planes namely the coronal and sagittal. The angle of the transducer may be changed to evaluate the periphery of the brain with special attention to the subcortical white matter and the grey-white matter differentiation. The visualization of the cerebellar hemispheres is enhanced by obtaining images through the right and left mastoid fontanels. This technique has also been shown to improve the detection of posterior fossa hemorrhages. The modern cranial US requires switching from the curved - to a linear - array transducer, which allows high-resolution imaging of the brain with the detailed interrogation of the subarachnoid space and superficial cortex as well as deeper brain structures. Important factors influencing USG findings are brain maturity, the duration and severity of insult, and timing of imaging studies.

Cranial ultrasonography (CUG) is the first choice for initial radiological evaluation as it is very convenient, portable and non-invasive.

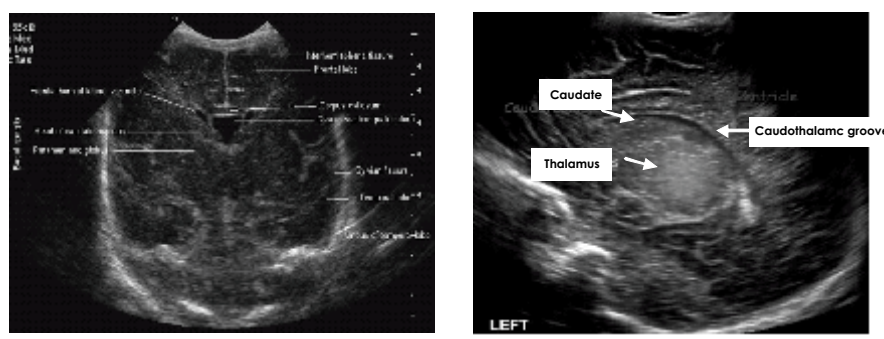


Fig. 1: Brain structures as seen in CUG

Acute changes in grey–scale sonography

The brain sites that are more vulnerable to hypoxic injury are determined largely by maturity of the brain. Less intense insults cause intraventricular hemorrhages and periventricular white matter injury in preterm neonates and parasagittal watershed territory infarcts in term neonates.[1] Severe hypoxia-ischemia in both preterm and term

neonates preferentially damages the deep grey matter like Basal ganglion (BG) and thalamus. The neurons of the cerebral cortex are the most vulnerable, most often hippocampus. Regional vascular factors play a certain role because of neuronal injury is more marked in vascular water-shed zones during ischemia, in parasagittal cerebral cortex.[3] The brainstem, cerebellum, and the deep grey matter are generally spared from injury in mild to moderate hypoxic-ischemic insults due to auto regulatory mechanisms. However, more prolonged insults may cause injury to the watershed zones, which are relatively hypoperfused as a result of shunting during a pressure passive state of cerebral circulation.[7]

USG changes in HIE can be classified as:

- Peripheral - mild to moderate Hypoxic ischemic insult
- Central - severe Hypoxic ischemic insult

Peripheral brain abnormalities include changes in the grey-white matter differentiation and changes in the echogenicity of the cortex and subcortical white matter (Fig. 2&3). Early US findings include a global increase in cerebral echogenicity and the obliteration of the CSF spaces, suggesting diffuse cerebral oedema (Fig. 2,3,4). However, the small size of liquor spaces alone is not specific for brain oedema and slit like ventricles can be seen in healthy newborns during the first 3 days of life.[4]

An increase of parenchymal echogenicity with partial or total obliteration of normally visible structures is correlated with severity of HIE. Although the phenomenon of increased echogenicity (the so- called "bright brain") is fully developed by the second–third day of life, the moderate to severe increase of parenchymal echogenicity as early as at the age of 12 ± 2 h has a high sensitivity (88%) for death or severe disability and can be an early predictor of permanent brain damage in asphyxiated infants.[4] By the second-third day of life, the predictive value of the "bright brain" phenomenon can be as high as 90-100%[5]. Long-lasting increase in parenchymal echogenicity (5-7 days and more) is a predictor of poor outcome at 18 months of age.[4,5]

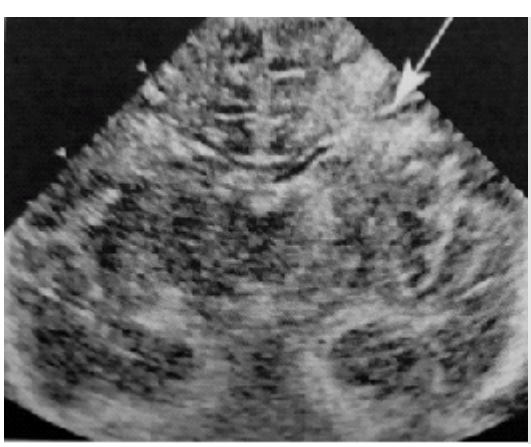


Fig. 2: Asymmetrical hyperechoic appearance of the brain in perinatal asphyxia

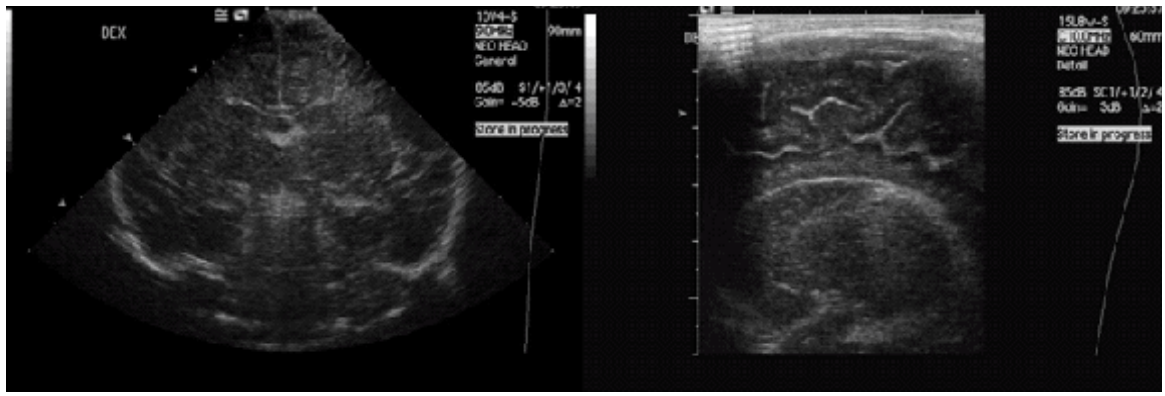


Fig. 3:
Left: Coronal US image shows ill-defined structures including basal ganglia, and slit like ventricles at the age of 12 hours.

Right: Magnified sagittal view using linear transducer shows the accentuation of the grey-white matter differentiation with prominent sulci at the age of 12 hours.

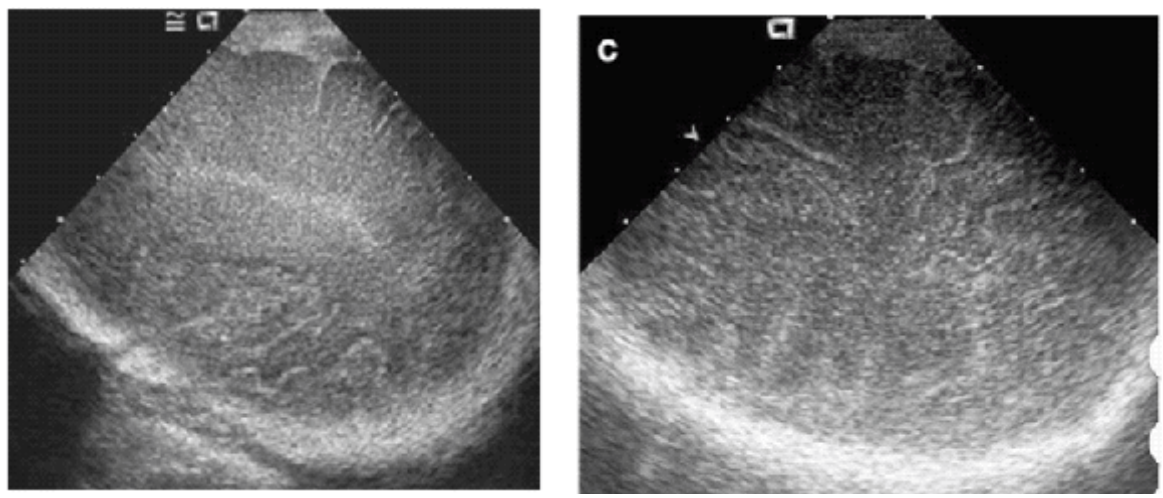


Fig. 4: Focused view of the periphery shows sulci effacement and blurring of the gray-white matter differentiation

Central brain abnormalities in infants with severe global asphyxia include changes in echogenicity of the deep grey matter (basal ganglia and thalami), brainstem and the periventricular white matter [6] (Fig. 5, 6). The presence of thalamic echogenicity (so-called "bright thalamus") generally suggests a more severe injury and correlates with a poorer outcome[8,9] Increased echogenicity in the basal ganglia, thalami, and brainstem is readily apparent after 7 days of severe HIE.[5,10]

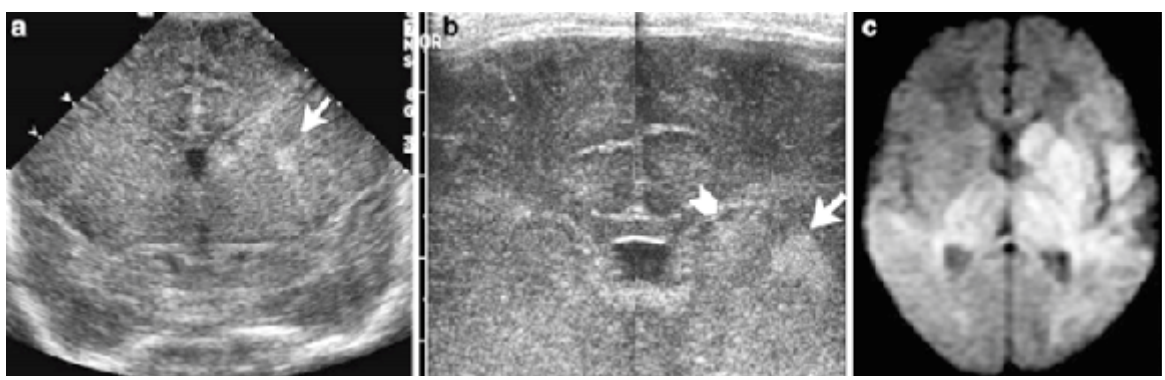


Fig. 5: a) Coronal US image obtained with a vector transducer shows ill-defined increased echogenicity in the left basal ganglia region with a more focal hyperechoic area (arrow) in the left putamen. b) Magnified coronal US view using a linear transducer shows diffuse increased echogenicity, with more focal areas of abnormally increased echogenicity in the left caudate head (arrowhead) and left putamen (arrow). c) Axial MR image shows restricted diffusion on DWI in the thalami and there are other findings in addition.

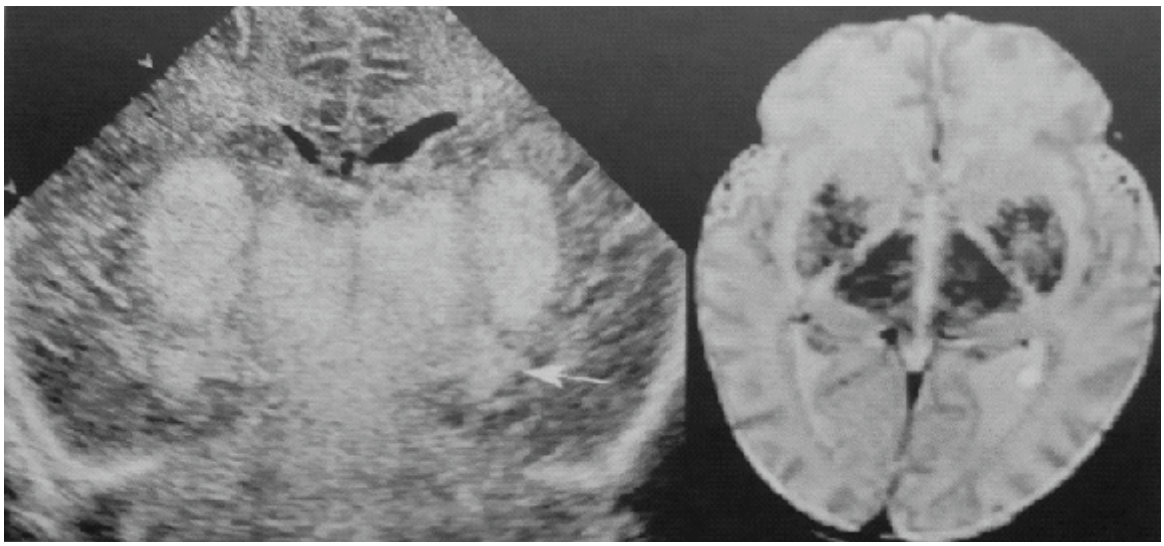


Fig. 6: Thalamic hemorrhage as seen on CUG (left) and MRI (right)

ACUTE CHANGES IN THE DOPPLER SONOGRAPHY: Cerebral vascular resistance index (RI) is used for predicting clinical outcome from 24 hours of age in the infants with moderate or severe HIE (Fig. 7). In severe HIE, RI below 0.55 had a positive predictive value (PPV) for death or disability of 75% and a negative predictive value (NPV) of 100%. High RI was found in most infants who subsequently had a poor outcome.[9] It is possible that hypothermia will affect the cardiovascular system in the ways that might change RI.[14,15] Outcomes of babies with HIE vary according to the severity of the injury. Low RI is not predictive of poor outcome during HT, but regains the predictive power after rewarming.

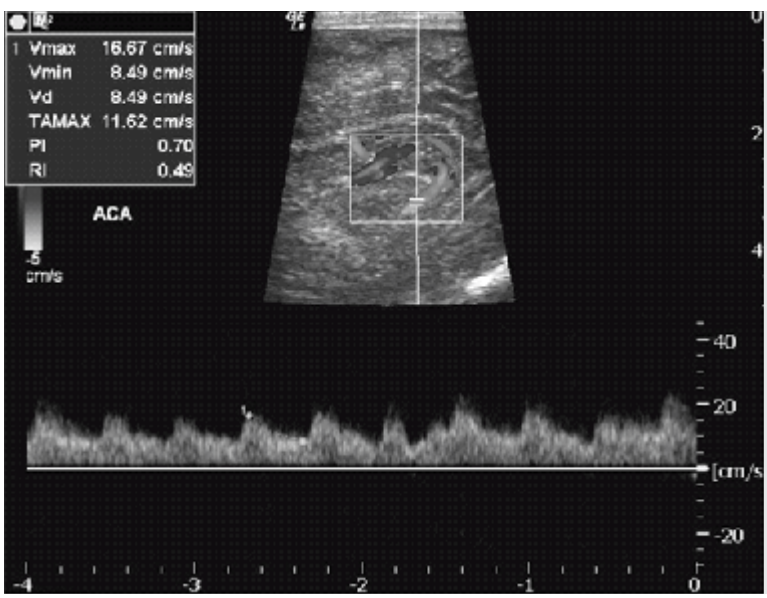


Fig. 7: Color Doppler indices of anterior cerebral artery in severe asphyxia

EVOLUTION OF SONOGRAPHIC CHANGES: The best way to visualize white matter is at 7.5 MHz or higher frequencies. Sonographic changes in the earlier phase are uncertain as cell reaction and microvascular changes develop after 48 hours. Under normal conditions a difference in echogenicity can be observed between relatively hypoechoic cortex and mildly hyperechoic white matter. Gyral white matter core echogenicity can be compared in patients in a sagittal or coronal section through the gyrus cinguli. Early indicators hinting at the need for further imaging are 1) fuzzy, swollen brain, 2) relative hypoechoic aspect of caudate, 3) appearance on day 2 or day 3 of four hyperechoic columns in coronal section through deep grey matter, 4) luxury perfusion or reversed diastolic flow in large arteries, 5) early hyperechoic haemorrhage in ischemic areas and 6) gyral core hyperechogenicity.

MRI and CUS: in the recently published data shows that modern CUS can pick up abnormalities including parenchymal almost similar to MRI except focal lesions near the cortex.[6,17]

IN SUMMARY

1. CUG is an excellent tool in screening and monitoring of asphyxiated infants with HIE and evaluating the prognosis of asphyxiated infants.
2. CUS may miss some lesions as compared to MRI but still very useful especially in babies who are critical.
3. In the infants with HIE treated with therapeutic hypothermia, the low resistance index is probably not as good a predictor of a poor outcome as in normothermia and further studies are needed in this area.
4. Repeat CUG at regular intervals may improve identification of brain abnormalities especially in centers where MRI facility is not available.

BIBLIOGRAPHY

1. Huang, BY. & Castillo, M. Hypoxic-ischemic brain injury: imaging findings from birth to adulthood. Radiographics2008; 28: 417–439.
2. Barkovich, AJ. MR and CT evaluation of profound neonatal and infantile asphyxia. Am J Neuroradiol1992;13: 959–972.
3. Volpe JJ. Neurology of the newborn. WB Saunders Company. 5th ed 2008.
4. Ilves, P., Lintrop, M., Talvik, I., Muug, K., Maipuu, L. &Metsvaht, T. Low cerebral blood flow velocity and head circumference in infants with severe hypoxic ischemic encephalopathy and poor outcome. Acta Paediatr 2009; 98: 459–465.
5. Babcock, DS. & Ball, W. Jr. Postasphyxial encephalopathy in full-term infants: US diagnosis. Radiology 1983; 148: 417–423.
6. Epelman, M., Daneman, A., Kellenberger, CJ., Aziz, A., Konen, O., Moineddin, R., White, H. &Blaser, S. Neonatal encephalopathy: a prospective comparison of head US and MRI. Pediatr Radiol2010; 40: 1640–1650.
7. Barkovich, AJ. 2005. Brain and spine injuries in infancy and childhood. In: Barkovich AJ, ed.Pediatric neuroimaging: 190–290, 4th ed, Lippincott Williams & Wilkins, ISBN 978-1-4160-4918-0, Philadelphia.
8. Connolly, B., Kelehan, P., O´Brien, N., Gorman, W., Murphy, JF., King, M. & Donoghue, V.The echogenic thalamus in hypoxic ischaemic encephalopathy. Pediatr Radiol1994;24: 268–271.
9. Eken, P., Toet, MC. Groenendaal, F. & de Vries, LS. Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic-ischaemic encephalopathy."Arch Dis Child 1995; 73: F75–80.
10. Hertzberg, BS., Pasto, ME., Needleman, L., Kurtz, AB. & Rifkin, MD. Postasphyxial encephalopathy in term infants: sonographic demonstration of increased echogenicity of the thalamus and basal ganglia. J Ultrasound Med 1987; 6: 197–202.
11. North, K., & Lowe, L. Modern head ultrasound: normal anatomy, variants, and pitfalls that may simulate disease. Ultrasound Clin 2009; 4: 497–512.
12. Lowe, LH.,& Bailey, Z. Sate-of-the-art cranial sonongraphy: Part I, modern techniques and image interpretation. AJR Am J Roentgenol2011; 196: 1028–1033.
13. Bennhagen, RG., Weintraub, RG., Lundström, NR. &Svenningsen, NW. Hypoxic-ischaemic encephalopathy is associated with regional changes in cerebral bblood flow velocity and alterations in cardiovascular function. Biol Neonate 1998;75:275–286
14. Elstad, M., Whitelaw, A. &Thoresen, M. Cerebral resistance index is less predictive in hypothermic encephalopathic newborns. Acta Paediatr 2011; 21.
15. Thoresen, M. & Whitelaw, A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics 2000;106: 92–99.
16. Archer, LN., Levene, MI. & Evans, DH. Cerebral artery Doppler ultrasonography for prediction of outcome after perinatal asphyxia. Lancet 1986; 2: 1116–1118.
17. Wei Shen, Jia-Hua Pan, Wei-Dong Chen. Comparison of transcranial ultrasound and cranial MRI in evaluations of brain injuries from neonatal asphyxia. Int J Clin Exp Med 2015;8(10):18319-18326.

CHAPTER

12

MAGNETIC RESONANCE IMAGING IN HYPOXIC ISCHEMIC ENCEPHALOPATHY PROCEDURE FOR WHOLE BODY COOLING

Dr. Umamaheswari B

Hypoxic Ischemic Injury in term neonates causes global hypoxic ischemic injury (HII) in MRI.

Hypoxic Ischemic Injury in term neonates causes global Hypoxic Ischemic Injury (HII) in MRI. HII occurs due to interruption of placental flow (antepartum), or events during delivery (intrapartum) or hypoxic damage after delivery (postnatal). MRI imaging is the most sensitive imaging technique to detect early hypoxic injury secondary to perinatal asphyxia. MRI injury is also considerably less in infants who have undergone TH. MRI helps in both diagnosis and prognosis of HIE. This chapter has been written with objective of highlighting the various hypoxic injuries occurring in term neonates.

ROLE OF NEUROIMAGING IN THERAPEUTIC HYPOTHERMIA (TH) INCLUDE

- Diagnosis
- Assess the pattern and severity of injury
- Prediction of clinical outcome based on pathologic lesions observed on imaging
- Information about long term prognosis

MR IMAGING- PRACTICAL TIPS

Transporting MR imaging in any sick neonate could be complex. The following should be done:

- Proper Communication - ICU and MRI
- Replace standard length tubes with extension tubes
- Transport in incubator to maintain temperature
- Monitoring of vital signs during transport and scan

- Time taken to complete all sequences: 30 to 45 minutes
- Use MR compatible equipment: Pulse oximeter, ECG system, Infusion pump, Ventilator, Resuscitation equipment. MR compatible incubator if available
- Temperature maintenance during the imaging
- Preventing Movement and Noise: Swaddling, Ear plugs/Muffs
- As far as possible avoid oral sedation, swaddling and timing after feeding if permitted
- If HIE stage III, baby may be already drowsy especially with the use of anti-convulsants
- If needed Oral sedation (Chloral hydrate) 25-50mg/kg could be used. Or Intranasal sedation with Midazolam (100 microgram) could be used

PROTOCOL

- MRI-preferably 3 Tesla; if unavailable 1.5 Tesla could be used
- Sequences to be included: Axial and sagittal T1 Weighted Images (T1WI) and T2WI, coronal T2 FLAIR(fluid attenuated inversion recovery), axial DWI(Diffusion weighted Images) and GRE (Gradient recalled echo) images, MRA (MR angiogram), MRV (MR venogram) and 1 or 2 MR spectroscopy sequences in ventro-lateral thalamus and lentiform nucleus and centrum semi-ovale (Calculate lactate/NAA ratio)
- MRI usually done between 5 and 14 days in infants who have undergone TH

PATTERN OF INJURY IN HIE IN TERM BABIES

Pattern of injury depends on the brain maturity, duration and severity of insult and type of MRI sequencing and timing of imaging

	Profound hypoxic injury	Partial hypoxic injury
Event	Acute severe event like cord prolapse, abruption, uterine rupture	Prolonged partial hypoxia-ischemia like difficult delivery, maternal fever
Pathology	Energy failure leading to cell necrosis followed by secondary energy failure and programmed cell death	Cortical necrosis; laminar necrosis and selective neuronal necrosis
Pattern of Injury	Basal ganglia and thalamus (BGT) pattern and posterior limb of internal capsule (PLIC) pattern. If severe entire cerebrum affected	Cortical/subcortical pattern
Sarnat Staging	HIE Stage II and III	Clinical manifestation may be subtle

INTERPRETATION OF NORMAL MRI

Structures in MRI (Fig. 1) Corresponding anatomical structure (Fig. 2)

Term MRI normal structure

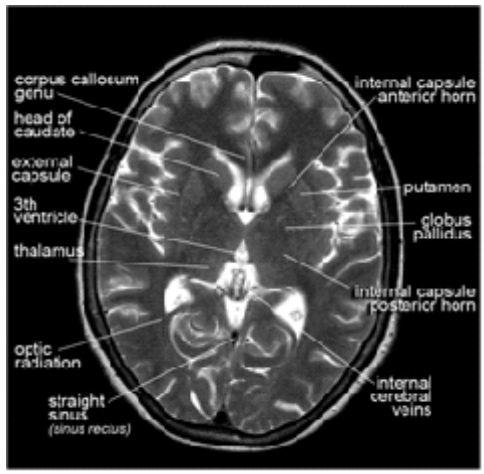


Fig. 3: T1 W image

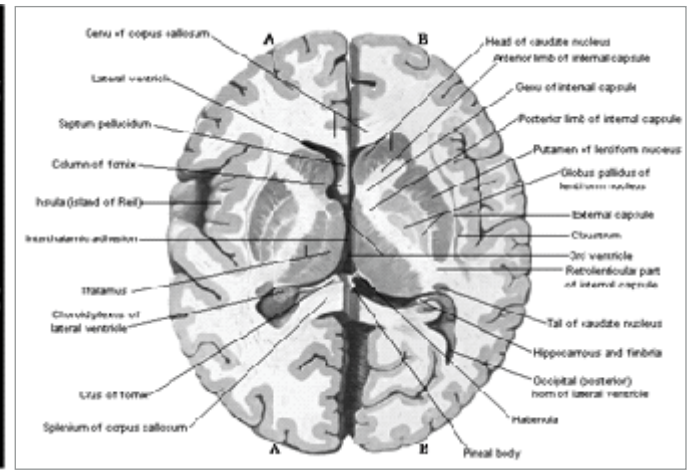
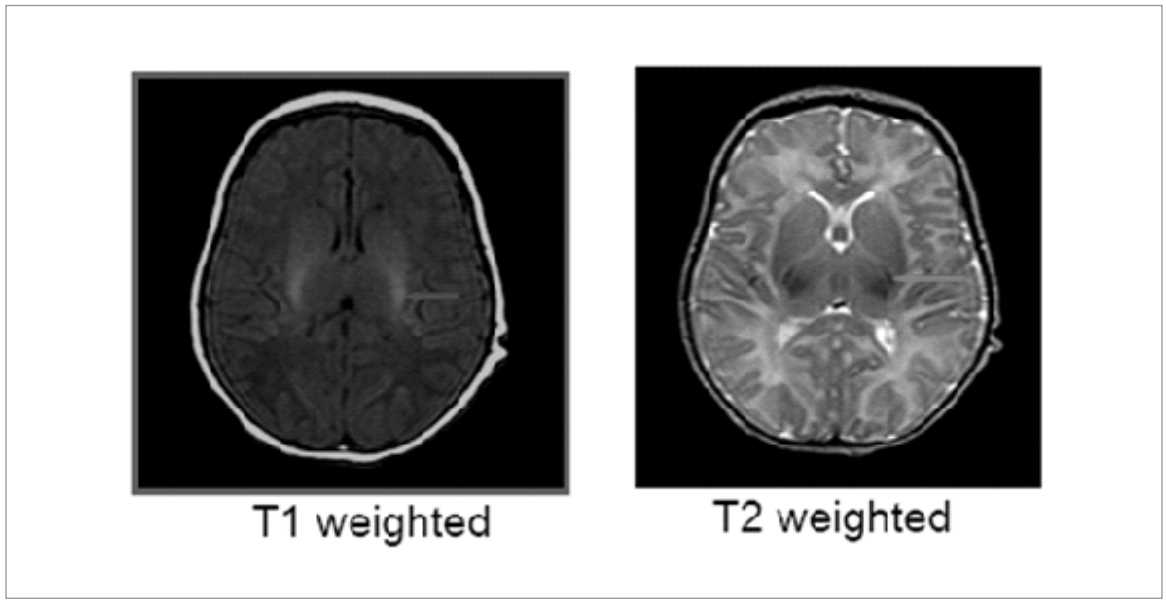


Fig. 4: T2 W image



Myelination of posterior limb of internal capsule (PLIC) appearing as hyperechoeic in T1W and hypoechoeic in T2W images (Fig. 3 and 4.). Under normal circumstances, PLIC is myelinated in term neonates. In HIE, myelination could be affected.

DW imaging detects the alteration in diffusion of free water. With acute injury, the intracellular water content increases and there is restriction in the movement of water in and out of the cell. Areas of diffusion restriction would be shown as increased signal. DW imaging signal intensity starts appearing within1 to 2 days of injury, peak by 4 to 5 days and pseudo-normalizes by day 7 of injury. T 1 and T2 W imaging changes starts by 3 days of injury and scan on day 7 continue to show more obvious changes. Interpretation of MRI should take into account the time of MRI imaging and the type of imaging.

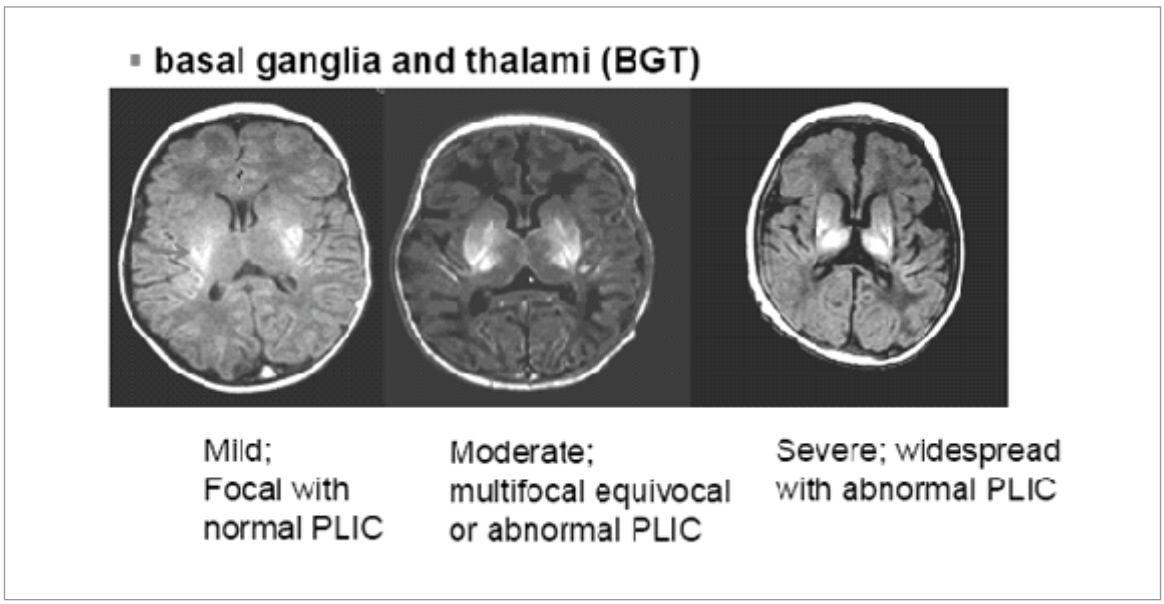
PATTERN OF MRI INJURY

BGT-Basal Ganglia thalamus pattern: Occur with or without PLIC changes

PLIC- Posterior limb of internal capsule myelination changes

Cerebral cortex and sub cortical white matter pattern

Fig. 5: BGT pattern (With or without PLIC changes) (T1W Images)



Conventional T1 and T2WI are most useful at end of 1st week. BGT pattern indicates acute hypoxic ischemic injury.

Fig. 6: DW changes (Diffusion weighted images in a term neonate with acute ischemic insult)

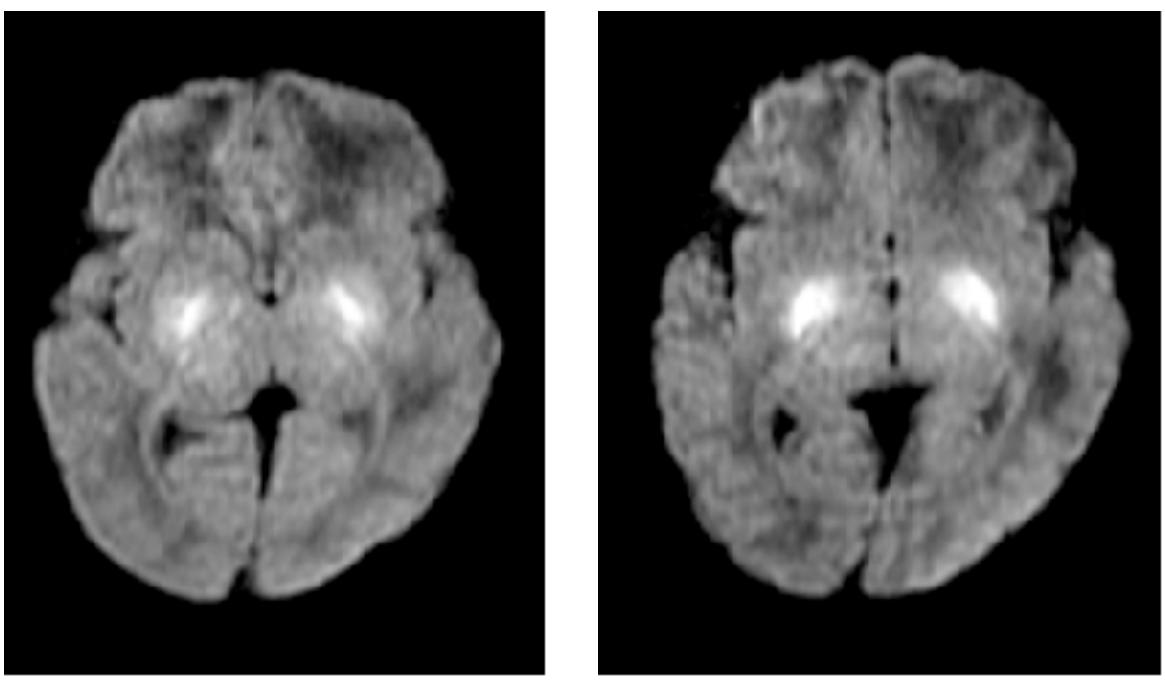


Fig. 6 is showing diffusion restriction in basal ganglia region. DW changes occur within 24 hours of injury, peaks at 5 days of life and pseudo-normalizes by end of 1st week.

CORTICAL AND SUB-CORTICAL WHITE MATTER PATTERN

Fig. 7: Partial hypoxic injury results in DW changes in water-shed area in cortical/ sub-cortical region

Fig. 8: Typical diffusion restriction in cortical and sub-cortical region including corpus callosum

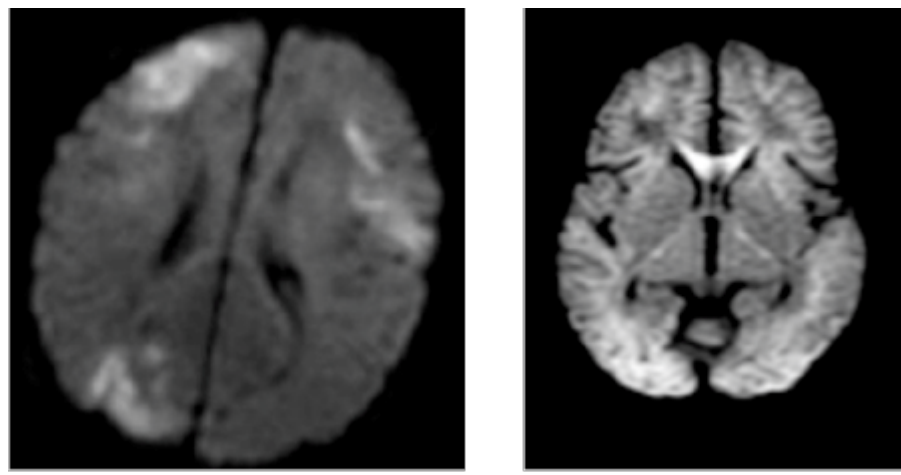
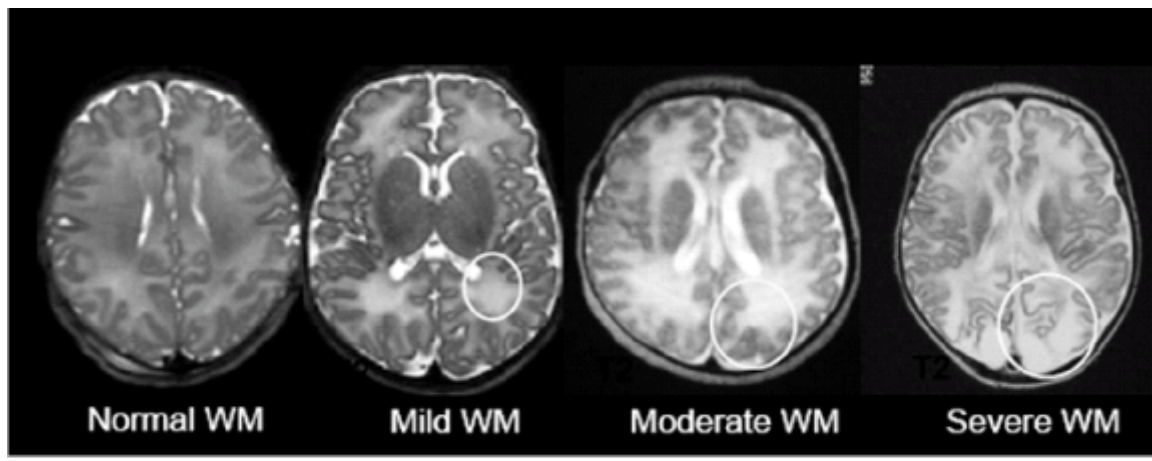


Fig. 7 is showing diffusion restriction in inter-vascular watershed zones involving both the cortex and subcortical white matter. This pattern is indicative of sub-acute/ prolonged partial hypoxia. DW image signal should be compared to that of cerebellar signal. That would indicate the degree of diffusion restriction in cortical and subcortical area.

Fig. 9: Grades of white matter injury



Severe WM injury involves loss of grey- WM differentiation as shown in Fig. 9

Fig. 10: Parasagittal injury in term Vs. periventricular injury in preterm hypoxia

In preterm injury, the lesion is near the ventricles and in term it is near parasagittal region as depicted in Fig. 10.

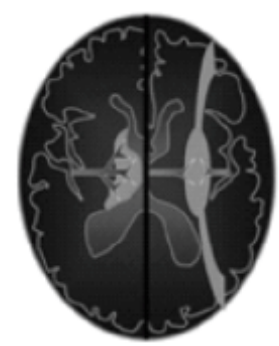


Fig. 11: Term HIE

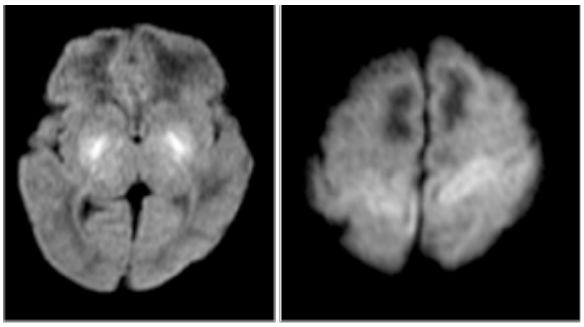
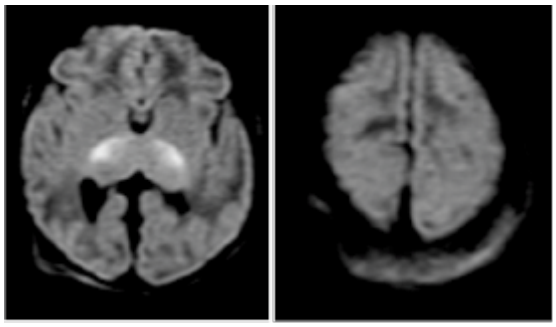


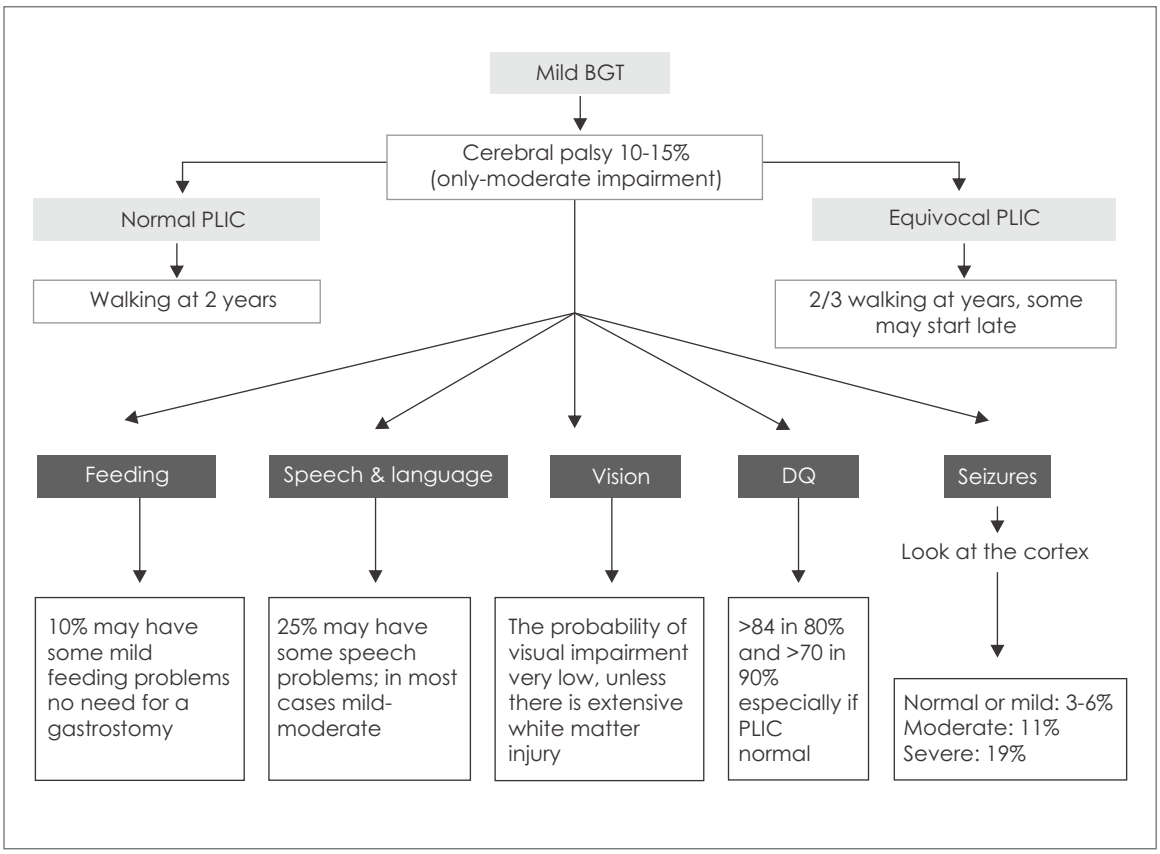
Fig. 12: Preterm HIE



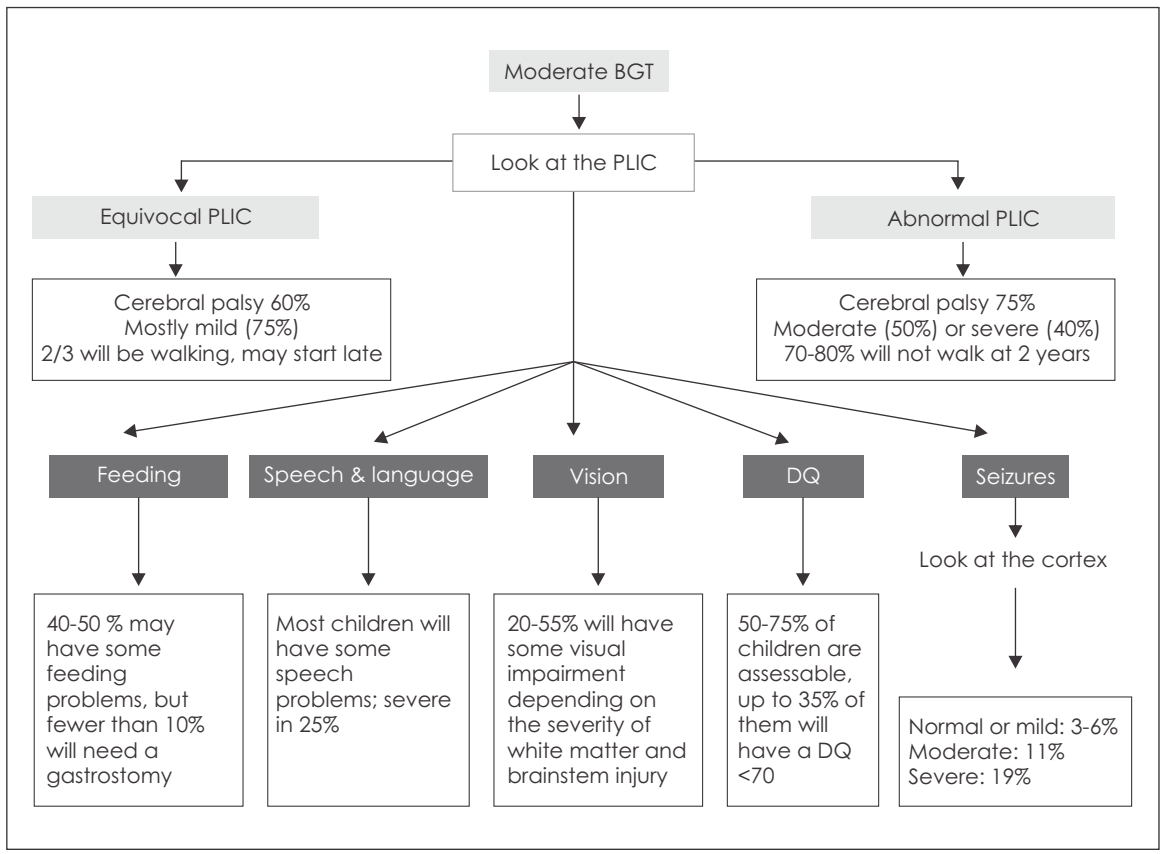
In preterm, perirolandic cortex spared, basal ganglia involvement is less severe as depicted in Fig. 11 and 12

LONG TERM NEURODEVELOPMENTAL CORRELATION OF DIFFERENT PATTERNS OF MRI INJURY

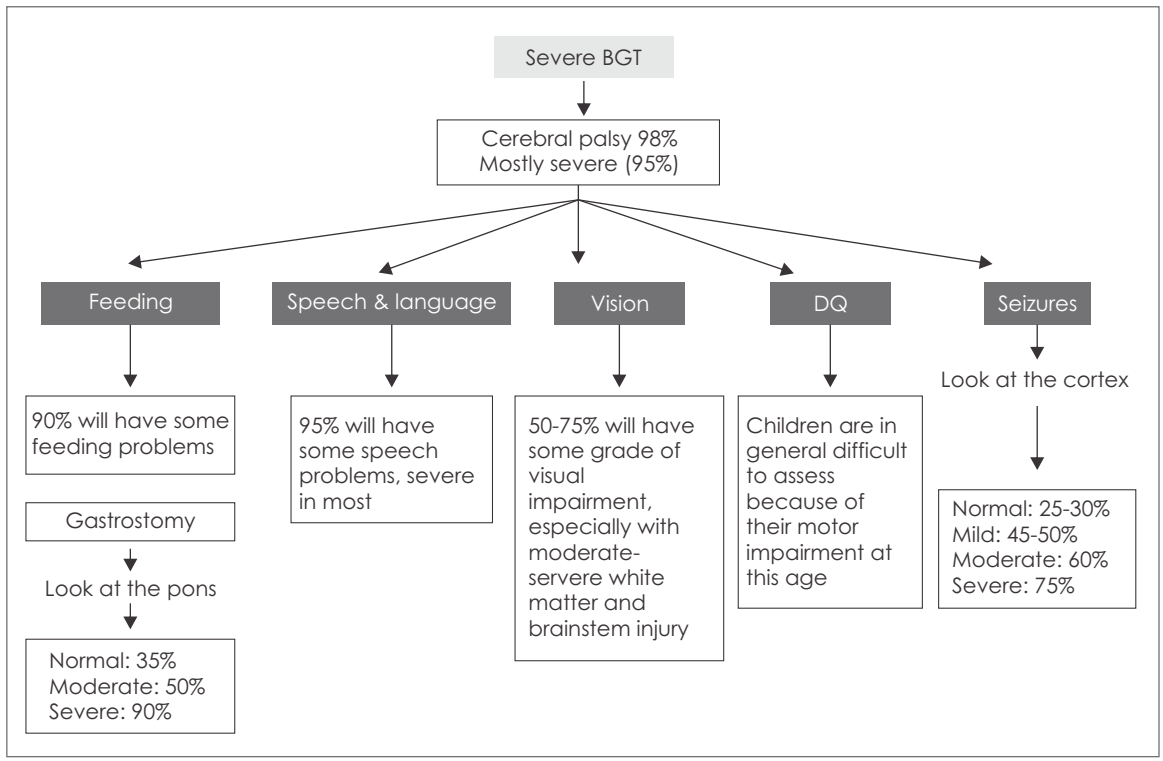
a. MILD BGT (Basal Ganglia Thalamus)



b. Moderate BGT pattern



c. Severe BGT pattern



Relatively better outcome have been seen with watershed predominant pattern of injury. There have been reports of suboptimal head growth, behavioral problems and delay in language.

MRS in TH

Concepts of MRS

MRS acquires signals from metabolites in predefined regions of brain. Regions to be included are deep grey matter and cortical region. The signals are acquired from choline (Cho), creatine (Cr), N-acetylaspartate (NAA) in normal status. Lactate peaks in Hypoxic damage due to alteration in oxidative metabolism.

Metabolite	Marker
N-acetylaspartate (NAA)	Neuron and their processes; Indicative of intact central nervous tissue
Choline (Cho)	Membrane turnover & myelination
Creatine (Cr)	Brain metabolism
Lactate	Anaerobic metabolism
NAA/Cho	Value of 0.62 indicative of poor neurodevelopmental outcome (De Vries 2001)
NAA/Cr ratio	Value >0.67 predictive of death or severe CP at 2 years (Ancora 2013)
Lac/NAA ratio	Value of > 0.29 in deep grey matter is indicative of poor neurodevelopmental outcome(Thayill 2010); Good marker for severity in sub-acute to chronic phase
Lac/Cho & Lac/Cr ratio	Value of > 1 indicative of poor neurodevelopmental outcome

Fig. 13

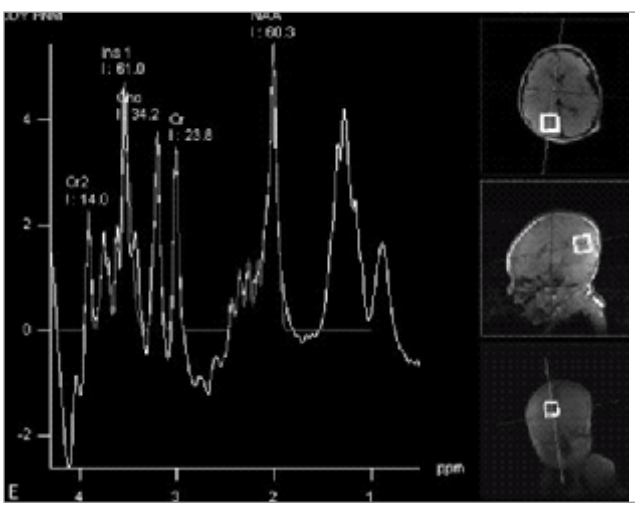


Fig. 14

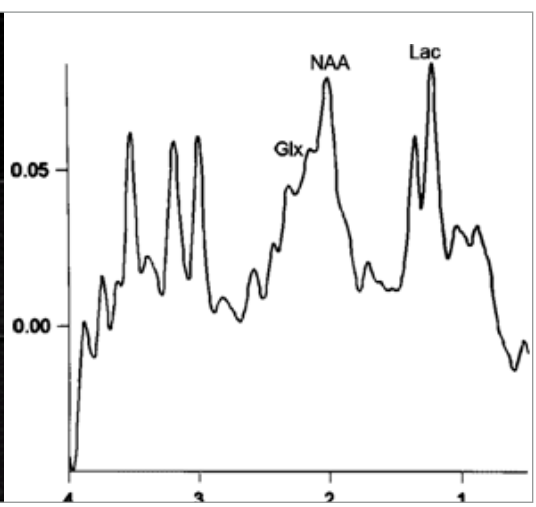


Fig. 13: MRS in occipital region shows lactate peak (superimposed with lipid peak), Choline levels are low indicating disrupted myelin

Fig. 14: MRS line diagram showing different peaks. NAA - N acetylaspartate; Cr - Creatine; Lac - Lactate; Cho - Choline

MRI IN INFANTS WITH HIE WHO HAVE UNDERGONE THERAPEUTIC HYPOTHERMIA (TH)

In babies undergoing Therapeutic Hypothermia, there are certain questions which need to be answered:

- Q1. When do we obtain MRI?
- Q2. Is there any specific MRI pattern in these babies?
- Q3. Does TH reduce the MRI abnormalities in babies with asphyxia?
- Q4. Does TH alter the predictive value of MRI in HIE?

Q1. When do we obtain MRI?

Ans. Mean 8 days for T1, T2 changes - Obtain in 1-2 weeks, DW changes 3-5days - Within 1 week; Interpretation of MRI should take into account the type and timing of MRI.

Q2. Is there any specific MRI pattern in these babies?

Ans. No; Same BGT pattern with or without PLIC changes and cortical and sub-cortical pattern occurs in infants undergoing TH. Smaller studies have shown that pseudo-normalization of diffusion restriction changes occurred later.

Q3. Does TH reduce the MRI abnormalities in babies with asphyxia?

Ans. Yes; In TOBY trial, they found that among 131 infants treated with TH, less BGT injury and fewer abnormalities of PLIC were identified.

Q4: Does TH alter the predictive value of MRI in HIE?

Ans. No; MRI retains the predictive value and abnormal MRI predicts adverse neuro-developmental outcome. The pooled sensitivity and specificity for DW imaging is 58% and 89%, respectively. Sensitivity and specificity for T1/T2 changes done $\leqslant$ 1 week is 84% and 90%, respectively. If done $\leqslant$ 2 wk, the sensitivity and specificity is 98% and 76%, respectively.

CONCLUSION

- MRI imaging is the most sensitive imaging technique to detect early hypoxic injury secondary to perinatal asphyxia.
- MRI is done between 5 and 14 days of life. Interpretation should take into consideration the type of imaging and the timing. DW changes occurs within 24, peaks in 3-4 days and pseudo-normalizes in 7 days, T1 and T2 changes are evident in 3 days and scan by 7 days continues to show new changes.
- MRI injury is less with TH. Both BGT and cortical/sub-cortical injury were observed less in those undergoing cooling.
- MRI remains as a good predicting tool for the outcome in infants undergoing TH.
- MRS in deep grey matter region measuring the ratios of Lac/NAA, Lac/Cho & Lac/Cr and NAA/Cr & NAA/Cho helps in predicting long term adverse outcome.

BIBLIOGRAPHY

1. Barnette AR, Horbar JD, Soll RF, et al. Neuroimaging in the evaluation of neonatal–encephalopathy. Pediatrics 2014;133:e150817.
2. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term–neonatal encephalopathy. J Pediatr 2005;146:45360.
3. Rutherford M, Counsell S, Allsop J, et al. Diffusion-weighted magnetic resonance imaging in term perinatal brain injury: a comparison with site of lesion and time–from birth. Pediatrics 2004;114:100414.
4. Gano D, Chau V, Poskitt KJ, et al. Evolution of pattern of injury and quantitative MRI on days 1 and 3 in term newborns with hypoxic-ischemic encephalopathy.– Pediatr Res 2013;74:827.
5. signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy. Pediatrics 1998; 102: 323-8
6. Thayyil S, Chandrasekaran M, Taylor A, et al. Cerebral magnetic resonance bio-markers in neonatal encephalopathy: a meta-analysis. Pediatrics 2010;125:–e38295.
7. Hayes BC, Ryan S, McGarvey C, et al. Brain magnetic resonance imaging and outcome after hypoxic ischaemic encephalopathy. J Matern Fetal Neonatal–Med 2016;29:77782.
8. Bednarek N, Mathur A, Inder T, et al. Impact of therapeutic hypothermia on MRI–diffusion changes in neonatal encephalopathy. Neurology 2012;78:14207.
9. Bonifacio SL, Saporta A, Glass HC, et al. Therapeutic hypothermia for neonatalencephalopathy results in improved micro-structure and metabolism in the deep–gray nuclei. AJNR Am J Neuroradiol 2012;33:20505.
10. Roelants-Van Rijn AM, Van Der Grond J, De Vries LS, et al. Value of (1)h-MRS us-ing different echo times in neonates with cerebral hypoxia-ischemia. Pediatr Res–2001;49:35662.
11. Alderliesten T, de Vries LS, Benders MJ, et al. MR imaging and outcome of term neonates with perinatal asphyxia: value of diffusion-weighted MR imaging and (1)–H MR spectroscopy. Radiology 2011;261:23542.

CHAPTER

13

FOLLOW UP OF COOLED BABIES

Dr. Nivedita M

With improved survival of high risk neonates, follow-up programs are becoming as important as the initial intensive care itself. In India owing to the high incidence of perinatal asphyxia,[1,2] survivors of neonatal encephalopathy (NE) form a significant proportion of all patients enrolled in any follow-up program. It has long being recognized that infants suffering from HIE deserve long term follow-up. With the advent of therapeutic hypothermia (TH), it has become even more important to follow-up these infants, in order to know the long term effects of TH.

With improved survival of high risk neonates, follow-up programs are becoming as important as the initial intensive care itself.

NEED FOR FOLLOW-UP

Neonates suffering from perinatal asphyxia and neonatal encephalopathy are at an increased risk of neuro motor/sensory impairments. The Cochrane meta-nalysis of 11 RCTs on TH has shown significant reduction in the composite outcome of mortality or major neurodevelopmental disability at 18 months of age. It also showed a significant reduction in neurodevelopmental disability in survivors (RR 0.77 (95% CI 0.63 to 0.94).[3] Though TH significantly reduces neuromorbidity as compared to controls, yet among the surviving infants a sizeable number suffer from varying degrees of neurodisablity, which emphasizes the need for rigorous long term follow-up of these children. Shankaran et al have published outcomes following TH at 6-7 years of age, in which though TH did not result in significant reduction in the combined outcome of death or an IQ score below 70 at 6 to 7 years of age, it was still shown to reduce the rate of death with no increase in the rates of a low IQ score or severe disability among survivors.[4] Since TH is now standard practice in NICUs, it is essential that long term neurodevelopmental outcome data become available soon, to determine if the benefit of TH at 1.5-2 years is indeed sustained beyond early childhood.

Survivors of TH need to be followed-up in the same manner as any other high-risk neonate, till long term data revealing any specific pattern of neurodevelopmental sequelae is available.

DURATION OF FOLLOW-UP

By 18-24 months of age motor impairments can be confirmed and formal assessment of cognitive and language function can be performed with good prediction to early school age performance.[4,5] Major neuroimpairment usually becomes overt in early childhood itself. However survivors of NE though apparently normal in early childhood may develop subtle cognitive and behavioural abnormalities later on.[6,7]

Like other high risk infants, it is necessary to follow up cases of TH till 8-10 years of age, if possible throughout their school years, even if they appear to be normal in early childhood.[8,9]At the least, they should be followed up till 18-24 months of corrected age (CA).

FREQUENCY OF FOLLOW-UP

The first visit may be planned at 2 weeks post discharge. Thereafter at 3, 6, 9, 12, 18 and 24 months or 2, 4, 8, 12, 18 and 24 months corrected age. As the child needs to come at 6, 10 and 14 weeks for immunization, the initial few visits may be combined with these. Then on, every 6 monthly or yearly till follow-up lasts.[10,11] The 18-24 months visit is mandatory for formal development assessment. In case the child develops any medical or neurodevelopmental concerns, more frequent visits will be required.

AGE CORRECTION

Corrected age is used for growth and development assessment of preterm (<37 weeks) till 24 months. Currently TH is offered only to neonates 36 weeks and above.

Table 1: Roles of each member of the follow-up team

Personnel	Responsibility
Pediatricians / neonatologists	Coordinator Assessment of growth and screening for developmental delay Management of inter-current illnesses Immunization
Pediatric neurologist	Management of neuro-disablities, seizures
Child psychologist	Formal development/IQ assessment Screening and management of behavioral disorders
Ophthalmologist	Assessment of visual acuity Screening and management of strabismus and refractive errors
Otorhinolaryngologist	Hearing assessment Management of hearing impairment
Dietician	Management of infants with failure to thrive
Speech therapist	Language assessment Management of oromotor dysfunction
Medical social worker/counsellor	Counselling parents Arranging disability certification, free bus pass etc.
Physiotherapist/ Occupational therapist	Physiotherapy and rehabilitation
Special educator	Special education

Those administering tests of neurodevelopmental assessment, depending upon the test used might require formal training and certification.

FOLLOW-UP DURING NICU STAY

Findings of a structured neuro exam needs to be documented daily during and at least until 1 week after TH,[12] though it is often not possible to perform a complete examination due to the infant's sickness, intubation and effect of sedatives and anti-seizure medications. Sarnat staging and Thompson scoring are two such examination methods. Levene's classification is a simplified system, shorter and easy to perform.

Though significant correlation exists between developmental status at 2 years and the Sarnat grade and persistently abnormal neuro exam on day 3, the best predictability of the outcome at 2 years is seen with the neurological examination at discharge (positive and

negative predictive values of 86% and 72% respectively). In infants with moderate Sarnat scores, abnormal outcome occurred in 25% if the discharge examination was normal and in 70% if it was abnormal. The time taken to establish oral feeding also correlated significantly with neurological outcome (r=0.40, p=0.008).[13]

The role of cranial sonography, MRI and EEG have been described in other chapters in this manual.

POST DISCHARGE FOLLOW-UP

FEEDING HISTORY

Infants with severe NE may suffer from significant oromotor disturbances leading to difficulties in feeding. Neonates suffering from perinatal asphyxia may be born with low birth weight or intrauterine growth restriction (IUGR), in which case adequate post natal feeding has to be ensured. A detailed history of the child's feeding pattern must be elicited inclusive of history of difficulty in sucking/chewing/swallowing, choking episodes, drooling, repeated lower respiratory infections and failure to thrive. Those with oromotor dysfunction need prompt referral to an occupational therapist or a speech and language pathologist.

MEDICAL PROBLEMS

Epilepsy has been reported to develop in 9-33% of HIE.[14] Though every attempt must be made to wean off all anti-convulsants by discharge, some infants may have to be discharged on anti-convulsant medication. Details of any episode of seizure post discharge must be obtained.

Apart from seizure disorder, cases of cerebral palsy suffer from a host of other medical problems as well like hypertonia, drooling, recurrent respiratory infections, skeletal deformities and contractures etc. Relevant history must be elicited and examination performed. As parents are often uneducated, instructions regarding medications are poorly understood. They must be requested to bring with them all the medications that the child is on at every visit, in order to explain prescriptions clearly. Also this way the physician knows for certain all the medications that the child is on, as drug interactions have to be borne in mind when prescribing new drugs.

IMMUNIZATION

Immunization must proceed in survivors of HIE in the same manner as that of normal children, including those with seizure disorder.

GROWTH

Weight, length/height and head circumference must be accurately checked at each visit. Weight should be checked on an electronic weighing scale, length up to 2 years must be checked with an infantometer and head circumference with a non-stretchable tape.

Growth must be plotted in the WHO child growth standards. For preterms Fenton growth charts (http://www.ucalgary.ca/fenton/2013chart) may be used till 40 weeks CGA.

NEUROLOGICAL ASSESSMENT

Neurological examination must be done at every visit with special attention to muscle tone. The NNF recommends neuro-motor assessment of high risk infants at least once during the first 6 months, once during the second six months and once yearly.[11]

Skull shape must be noted, fontanelles and sutures must be palpated.

Amiel-Tison neurological assessment at term (ATNAT) is a systematic way of performing the neurological examination. If the full exam is not possible, then a general neuro-exam with measurement of AT angles for assessment of muscle tone may be done.

Table 2. Amiel –Tison angles

Age (months)	Adductor angle	Popliteal angle	Dorsiflexion angle	Scarf sign
0-3	40°-80°	80°-100°	60°-70°	Elbow does not cross midline
4-6	70°-110°	90°-20°	60°-70°	Elbow crosses midline
7-9	110°-140°	110°-160°	60°-70°	Elbow goes beyond axillary line
10-12	140°-160°	150°-170°	60°-70°	

ATNAT at term age has been shown to have good agreement with neurological examination (k=0.83) and BSID scores (MDI, k=0.64; PDI, κ=0.74) at 12-15 months of age.[15]

Measuring the AT angles

Check the angles when the infant is in a quiet alert state. Maintain the head in midline.

Adductor angle-With the infant in supine position, hold both lower limbs extended and pull them apart gently as far as possible. Measure the angle formed between the two legs. Look for asymmetry between the two sides.

Popliteal angle-Bring the thighs by the side of the abdomen and extend the knee. Measure the angle formed between the leg and the thigh. Check both sides simultaneously.

Ankle dorsiflexion-Check each side separately. Extend the knee with one hand and with the other apply slow pressure on the sole to flex the foot. Measure the angle formed between the dorsum of the foot and the anterior aspect of the leg. This is the 'slow angle'. Repeat the manoeuver with rapid flexion of the foot, this gives the 'rapid angle'. Normally both angles are equal. A difference of more than 10° is abnormal.

Scarf sign-Lift the infant's head to 45°, hold the wrist and try to pull the hand towards the opposite shoulder.

Angles smaller and larger than the normal indicate hypertonia and hypotonia respectively

MOTOR SKILLS

Observation of spontaneous movements of the infant **(Prechtl's assessment of general movements)** has been found to be predictive of future motor development. The first stage is that of writhing general movements (GMs) which are present inutero to 6 to 9 postterm weeks and are characterized by small to moderate amplitude and slow to moderate speed movements. From 9 to 20 postterm weeks, writhing movements are replaced by fidgety movements involving the neck, trunk and limbs. These are small-amplitude movements of moderate speed and variable acceleration in all directions.

Abnormal GM has been found to correlate with lesions in MRI in term infants with HIE. Cramped-synchronized GM, a type of abnormal rigid movements, lacking fluency with the limbs and trunk contracting and relaxing almost simultaneously have been found to correlate with central gray matter lesions in the MRI. They have been reported to be 100% specific and 68.7% sensitive for prediction of cerebral palsy.[16]

Assessment of GMs may be done during an outpatient visit by video recording the infant's spontaneous movements during wakeful state for 10-15 minutes at 1 month and 3 months.[16]

Other methods of motor examination are the Alberta Infant Motor Scale (AIMS), Test of Infant Motor Performance (TIMP) and Peabody Developmental Motor Scales (PDMS). In a case of cerebral palsy, assessment of severity of disability is to be done using the **GMFCS (The Gross Motor Function Classification System)**. It classifies the functional status of the child into 5 levels.[8]

1. Walks without restrictions; limitations in more advanced gross motor skills
2. Walks without assistive devices; limitations walking outdoors and in the community
3. Walks with assistive mobility devices; limitations walking outdoors and in the community
4. Self-mobility with limitations; children are transported or use power mobility outdoors and in the community
5. Self-mobility is severely limited even with the use of assistive technology

DEVELOPMENT ASSESSMENT

DEVELOPMENT SCREENING TEST

A developmental screening test has to be done once within the first 6 months, once within the next 6 months and yearly thereafter.[11]

DIAGNOSTIC DEVELOPMENT TEST

A formal assessment of development is to be done at corrected age of 12 months and again between 18-24 months. If an assessment has to be done before 12 months, it is best

done only by 6-8 months.[8] If at any point the screening test has abnormal results or there is any caregiver concern regarding development then a formal assessment must be completed within 2 months.[11]

Table 3: Commonly used tests for developmental assessment

	Responsibility	Age range
Direct assessment	Denver Development Screening Test (DDSTII)	0-6 years
	Bayley Infant Neurodevelopment Screener (BINS)	3 months-2 years
Parent-completed tool	Ages and Stages Questionnaire (ASQ) III	1 month-5.5 years
	Parents Evaluation of Developmental Status(PEDS)	0-8 years
	Diagnostic test	
	Griffiths III III Mental Development Scales	1 month-5 years 11 months
	Bayley Scales of Infant and Toddler Development III	1 month-3.5 years
	Developmental Assessment Scales for Indian Infants (DASII)	0-2.5 years

Mukherjee et al in a comparison of various screening tests recommend BINS and the ASQ for screening of high risk children.[17]

ASSESSMENT IN THE PRESENCE OF DISABILITIES

The usual tests of development cannot be administered to those with visual and hearing impairment. In those with hearing impairment the Leiter International Performance Scale-Revised can be used to assess nonverbal cognitive function. For children with visual impairment without significant motor impairment the Verbal Comprehension Index of the Wechsler scales can be used.[18]

In the protocol of the TRUFFLE study if BSID could not be administered due to impairments, an estimate of cognitive delay was made as-no delay, 3-6 months delay or more than 6 months delay.[19]

OPHTHALMOLOGICAL EVALUATION

Mercuri et al reported abnormalities of visual function in 41% of cases of NE secondary to HIE, at school age.[20] The Cochrane meta-analysis showed a non-significant decrease in blindness among survivors of TH.[3]

Prior to discharge, red reflex must be checked in every neonate. At each visit visual milestones must be elicited from the mother. In infants, clinical assessment of visual function is mainly by fixation and following. One should also look for squint, roving eye movements and nystagmus. With the infant lying down or seated on the mother's lap, a red wool, target or any attractive toy can be used to check for fixation and following. The assessment must be done binocularly and then monocularly. Care should be taken that the objects do not make noise as the child may respond to the auditory rather than the visual signals. Visual acuity can be formally assessed in young children using Cardiff cards or Teller Acuity Card.

Formal assessment by an ophthalmologist for refraction, strabismus and any other visual problems should be done at 1 year and annually thereafter till 5 years of age .[11] Robertson et al recommend early referral to a pediatric ophthalmologist in case of: HIE III, HIE II with abnormal neurological examination or reduced visual awareness at hospital discharge and stroke associated with HIE.[9]

HEARING EVALUATION

Of HIE survivors, up to 17% of those with and 6.3% of those without residual neurological deficits, have been found to have hearing loss.[21] Incidence of permanent hearing loss has been reported to be 6% to 10% in follow-up cases of TH.[22] The Cochrane meta-analysis of seven studies failed to show any significant reduction in the incidence of sensorineural hearing loss requiring aid in neonates subjected to TH.[3]

Hearing screening is to be done via Brainstem Auditory Evoked Responses (BAER/BERA), as OAE misses auditory neuropathy. However if unavailable, then at least a screening OAE must be done. Hearing screening is usually prior to discharge, in any case it must be completed before 1 month of age.[23] Mietzsch et al in a pilot study in moderate to severe HIE reported transient suppression of DPOAEs and prolongation of ABR waveforms in the first week which normalized by the third week. They suggested that cooling might hasten recovery of this transient auditory dysfunction. However this was only a pilot study with a small sample size of 9 (4 cases and 5 controls).[24] Further research will provide directions as to whether screening in these infants should be delayed beyond the first week.

If the neonate fails the screening test, a diagnostic BERA has to be done before 3 months of age and appropriate intervention initiated before 6 months of age.[23]

For those at high risk for hearing loss even if the initial screening test is passed, the NNF recommends a behavioral audiometry at 1 year of age.[11] The American Academy of Paediatrics recommends diagnostic audiologic testing between 24 and 30 months in the presence of risk factors.[25] Perhaps it would be prudent to say that in follow-up cases of TH, irrespective of the initial screen result, auditory milestones must be elicited at every visit along with a clinical assessment of hearing and a repeat diagnostic test must be performed between 1 to 2 years of age.

TFT SCREENING

Thyroid screening must be offered universally to all infants.

LANGUAGE ASSESSMENT

The NNF recommends a language assessment between 1 and 2 years of age.[11] Robertson et al recommend one between 3 and 5 years.[9] Language assessment must include testing of skills of expressive and receptive language, organization and grammar. Few of the tests used are Receptive-Expressive Emergent Language Test, Peabody Picture Vocabulary Test (PPVT), Linguistic Profile Test and Three Dimensional Language Acquisition Test (3D- LAT).

COGNITIVE ASSESSMENT

Shankaran et al reported an IQ <70 in 27% of survivors of TH at 6-7 years of age.[4] Survivors of moderate encephalopathy have been found to have lower scores on school readiness test conducted at 5.5 years.[7] Performance in intellectual, scholastic and neuropsychological tests are uniformly poor in survivors of severe NE. Those with moderate NE show more varied results with intelligence scores below those of children with mild NE and age-matched peers, but within the normal range. They perform poorly in reading, spelling and mathematical skills.[6] Cognitive dysfunction of low severity may not become apparent till the child faces complex tasks, which will happen only at later school age. Due to these reasons, cognitive assessment needs to be done during the child's schooling years.

Cognitive assessment should include assessment of intelligence, executive function, sensorimotor functions (visual-motor precision, fine motor speed), visual spatial processes (design-copying, visual closure) and memory and learning. IQ can be assessed from 3 years of age. A battery of tests have to administered to the child at different ages (3-4 years, 6-7 years and 8-10 years of age)in order to complete a comprehensive assessment of cognitive functions.[8]

In the Indian setting, extensive testing over several years would not be practicable. In our country a practical approach might be to conduct an IQ test between 3-4 years and repeat it at 8-10 years. IQ determined at 8 years predicts IQ at older age better than if determined earlier.[8]Like development assessment tests, there are a host of tests for assessing intelligence. Worldwide the most commonly used tests are the Wechsler's tests. Wechsler's Preschool and Primary Scale of Intelligence for young children (WPPSI, IVth edition is applicable from 2:6 – 7:7 years of age) and the Wechsler Intelligence Scale for Children (WISC, Vth edition is for children aged 6:0–16:11 years) for older ones. Stanford-Binet Intelligence Scales and Seguin Form Board (SFB) are other commonly used tests. Specific neuropsychological tests like NEPSY II (A developmental neuropsychological assessment) are required in order to diagnose attention, memory, executive function and information processing deficits.

BEHAVIOURAL ASSESSMENT

Children suffering from moderate to severe NE are 5.9 times more likely to be diagnosed with an autism spectrum disorder as compared to controls at 5 years.[26] Autism screening should be conducted universally in all children between 18-24 months. Modified Checklist for Autism in Toddlers (M-CHAT), Social Communication Questionnaire, Trivandrum Autism Behavior Checklist are few of the tools available. Diagnosis can be established using Childhood Autism Rating Scale (CARS), INCLEN diagnostic tool for ASD (INDT-ASD) or Indian Scale for Assessment of Autism (ISAA)[27]

The Achenbach Child Behavior Check List (CBCL) is a good tool to identify behavioural abnormalities based on parental perception of child's behaviour.

Assessment of functional status which would also reflect the quality of life can be measured using the Vineland Adaptive Behavior Scales (VABS). Robertson et al recommends evaluation of adaptive behaviour at 3-5 years and the 8-10 years.[9]

There is no consensus regarding the timing, frequency and tests for developmental assessment in the follow-up of TH. If further research reveals a specific profile of neurodevelopmental sequelae in this group of infants, that would guide the choice of tests to be used. Till then each centre may design its protocol depending on the manpower, patient load and funds available. The tests for development/behaviour assessment must have a sensitivity and specificity of >/=70%.[28] Some of the development assessment tools are freely available, whereas others have to be purchased and are expensive. A reasonable protocol is suggested in Table 3.

2 weeks post discharge	Med & Neuro exam
1.5 months (immunization visit)	Screening BERA, thyroid screening if not done earlier
3 months	Med & Neuro exam
	Clinical assessment of vision and hearing
	Prechtl's assessment of general movements
	Complete audiological evaluation if failed BERA
	DDST II/BINS
6 months	Med & Neuro exam
	DDST II/BINS
9 months	Med & Neuro exam
	DDST II/BINS
12 months	Med & Neuro exam
	BSID III/DASII
	Ophthalmological exam
18-24 months	Med & Neuro exam
	BSID III/DASII
	MCHAT
	Behavioural audiometry
	Ophthalmological exam
	REELS III
Every year, after 2 years	Med & Neuro exam
	DDST II/ASQ III
	Ophthalmological exam (till 5 years)
3-4 years	WPPSI-IV
	CBCL
	VABS
8-10 years	WISC -V
	CBCL
	CBCL

The RBSK guidelines on examination and follow up of a child with suspected developmental delay are easy to understand and implement. The website provides freely downloadable material (http://nhm.gov.in/nrhm-components/rmnch-a/child-health-immunization/rashtriya-bal-swasthya-karyakram-rbsk/2013-12-19-08-13-49.html)

HOW TO MAINTAIN GOOD FOLLOW-UP

Follow-up rates must be at least 80% at the 18-24 months visit.[8] In India most follow-up programs face huge lost to-follow-up. Few measures that can help improve follow-up rates.

Enrol patients into the follow-up program before discharge itself. Prior to discharge counsel the parents regarding the need for follow-up and inform them about the date, time and venue of the first post-discharge visit.

Maintain a database of patient address and contact details. Collect back-up contact numbers.

Make phone call or SMS reminders of the appointments. If patients miss an appointment, call up and find out why and fix another date of visit.

Provide parents with the number of a contact person.

According to the NICHD network, if a single assessment alone is possible it should be performed at 18-22 months corrected age. Therefore if the patient is unable to come for regular visit, request them to come for a single visit at 18-22 months corrected age.[8]

Screening tools like Ages and Stages (ASQ) and Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS) may be administered over the phone.

All the above measures will be possible only if there exists adequate manpower and funds dedicated to running the follow-up program.

KEY MESSAGE

Detailed neurological examination must be performed and documented at discharge.

Follow-up of cases of post-TH should be done in a structured manner.

Separate assessment of vision and hearing are mandatory.

Long term follow till at least till 8-10 years of age is needed.

BIBLIOGRAPHY

1. National Neonatology Forum NNPD Network. National Neonatal-Perinatal Database Report 2002-2003. New Delhi, Jan 2005.
2. Dhinagar S, Srinivasan S, Bhat BV. Hypoxic-ischemic Encephalopathy: an analysis of perinatal factors and outcome. Curr Pediatr Res.1999;3:37-41.
3. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews 2013, Issue 1. Art.No.:CD003311.DOI: 10.1002/14651858.CD003311.pub3.
4. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy.NEJM.2012;366:2085–92.
5. Shankaran S, Woldt E, Koepke T, Bedard MP, Nandyal R. Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants. Early Hum Dev 1991;25:135-48.
6. Van Handel M, Swaab H, de Vries LS, Jongmans MJ. Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: a review. Eur J Pediatr. 2007;166:645-54.
7. Robertson CM, Finer NNJ. Educational readiness of survivors of neonatal encephalopathy associated with birth asphyxia at term. Dev Behav Pediatr.1988;9 298-306.
8. AAP.Follow-up care of high-risk infants.Pediatrics.2004,114 (Supplement 5) 1377-97.
9. Robertson CMT, Perlman M. Follow-up of the term infant after hypoxic-ischemic encephalopathy. Paediatr Child Health.2006;11:278–82.
10. Kumar P, Sankar MJ, Sapra S, Agarwal R, Deorari A and Paul V. Follow up of high risk neonates. AIIMS-NICU protocols 2008. (Internet). [cited 2017 Sept 25]. Available at www.newbornwhocc.org.
11. Bhakoo O, Kumar P, Jain N, Thakre R, Murki S, S Venkataseshan. Follow up of high risk newborns. In: Evidence based clinical practice guidelines.NNF. 2010.Pg 217-252
12. Ergenekon E. Therapeutic hypothermia in neonatal intensive care unit: Challenges and practical points. J Clin Neonatol.2016;5:8-17.
13. Murray DM, Bala P, O'Connor CM, Ryan CA, Connolly S, Boylan GB. The predictive value of early neurological examination in neonatal hypoxic-ischaemic encephalopathy and neurodevelopmental outcome at 24 months. Dev Med Child Neurol.2010;52:e55-9.
14. Glass HC, Hong KJ, Rogers EE, Jeremy RJ, Bonifacio SL, Sullivan JE, Barkovich AJ, Ferriero DM. Risk factors for epilepsy in children with neonatal encephalopathy. Pediatr Res. 2011;70:535-40.
15. Paro-Panjan D1, Neubauer D, Kodric J, Bratanic B. Amiel-Tison. Neurological Assessment at term age: clinical application, correlation with other methods, and outcome at 12 to 15 months. Dev Med Child Neurol.2005;47:19-26.
16. Ferrari F, Todeschini A, Guidotti I, Martinez-Biarge M, Roversi MF, Berardi A et al. General movements in full-term infants with perinatal asphyxia are related to Basal Ganglia and thalamic lesions. J Pediatr.2011;158:904-11.

17. Mukherjee SB1, Aneja S, Krishnamurthy V, Srinivasan R. Incorporating developmental screening and surveillance of young children in office practice. Indian Pediatr.2014;51:627-35.

18. Yin Foo R, Guppy M, Johnston LM. Intelligence assessments for children with cerebral palsy: a systematic review.Dev Med Child Neurol.2013;55:911-8

19. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, M Bilardo CM, Brezinka C et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet.385;2162 – 72.

20. Mercuri E, Anker S, Guzzetta A, Barnett AL, Haataja L, Rutherford M et al. Visual function at school age in children with neonatal encephalopathy and low Apgar scores. Arch Dis Child Fetal Neonatal Ed. 2004; 89: F258-F262.

21. Jiang ZD. Long-term effect of perinatal and postnatal asphyxia on developing human auditory brainstem responses: peripheral hearing loss. Int J Pediatr Otorhinolaryngol 1995; 33: 225-238

22. Stewart JE, Bentley J, Knorr A. Hearing Loss in Neonatal Intensive Care Unit Graduates. In: EC Eichenwald, AR Hansen, CR Martin, AR Stark, editors. Cloherty& Stark's Manual of neonatal care. 8th Edition.Wolters Kluwer.2017. Pg 994-999.

23. From National Consultation Meeting for Developing IAP Guidelines on Neurodevelopmental Disorders under the aegis of IAP Childhood Disability Group and the Committee on Child Development and Neurodevelopmental Disorders, Paul A, Prasad C, Kamath SS, Dalwai S, C Nair MK, Pagarkar W. Consensus Statement of the Indian Academy of Pediatrics on Newborn Hearing Screening. Indian Pediatr. 2017;54:647-651.

24. Mietzsch U, Parikh NA, Williams AL, Shankaran S, Lasky RE. Effects of hypoxic-ischemic encephalopathy and whole-body hypothermia on neonatal auditory function: a pilot study. Am J Perinatol.2008;25:435-41.

25. Allen D, BuzHarlor Jr, Charles Bower. Neonatal screening hearing assessment in infants and children: recommendations beyond neonatal screening. Pediatrics 2009;124;1252-63.

26. Badawi N1, Dixon G, Felix JF, Keogh JM, Petterson B, Stanley FJ, Kurinczuk JJ. Autism following a history of newborn encephalopathy: more than a coincidence? Dev Med Child Neurol. 2006;48:85-9.

27. National Consultation Meeting for Developing IAP Guidelines on Neuro Developmental Disorders under the aegis of IAP Childhood Disability Group and the Committee on Child Development and Neurodevelopmental Disorders, Dalwai S, Ahmed S, Udani V, Mundkur N, Kamath SS, C Nair MK. Consensus Statement of the Indian Academy of Pediatrics on Evaluation and Management of Autism Spectrum Disorder. Indian Pediatr.2017;54:385-393.

28. Carol Weitzman, Lynn Wegner and the Section on developmental and behavioral pediatrics, Committee on psychosocial aspects of child and family health, Council on early childhood and Society for developmental and behavioral pediatrics. Promoting Optimal Development: Screening for Behavioral and Emotional problems.Pediatrics.2015;135;384

MiraCradle®
Neonate Cooler

MIRACLES SPEAK FOR THEMSELVES

DR. B.VISHNU BHAT
Professor and Head, Department of Pediatrics,
Division of Neonatology, JIPMER, Pondicherry

There is sufficient evidence in support of therapeutic hypothermia in term and late preterm newborns with hypoxic ischemic encephalopathy and it reduces mortality without increasing major disability in survivors. We have been practising therapeutic hypothermia for hypoxic neonates since 2009 in our level III NICU. We have used cooling gel packs, phase change material and servo controlled equipment both for service and research purposes. Phase change material - **MiraCradle®** will be a good investment for the Neonatologists and Pediatricians dealing with cases of perinatal asphyxia. It is easy to use and an affordable equipment in resource limited settings. However, the cooling procedure should be undertaken with close monitoring of the neonate.

DR. SANJAY WAZIR
Consultant Neonatologist, Cloudine Hospital, Gurgaon

Birth asphyxia is one of the largest contributors to neonatal mortality in the developing countries and only approved and proven therapy which has been shown to decreased mortality and morbidity in this condition is therapeutic hypothermia or cooling the brain to reduce further damage. Unfortunately, like most technologies, the servo controlled hypothermia machines are outside the budget of most government and even private hospitals in India and other developing parts of the world. We have had **MiraCradle®** since 2014 and have cooled more than 70 babies till now. I feel this is one innovation which is totally "Made in India" and holds promise as a low-cost device to help babies with perinatal asphyxia.