Review Article

Therapeutic Hypothermia in Perinatal Asphyxia

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Abstract

Therapeutic hypothermia for infants with perinatal asphyxia has been studied in several randomised controlled trials. There is convincing evidence that moderate therapeutic hypothermia (33-34°C for 72 h), when initiated within 6 h after birth among term & near-term infants (≥35 weeks) with moderate to severe HIE reduces the risk of death or major disability & increases the rate of disability-free survival at 6-7 years of age

Key words: Therapeutic hypothermia, Asphyxia, perinatal asphyxia.

Introduction

Asphyxia is a major problem worldwide as 10% to 60% of affected infants die, & at least 25% of survivors have long-term neurodevelopmental sequelae. Therapeutic hypothermia for infants with perinatal asphyxia has been studied in several randomised controlled trials. There is convincing evidence that moderate therapeutic hypothermia (33-34°C for 72 h), when initiated within 6 h after birth among term & near-term infants (≥35 weeks) with moderate to severe HIE reduces the risk of death or major disability & increases the rate of disability-free survival at 6-7 years of age. Hypothermia results in a graded reduction in cerebral metabolism, suppresses apoptotic processes & also suppresses the release of pro-inflammatory cytokines & interleukins.The target body temperature is 34.5 ◦C for selective head cooling & 33.5 ◦C for total body cooling. Active cooling should be done for 72 hours & then gradual rewarming is done over 12 hours. Whole body cooling provides homogeneous cooling whereas selective head cooling provides greater cooling to the periphery of the brain than to the deeper brain structures. Though there were no reported serious adverse effects in the initial pilot studies of hypothermia in newborns, potential side effects reported later include bradycardia, arrhythmias, Hypotension, Reduction in surfactant production, Altered coagulation cascade, Thrombocytopaenia, Leukopaenia, lactic acidosis, Hypokalaemia & Hypoglycaemia. With the development of newer modes of servo controlled hypothermia devices the cerebral insult due to asphyxia can be reduced & severe sequlae of HIE can be prevented.

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Asphyxia-Problem Statement: Perinatal asphyxia affects 3-5 newborns per 1000 live births with subsequent moderate or severe hypoxic ischaemic encephalopathy (HIE) in 0.5 to 1 per 1000 live births [1,2]. HIE is a major problem worldwide as 10% to 60% of affected infants die, and at least 25% of survivors have long-term neurodevelopmental sequelae [3,4]. Globally, perinatal asphyxia is responsible for 42 million disability life adjusted years, double that due to diabetes & three quarters of that due to HIV/AIDS [5]. Almost one quarter of the world's 4 million annual neonatal deaths are caused by perinatal asphyxia [6]. These account for as many deaths as does malaria.

Therapeutic Hypothermia-Evidence: Therapeutic hypothermia for infants with perinatal asphyxia has been studied in several randomised controlled trials (RCT) [7-10]. Meta-analyses show that therapeutic hypothermia increases survival with normal neurological function (pooled risk ratio of 1.53) with a number needed to treat (NNT) of 8 & in survivors reduces the rates of severedisability & cerebral palsy [11,12]. A systematic review of three trials showed a significant reduction of combined rate of death &

severe disability with NNT of 9 & increased normal survival (survival without cerebral palsy & with MDI & PDI >84 & normal vision & hearing) with a NNT of 8 [12]. In a Cochrane review of 11 RCT comprising 1505 infants with moderate/severe encephalopathy &evidence of intrapartum asphyxia, therapeutic hypothermia resulted in a statistically significant reduction in combined outcome of mortality or major neurodevelopmental disability to 18 months of age (RR 0.75,RD -0.15); NNT for an additional beneficial outcome being 7. Cooling resulted in statistically significant reductions in mortality (RR 0.75, RD -0.09); NNT 11 & significant reductions in neurodevelopmental disability among survivors (RR 0.77, RD -0.13); NNT 8 [13]. A 2013 Cochrane review found that therapeutic hypothermia is useful in full term babies with encephalopathy [13]. There is convincing evidence that moderate therapeutic hypothermia (33-34°C for 72 h), when initiated within 6 h after birth among term & near-term infants (≥35 weeks) with moderate to severe HIE reduces the risk of death or major disability [12,13,14] & increases the rate of disability-free survival at 6-7 years of age [10,15].

Hypothermia Trials: Cool Cap trial used selective head cooling with mild systemic hypothermia (rectal temperature 34-35°C) commenced within 5.5 hours of age for 72 hours & showed an independent protective effect of hypothermia on the primary outcome of death or disability at 18 months (odds ratio 0.52) [7,16]. **NICHD trial** of whole body cooling (oesophageal temperature 33.5°C for 72 h) showed a significant reduction in the risk of death & moderate to severe disability at 18 months in the hypothermia group [8]. **TOBY trial** of whole body cooling (rectal temperature 33.5°C for 72h) showed a significant improvement in neurologic outcome in survivors from the hypothermic group [10]. **Neo Neuro Network study** [17] & **ICE trial** [18] further support a beneficial effect of hypothermia.

Proposed Mechanisms of Hypothermia: Hypothermia results in a graded reduction in cerebral metabolism by approximately 5% for each 1◦C decrease in body temperature [3,4,7,12,19] that slows cell depolarization, reduces accumulation of excito-toxic neurotransmitters (aspartate, glutamate, dopamine) [20-22] & suppresses oxygen free radical release [23] as well as lipid peroxidation of cell membranes thereby lowering production of toxic nitric oxide (NO) & free radicals [23]. It suppresses apoptotic processes in the developing brain via inhibition of caspase enzymes [13,24-26]. Cytochrome C translocation is diminished by hypothermia [26, 27] & there is increased expression of anti-apoptotic protein BCl-2 [28]. It also suppresses the release of pro-inflammatory cytokines & interleukins during reperfusion injury phase, thereby reducing direct neurotoxicity via suppression of microglial activation [29,30].The simultaneous increase in cytotoxic oedema& loss of cerebral cortical activity that accompanies secondary energy failure is also prevented [31].

Cooling Protocol: The target body temperature is 34.5 ◦C for selective head cooling & 33.5 ◦C for total body cooling. Temperatures lower than 32 ◦C are less neuroprotective & temperatures below 30 ◦C are very dangerous with severe complications [32]. Therapeutic hypothermia must be started within the first 6 h after birth which is the therapeutic window for hypoxic-ischemic event. Active cooling should be done for 72 hours from the initiation of cooling with very strict control of newborn's body temperature. Then gradual rewarming is done over 12 hours by increasing temperature by 0.5ºC every 2 hours.

Eligibility/criteria for therapeutic hypothermia:

1) More than 35 weeks of gestation.

2) Less than 6 hours of age.

3) Presence of evidence of asphyxia - at least two of the following four criteria:
i) Apgar less than 6 at 10 min or continued need for resuscitation with positive pressure ventilation with / without chest compressions at 10 min of age.

ii) Any acute perinatal event that may result in HIE (i.e. Abruption placenta, cord prolapse, severe foetal heart rate abnormality).

iii) Cord pH less than 7.0 or base deficit of 12 or more.

iv) If cord pH is unavailable, arterial pH less than 7.0/ BE more than12 mmol/L within 60 min.
4) Clinically defined moderate or severe HIE (stage 2 or 3 based on modified Sarnat Classification).
5) Moderate to severely abnormal background activity on amplitude-integrated EEG (.i.e. discontinuous, burst suppression or low voltage +/- seizure activity).

Modes of Cooling: Therapeutic hypothermia lowers the temperature of vulnerable deep brain structures, basal

ganglia to 32-34 °C. Brain hypothermia can be achieved by cooling the body, cooling the head selectively, or by cooling the head & body together. Whole body cooling provides homogeneous cooling to all brain structures, including the peripheral & central brain regions, whereas selective head cooling provides greater cooling to the periphery of the brain than to the deeper brain structures [33]. The combination of head& body cooling minimises the temperature gradients across the brain & also facilitates the cooling of the deeper regions. To provide adequate neuroprotection with minimal risk of systemic adverse effects, ideally the brain only should be cooled. However, in view of a temperature gradient between the cerebral cortex & deep grey nuclei, i.e. structures that are often affected in acute asphyxia, mild systemic hypothermia (34.5°C) is preferred to limit the steepness of the intra-cerebral gradient.

Devices for Cooling: Various devices have been used for therapeutic hypothermia.
1) Selective head cooling by circulating water at 10°C through a coil of tubing wrapped around the head (CoolCap). A servo-controlled overhead heater was used to maintain rectal temperature at 34°C to 35°C [16].
2) Placing a cap formed from cooled packs around the head at a temperature of 10°C, to maintain a nasopharyngeal temperature of 34°C to 35°C [34].

3) Placing infant on a water blanket pre-cooled to 5°C &the blanket temperature was servo-controlled to maintain an oesophageal temperature of 33.5°C [8].

4) Blowing cool air through a translucent perforated paper blanket placed over the infant to achieve the target rectal temperature between 33.0°C to 34.0°C [16]. Nowadays hypothermia is maintained with servo controlled systems aimed at reducing fluctuations in body temperature.

Adverse Effects of Cooling: There were no reported serious adverse effects in initial four pilot studies of hypothermia in newborns [35-38]. The potential side effects reported later include Delayed intracardiac conduction with sinus bradycardia [39,40], Prolonged QT interval, Ventricular arrhythmias, Reduced cardiac output, Hypotension, Hypertension,Reduction in surfactant production, Increase in pulmonary vascular resistance, Increase in oxygen consumption & oxygen requirement, Altered coagulation cascade& viscosity leading to coagulopathy that may be complicated by thrombus or haemorrhage, Anaemia, Thrombocytopaenia, Leukopaenia with increased risk of sepsis, Renal impairment, Metabolic & lactic acidosis, Hypokalaemia, Hypoglycaemia, Impaired liver function, Increase in vascular resistance, Platelet dysfunction, Excessive fibrinolytic activity, Diuresis due to suppression of antidiuretic hormones, Pulmonary hypertension, Impaired leukocyte mobility &phagocytosis [16]. Adverse effects, such as sinus bradycardia, increased blood pressure and increased oxygen requirement, were all transient and reversible with re-warming [36]. Cooling in the presence of infection might be deleterious as hypothermia may impair innate immune function, including neutrophil migration and function [41]. When lowering the body temperature, blood becomesmore viscous &the solubility of the gases in theblood increases; for example, in vivo values at33.5°C of PaCO2 are approximately 0.83 the valueread at 37°C. Correcting for temperature may resultin an increase in PaCO2 with a resultant increasein cerebral blood flow, whereas notcorrecting may result in the opposite effect, i.e.hypocapniainduced vasoconstriction. During hypothermia, there may be an increasedrisk of endotracheal tube obstruction due to stickysecretions which can be avoided by setting the temperatureof the humidifier at 37°C. During re-warming, seizures, hypotension [42], hypoglycaemia or hypokalemia can occur.

Conclusion

Therapeutic hypothermia is a proven therapy in perinatal asphyxia provided prompt selection of babies & religious monitoring of temperature is done. Strict surveillance for the development of adverse effects is mandatory. With the development of newer modes of servo controlled hypothermia devices the cerebral insult due to asphyxia can be reduced & severe sequlae of HIE can be prevented.

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