COOLING THERAPY FOR NEWBORNS WITH DIAGNOSIS OF MODERATE TO SEVERE HYPOXIC-ISCHEMIC ENCEPHALOPATHY.

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Lack of oxygen to neonatal brain because of perinatal asphyxia can lead to Hypoxic Ischaemic Encephalopathy (HIE) that can manifest as mild, moderate or severe forms(Severity ranging from hyperactivity to seizures or coma after birth) This remains an important cause of Neuro developmental deficit in childhood.
Infants with moderate encephalopathy have a 10 percent risk of death, and those who survive have a 30 percent risk of disabilities.
Sixty percent of infants with severe encephalopathy die, and many, if not all, survivors are handicapped.
Treatment is currently limited to supportive intensive care

Incidence:

In developed countries incidence of Perinatal/Birth Asphyxia is about 1 in 8 per thousand live term births and incidence of Neonatal Hypoxic Encephalopathy is about 2 to 4 per thousand live term births.

Mechanism:

Major pathophysiological events start with Asphyxia that occur because of Hypoxemia, Ischemia and Hypercapnia at birth

Asphyxia: refers to impairment in the exchange of respiratory gases, oxygen and carbon dioxide.

Perinatal brain can be deprive of oxygen by two major pathogenic mechanisms: -

Hypoxemia: diminished amount of oxygen because of lack of supply

Ischemia: diminished amount of blood perfusion to the brain → oxygen and glucose deprivation

Hypercapnia: is a additional major feature, which exacerbate metabolic acidosis and leads to initial increase in cerebral blood flow

Pathophysiology:

Can be divided into primary, latent and secondary phases

Primary Phase: cell injury occurs due to lack of oxidative energy failure/hypoxic depolarization of cells leading to cytotoxic oedema and activation of excitatory amino acids

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Latent Phase ---Transient resolution of hypoxia and partial recovery of cerebral oxidative metabolism

Secondary Phase---Secondary Cytotoxic Oedema due to to accumulation of exitotoxins and failure of oxidative energy metabolis and mitochondrial activity leading to apoptotic Neuronal Cell Death

Timing of Pathophysiological events after Hypoxia or Ischaemia due to birth asphyxia are very important as one has to start Hypothermia Therapy in the Latent Phase before the beginning of Secondary Phase or in other words the time period between primary cell death and the onset of secondary cell death represents a window of opportunity where hypothermia therapy can modify and ameliorate neuronal cell death.
All studies in animal models have shown encouraging results with Hypothermia Therapy before the onset of Secondary Phase.

How Hypothermia Therapy Works:

It works by its protective effects from a graded reduction in cerebral metabolism that slows cell depolarization and development of edema .It reduces accumulation of excitotoxic neurotransmitters (e.g. glutamate) Hypothermia attenuates secondary energy failure and suppresses oxygen free radical release by lipid peroxidation of cell membranes and prevent apoptotic processes (e.g. caspase activity) preventing neuronal cell death in Secondary Phase

Timing of Initiation of Hypothermia:

Cooling should be started as soon as possible after resuscitation is completed. Current evidence suggests that cooling is unlikely to be beneficial if started more than six to eight hours after birth. The TOBY trial has suggested that results are better for those babies cooled within four hours after birth.

Methods of Hypothermia:

Two methods are being evaluated in newborn infants with moderate to severe HIE (Hypoxic Ischaemic Encephalopathy)
Whole Body Cooling (WBC) and Selective Head Cooling (SHC)
Hypothermia Blankets are used for Whole Body Cooling (WBC)
The TECOTHERM TS Med 200 cooling blanket is used for active cooling.
Cool Cap are recommended for Selective Head Cooling (SHC)
Therapeutic hypothermia aims to: - lower the tempera-

ture of the deep brain structures to 33 to 34 C°with WBC and 34 to 35 C°with SHC
Latest trials have shown that WBC is much safer than SHC and WBC is recommended for Therapeutic Hypothermia.

Evidence of Hypothermia:

Is derived primarily from three Randomized Controlled Trials (RCT) e.g Cool Cap Trial, NICHD trial and the TOBY trial. The Cool Cap and NICHD Trials form the basis of a Cochrane review. The Cochrane review reports a reduced risk of death and or major disability among survivors RR 0.76 [0.65, 0.89]. Importantly mortality was reduced mortality RR 0.68 [0.57, 0.92] The primary TOBY results have provided strong support for the role of cooling as follows; (death ore severe disability RR 0.86 [0.69, 1.08], mortality 0.96[0.66, 1.35], severe disability among survivors 0.74 [0.6, 1.1]
Most of the centres follow Toby Guidelines

TOBY GUIDELINES:

This guidance is important for two main reasons:
Firstly, specific guidance is needed to promote uniform practice and avoid inappropriate treatment.
Secondly, Guidance will help in future studies and future recommendation regarding preventing ischaemic brain injuries.
According to Toby Guidelines It may be appropriate to consider treatment with cooling for infants that meet the Criteria A and Criteria B

Criteria A

(One of the following have to be present)
Infants ≥36 completed weeks gestation admitted to the neonatal unit with at least one of the following:
Apgar score of ≤5 at 10 minutes after birth
Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
Acidosis within 60 minutes of birth (defined as any occurrence of umbilical cord, arterial or capillary pH <7.00)
Base Deficit ≥ 16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth
Infants that meet criteria A should be assessed for whether they meet the neurological abnormality entry criteria (B):

Criteria B

Seizures or moderate to severe encephalopathy, consisting of:
Altered state of consciousness (reduced response to stimulation or absent response to stimulation) and
Abnormal tone (focal or general hypotonia, or flaccid) and
Abnormal primitive reflexes (weak or absent suck or Moro response)
Infants who meet criteria A and B may be considered for treatment with cooling.

Criteria for defining Moderate or Severe Encephalopathy are listed in following table.

Parameters	Moderate Encephalopathy	Severe Encephalopathy
Level of Consciousness	Reduce response to stimulation	Absent response to Stimulation
Spontaneous Activity	Decreased Activity	No Activity
Posture	Distal Flexion Complete Extension	Decerebrate
Tone	Hypotonia (Focal or Generalized)	Flaccid
Suck	Weak	Absent
Moro	Incomplete	Absent
Pupils	Constricted	Constricted
Heart Rate	Bradycardia	Variable
Respiration	Periodic Breathing	Apnoea

When to start cooling

Cooling should be started as soon as possible after resuscitation is completed. Current evidence suggests that cooling is unlikely to be beneficial if started more than six to eight hours after birth.

Other Assessments

Vital signs monitoring
Encephalopathy Score,
Amplitude integrated EEG (aEEG) monitoring,
Rectal or Oesophageal Temperature and
Core Body Temperature Monitoring.

Encephalopathy Score

The severity of encephalopathy should be assessed using the criteria in the table, but there is no specific score threshold that indicates treatment with cooling. This score should be recorded daily for the first four days after birth.

SIGN	0	1	2	3	SCORE
TONE	Normal	Hyper	Hypo	Flaccid	
LOC	Normal	Hyper Alert Staring	Lethargic	Commatose	
Fits	None	Infrequent <3/day	Frequent >3/day		
Posture	Normal	Fisting Cycling	Strong Distal Flexion	Decerebrate	
Moro	Normal	Partial	Absent		
Grasp	Normal	Poor	Absent		
Suck	Normal	Poor	Absent/ Bites		
Respiration	Normal	Hyperventilation	Brief Apnoea	Apnoea	
Frontanelle	Normal	Full not tense	Tense		
Total Score					

aEEG assessment
The amplitude integrated EEG (aEEG) should be recorded in all infants treated with cooling but cooling need not be delayed until the aEEG is initiated.
A normal aEEG record (confirmed by assessing the underlying EEG and excluding artefact distortion of aEEG) indicates a high probability of normal outcome, and clinicians may consider that treatment with cooling is not required.
Continued aEEG recording during the treatment period is helpful clinically, to assess occurrence of seizures and monitor the severity of encephalopathy.
IV anticonvulsant therapy may cause transient suppression of EEG activity. Ideally the aEEG should be performed before administering anticonvulsant therapy.
Apparent improvement of the aEEG after 6 hours of age is not an indication for discontinuing cooling. However, if the aEEG becomes normal by 6 hours of age, and
the infant appears to be recovering clinically, the risk of cerebral damage is low, and the need for continuing cooling can be reconsidered.

Temperature Monitoring

The target rectal temperature when using selective head cooling is 34.5°C, maintained for 72 hours, followed by slow rewarming to normothermia.
During whole body cooling the target rectal temperature is 33-34°C, for 72 hours, followed by slow rewarming to normothermia.
The rectal temperature probe needs to be inserted 2-3 cm and secured to the thigh. The probe position must be checked regularly, especially if the baby is not behaving as expected clinically, for example, if the baby has been over-cooled the heart rate will be lower than anticipated.
Cooled babies at the correct temperature of 33-34°C often have mild bradycardia of around 100 bpm. “Normal” heart rate of >120 bpm in cooled babies may be an indication of distress and sedation should be considered or increased if appropriate.
If cooled babies are slow to adjust their temperature and are too cold, it might be helpful to lighten sedation, to make the baby more responsive.

When is Cooling Not Appropriate?

Cooling is not appropriate if:
The infant is likely to require surgery during the first 3 days after birth .There are other abnormalities indicative of poor long term outcome for example chromosomal abnormalities etc.
Cooling may not be appropriate if the infant appears moribund or has persisting extremely severe encephalopathy such that further treatment is likely to be futile, for example if the aEEG/EEG is isoelectric beyond 12-24 hours of age.
Cooling may produce adverse respiratory or cardiovascular effects and should be used with caution in infants with an unstable respiratory or cardiovascular condition.

Side Effects of Hypothermia

Reported side effects are thrombocytopenia, hypotension, and hypoglycaemia. Always keep an eye on development of any arrhythmias. Bradycardia up to 100 beats per minute is acceptable but tachycardia of >120 with cooling can be a sign of distress.

Management

Fluid Restrict to 40 to 50ml/kg/day and with renal failure reduce to 30ml/kg/day
Anticonvulsunts like Phenytoin or phenobarbitones should be used to treat seizures
Mechanical Ventillation If needed keeping Pco2 to 5-6kp

Sedatives and Analgesics
Stress may have adverse effects in asphyxiated infants and may influence the therapeutic effect of hypothermia. In addition, neonatal intensive care procedures may cause considerable stress to infants and cooling may also be associated with stress.
Signs of distress include tachycardia, facial grimacing and irritability. A heart rate consistently above 120 bpm in cooled infants suggests that the infant is distressed.
Ventilated infants may be sedated with intravenous morphine, maximum loading dose 50 micrograms/kg over 30 minutes followed by 10-20 micrograms/kg/hour. Morphine should be discontinued after 24-48 hours to lessen the risk of accumulation and toxicity.
Non-ventilated infants who appear distressed will also require sedative therapy, for example with chloral hydrate, 50 mg/kg. Respiratory function must be monitored.

Cardiovascular support
Alterations in heart rate and blood pressure are common during cooling. In general the heart rate is reduced and blood pressure increases with a reduction in body temperature.
Most infants with a rectal temperature of 33-34°C (the target rectal temperature for whole body cooling) will have a heart rate around 100 bpm and a mean blood pressure greater than 40 mmHg.
A rapid rise in body temperature may cause hypotension by inducing peripheral vasodilatation. Volume replacement 20ml/kg saline or inotropes Dopamine or Dobutamine can be used 5-20 microgram/kg/minute.

Rewarming Procedures

Cooling is concluded after 72 hours, (or earlier if clinical circumstances dictate).
The rectal temperature should be allowed to rise by no more than 0.5°C per hour, to 37±0.2°C.

Magnetic Resonance Imaging (MRI)

An MRI should be done in all babies within about 2 weeks of birth. MRI is the imaging modality of choice for assessing the distribution of injury, and likely prognosis and to support a diagnosis of hypoxic ischaemic encephalopathy.
Normal anatomical features of the brain with no evidence of antenatal injury or malformation e.g. dilated ventricles, widened extra cerebral space or abnormal cortical folding, should be confirmed.

The presence of extra cerebral haemorrhage or collections should be noted, in particular, evidence of subdural or large subarachnoid haemorrhage. Where possible the presence of normal flow in the sinuses should be confirmed and any thrombosis documented particularly internal capsule, thalamus etc.

Long Term Outcome

Infants should be followed up regularly after discharge and a formal neurological examination and psychomotor assessment should be carried out at approximately 2 years of age.

Practical Points (Summary)

Hypothermia Therapy should be considered within first 4 hours in babies who are showing signs of moderate or severe encephalopathy and continue for 72 hours.

In newborn babies with encephalopathy Whole Body Cooling is much safer than Selective Head Cooling.

Continuous Rectal temperature monitoring and encephalopathy score should be done along with EEG monitoring.

Babies should be cooled up to 33-34ºC

Expect heart rate 100 beats per minute in a cool baby and heart rate 120 or more is a sign of distress in a cool baby.

Recommended management of HIE like cardiovascular support, mechanical ventilation, fluid restriction, use of anticonvulsant etc. Should be followed.

MRI at 2 to 3 week should be done

Developmental follow up at 18months and 24 months should be done.

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