Use of Hypothermia in the Asphyxiated Infant

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Clinical Case

A 32 year old primiparous woman presented with decreased fetal movements and her cardiotocograph (CTG) showed sinusoidal trace. She was taken up for emergency Cesarean section. A 39 weeks female baby was delivered. She was pale; there was no spontaneous breathing and the heart rate was less than 100/min. She was dried and wrapped, intubated and CPR was commenced. Venous cord pH was 6.9, base deficit 23 mmol/L and pCO_2 72 mmHg; arterial cord pH was 7.01, base deficit 16 mmol/L and pCO_2 50mmHg.

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Introduction

Hypoxic ischemic encephalopathy [HIE] remains a devastating complication in term newborn infants occurring in about 1-6 babies per 1000 live births [1]The risk of death or severe disability in survivors of moderate to severe HIE is about 60%. Even infants without motor impairments may have cognitive deficits, poor scholastic achievement and often require special educational needs [2,3] Asphyxia is the impairment of placental gas exchange leading to hypoxemia, hypercapnia and metabolic acidosis in the fetus. The hypoxic ischemic insult results in encephalopathy and other organ dysfunction (liver, renal etc.) Some brain cells die during the hypoxic-ischemic insult (primary cell death). Following the latent phase whose duration depends on the severity of the hypoxic-ischemic insult [4], secondary energy failure with delayed neuronal

death occurs which can last for several days [5]. During the latent phase, there is an apparent normalisation of cerebral metabolism followed by initiation of cytotoxic mechanisms, activation of necrosis and apoptosis pathways, release of excess neurotransmitters leading to excitotoxicity during the secondary energy failure [5] .

Hypothermia

Experimental studies & mechanism

Many years of experimental work support the use of hypothermia after hypoxic-ischemic insult [6]. Animal studies have shown a reduction in cerebral injury and improvement in neurological function, when the core temperature is reduced by 3-5°C after the hypoxic-ischemic insult [7-9]. The precise neuroprotective mechanism of hypothermia is not fully described; however hypothermia suppresses many of the pathways leading to delayed cell death. Hypothermia reduces cellular metabolic demands [10], reduces excessive accumulation of cytotoxins such as glutamate, nitric oxide and oxygen free radicals [11], and suppresses necrosis and apoptosis [12, 13]

Clinical Trials

Three published multicentre randomised controlled trials of hypothermia in newborn infants with HIE and two trials which presented only the results [14, 15] have shown improved outcome in the cooled group. The CoolCap trial used selective head cooling with mild systemic hypothermia (rectal temperature 34-35° C) commenced within 5.5 h of age for 72 h; and showed an independent protective effect of hypothermia on the primary outcome of death or disability at 18 months (odds ratio 0.52, 95% CI 0.28–0.70, p=0.04) in the full study population (n=218), when modified Sarnat score, Apgar scores, aEEG background and seizures were used in logistic regression [16, 17] The NICHD trial of whole body cooling (oesophageal temperature 33.5°C for 72h) showed a significant reduction in the risk of death and moderate to severe disability at 18 months in the hypothermia group [18]. The TOBY trial of whole body cooling (rectal temperature 33.5°C for 72h) did not show a significant effect on the same primary outcome, however there was significant improvement in neurologic outcome in survivors from the hypothermic group [19]. The preliminary results of additional primary trials from Shanghai, China (Wen-hao Zhou and colleagues), neo.nEuro.network study [15] and ICE trial [14] further support a beneficial effect of hypothermia. Systematic review of the three trials showed a significant reduction of combined rate of death and severe disability with a number needed to treat of 9 (95% CI 5 to 25) and increased normal survival (survival without cerebral palsy and with MDI and PDI>84 and normal vision and hearing) with a NNT of 8 (95% CI 5 to 7) [20]. The eligibility criteria used in the clinical trials are given in Table 1.

Current situation

Many countries and individual hospitals have introduced cooling as standard of care for term infants who fulfill the trial entry criteria for therapeutic cooling but others are awaiting guidelines from International Liaison committee on Resuscitation ILCOR (http://www.ilcor.org/en/home/). National Institute for health and Clinical Excellence (NICE) in the UK recommended recently that cooling after perinatal asphyxia should be supported (http://guidance.nice.org.uk/IPG347/Guidance/pdf/English) .

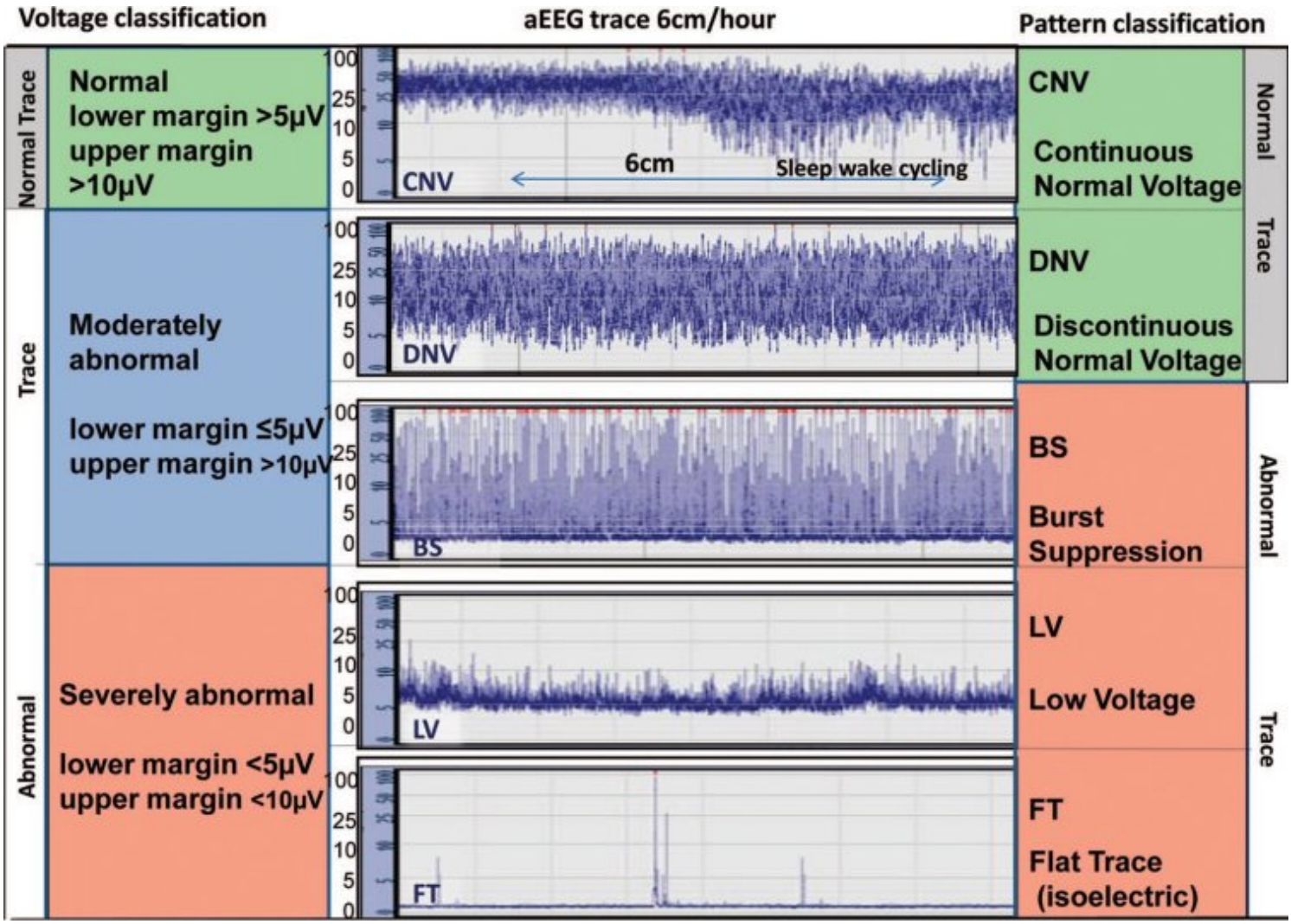
Table 1. Eligibility Criteria for Therapeutic Hypothermia

Entry criteria ≥ 36 weeks' gestation	CoolCap &TOBY trial	NICHD trial
Metabolic A	pH < 7 OR Base deficit ≥ 16 mmol/L in the first hour OR Apgar ≤ 5 @ 10 min OR 10 min continued resuscitation	pH ≤ 7 OR Base deficit ≥ 16 mmol/L in the first hour If blood gas unavailable, pH 7.01-7.15, or base deficit between 10 and 15.9 then Acute perinatal event AND Apgar ≤ 5 @ 10 min OR ≥ 10 min assisted ventilation
Neurology B	Lethargy, stupor, or coma AND One or more of below • Hypotonia • Abnormal reflexes : oculomotor / pupillary • Suck: weak / absent • Clinical seizures	One or more signs in at least 3 categories • Consciousness: Lethargy, stupor or coma • Tone: Hypotonia, flaccid • Autonomic : Pupils – constricted / dilated / unreactive; • Heart rate – Bradycardia / variable ; • Respiration- periodic breathing / apnea • Primitive reflex: suck : weak / absent • Moro: incomplete / absent • Spontaneous activity : decreased / nil activity • Posture: distal flexion / complete extension. • Clinical seizures
aEEG C	Abnormal aEEG	No aEEG

Abnormal amplitude integrated EEG [21] can be of moderately to severely abnormal category in the voltage classification system [22]; or discontinuous normal voltage to flat trace in the pattern classification system [21, 23].

Figure 1. Classifications of 5 example traces by using the pattern recognition method

(right) and voltage method (left) to assess the aEEG background at 3 to 6 hours of age. (Click image to enlarge)



From Thoresen M, et al. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010 Jul;126(1):e131-9. PMID:9563847 Reprinted with permission of The American Academy of Pediatrics

Clinicians who do not have access to the technology or the expertise of aEEG can use the clinical criteria as enlisted in the NICHD criteria in the table above. It is highly recommended to adhere to the eligibility criteria of the trials while considering asphyxiated term infants for cooling with regards to the gestation, duration, depth and the therapeutic window, and cooling infants outside these criteria will be experimental.

Management of Asphyxiated Infants in the Delivery Suite

If severe clinical asphyxia is apparent, the overhead heater should be turned off as soon as effective ventilation and heart rate is achieved. Active heating in the transport incubator and wearing hats are actively discouraged. Rectal (6cm from the anal verge) or oesophageal temperature monitoring should be commenced within 20 minutes of birth [24]. Active cooling is rarely needed as the reduced heat production and impaired metabolism will reduce the core temperature.

Cooling devices

There are several servo-controlled cooling devices which can be used to cool and maintain core temperature at the target of 33.5°C during transport. The following table from the review about techniques of cooling devices [25] lists the available devices. A recent comparison of Tecotherm TS med 200,MTRE criticool and CoolCap showed that these devices respectively maintained target temperature for 81%, 97% and 76% of the duration of cooling. There was no difference in mean BP or HR during cooling between the the three methods. There was greater variation in rectal temperature during rewarming in selective head cooling compared to whole body cooling [26].

Table 2. High-Tech Cooling Devices (Click image to enlarge)

High-tech cooling devices

Parameter	Blanketerol III	Tecotherm TS med 200	MTRE CritiCool	Cool-Cap	Tecothermo-Servo
Design	Mattress and wraps	Mattress	Body wraps	Caps over head along with radiant warmers	Mattress (can be wrapped around if required)
Coolant	Water	Alcohol-based	Water	Water	Alcohol-based
Type of cooling	Whole body	Whole body	Whole body	Selective head cooling	Whole body
Precooling required	Yes	No	No	No	No
Typical site of record	Oesophageal	Rectal	Rectal	Rectal	Rectal
Induction	Rapid, overcooling occurs	Rapid, overcooling occurs	Rapid, overcooling is minimal		Rapid, overcooling is minimal
Maintenance	Low nursing input	High nursing input	Low nursing input	High nursing input	Minimal nursing input (must check that the rectal probe is in situ)
Rewarming	Manual	Manual	Semi-automated	Manual	Fully automated
User-friendliness of panel	Water flow indicator	Digital temperature display	Graphic and digital displays	LCD touch screen Colour LCD	Graphic and digital displays with three different modes of operation
Effective cooling time	Low	Low	High	Low	High
Recurrent expenses	Cooling wraps	Nil	Cooling wraps	Cooling cap	Cooling mattress and coolant top-ups
Weight (kg)	55.3	10	35	52	7
Portable	No	Yes	No	No	Yes
Use in transport	No	No	Yes	No	Yes
Battery operation	No	No	No	No	Yes
Space required (cm)	43.2 × 43.2 × 950.2	42.0 × 19.0 × 35.0	26.0 × 62.5 × 94.0	132.1 × 43.4 × 56.6	42.0 × 19.0 × 35.0

LCD, liquid crystal display.

Table 3. Low-Tech Cooling Devices (Click image to enlarge)

Low-tech cooling devices

	Natural cooling	Water bottles	Fan	Gels	PCM
Design	Occurs in settings without radiant warmers	Whole-body cooling with mattress made of three water bottles laid sideways and filled with cool tap water	Servo-controlled fan. Overcooling prevented by servo-controlled radiant warmer	Soft, cold gel bags (12 cm × 12 cm, 250 g, refrigerator kept at 7–10 °C) applied to the head. Infant warmed with radiant warmer	Naked baby on PCM mattress (melting point 32 °C). Blankets used when needed
Induction time	Soon after birth	Within 1 h	Within 1 h	Within 1 h	Within 1 h
Maintenance	May last up to 15 h, if radiant warmers not used	Core/rectal temp. 33–34 °C	Rectal temp. 33.4–33.7 °C	Rectal temp. at 33–34 °C	Rectal temp. 33–34 °C
Rewarming	Passive and slow, generally <0.5 °C/h	Passive and slow, generally <0.5 °C/h	Stepwise increase of radiant warmer	Stepwise increase of radiant warmer	Passive and slow, generally <0.5 °C/h
Ambient temperature	<26 °C	25–26 °C	24 °C	24 °C	<30 °C
Shivering	No	No	Yes	Yes	No
Temperature stability	Poor	Acceptable	Acceptable	Variable	Acceptable

PCM, phase-changing material.

Tables 2 and 3 reprinted from Semin Fetal Neonatal Med doi:10.1016/j.siny.2010.03.006 .Robertson NJ , et al. Techniques for therapeutic hypothermia during transport and in hospital for perinatal asphyxial encephalopathy Copyright (2010) with permission from Elsevier

Initiation of Therapeutic Hypothermia

Initiation of therapeutic hypothermia comprise of induction, maintenance and rewarming phases. Experimental studies indicate that the earlier the cooling is commenced the better the outcome [27]. The natural reduction in core temperature after asphyxia and avoiding active warming has reduced the induction phase in most situations. A systematic neurological assessment as in Table 1 with aEEG assessment is needed to decide if the infant qualifies for therapeutic hypothermia. In the clinical trials, a minimum of 20 minutes of aEEG was recorded within the first 6 hours to decide eligibility. aEEG should be monitored for a longer duration preferably 6 hours before concluding the ineligibility for therapeutic hypothermia. If the infant does not qualify for hypothermia, slow rewarming can be commenced at a rate of 0.2°-0.4°C/h. There can be overshooting of the target temperature during induction of cooling in some cases. However, with the servo-controlled devices, overshoot does not occur [26].

Maintenance Phase

The target core temperature of 33.5°C and 34.5°C is maintained for 72 hours with whole body cooling and selective head cooling respectively. The goal during the maintenance phase is to avoid large fluctuations in the core temperature, monitor and maintain physiology within the normal range. Though there is no data delineating the independent effect of the fluctuations of core temperature on the neurological outcome, it is possible that large temperature fluctuations can lead to unfavourable cardiovascular and cerebral hemodynamic fluctuations.

Re-warming Phase

In animal studies, fast re-warming may transiently affect the cerebral blood flow- metabolism balance and affect the neuronal cytoskeleton [28, 29]. During re-warming, seizures, hypotension [24], hypoglycaemia or hypokalemia can occur. Seizures usually respond to anticonvulsants; slowing down the pace of rewarming or halting the rewarming briefly is recommended [24]. During rewarming, the dilation of skin blood vessels and decreased effective blood volume can lead to hypotension if the intravascular compartment is not adequately filled. Though the clinical trials have re-warmed at a rate of 0.5°C/h, we suggest a slower rate of 0.2°C/h in the first two hours and 0.4°C/h thereafter to reach the normothermic target of 36.5°C [30]. We also recommend monitoring core temperature for a further 24 hours after attaining normothermia to avoid

hyperthermia after rewarming, as hyperthermia (> 36.5°C) can affect the neurodevelopment outcome [30, 31].

Intensive Care During Hypothermia

Ventilation

Most of the asphyxiated infants present with mixed metabolic and respiratory acidosis. Most severely asphyxiated infants need respiratory support. We aim to maintain normocapnia, as fluctuations in pCO2 may worsen the cerebral blood flow perturbations in the asphyxiated infants. However, their own and compensatory respiratory drive often causes hypocapnia, despite mechanically ventilated. Though there is evidence for hypocapnia causing adverse neurodevelopmental outcome in preterm ventilated infants [32, 33], this has not been documented in the term infants and spontaneously breathing hypocapnic postasphyxic term infants can have good short term neurologic outcome [34]. Hypocapnia < 2.6 KPa (OR 2.34, 95% CI 1.02 to 5.37) and hyperoaxemia >26.6KPa (OR 3.85, 95% CI 1.67 to 8.88) individually increased the risk of adverse outcome in normothermic asphyxiated term newborn infants, and the combination of both hypocapnia and hyperoxaemia further increased the risk of adverse outcome (OR 4.56, 95% CI 1.4 to 14.9) [35].
The decreased metabolism associated with hypothermia will reduce the CO_2 production [10] The incidence of Persistent Pulmonary Hypertension (PPHN) in the clinical trials is similar in the normothermic and hypothermic groups [16, 18, 19]. In asphyxiated infants with PPHN, we provide hypothermia along with the standard therapy for PPHN (i.e, high Fraction of inspired oxygen and inhaled nitric oxide). There is no difference in the occurrence of PPHN between selective head cooling or whole body cooling [36].

The partial pressure of CO_2 is reduced by 4% per degree centigrade reduction in core temperature [37]. There is higher cerebral blood flow with higher PCO_2 [38] and reduced threshold for seizures with hypocapnic alkalosis [39]. Hence, in ventilated infants cooled to 33.5°C, we shift the normal PCO_2 range of 36-44mmHg at 37°C to 41-51mm Hg. We use the same normothermic range for pO_2 and pH as the influence of temperature on these variables is less [24].

Cardiovascular function

Hypothermia decreases cardiac output and heart rate (sinus bradycardia). No large effect on stroke volume, blood pressure and cardiac performance has been reported during hypothermia [40, 41]. Hypothermia does not cause arrhythmia; in fact low temperature stabilizes cardiac conduction and is a recommended treatment for junctional ectopic tachycardia [42]. Hypotension needs prompt correction as it may affect cerebral blood flow in the face of deranged cerebral autoregulation.

Central nervous system

Electrical and clinical Seizures should be actively monitored using aEEG and treated, as seizures worsen neurodevelopmental outcome independent of the severity of hypoxic-ischemic brain injury [43]. Though hypothermia has been reported to reduce the duration of seizures in experimental studies, [9, 44] there has been no substantial difference in the clinical trials [16, 18, 19].

Infection

The incidence of proven sepsis in the normothermic and hypothermic groups in the 3 trials vary between 2 and 12%. Infection is not an exclusion criterion for cooling as this diagnosis is rarely known at birth. There is no evidence that infection in asphyxiated newborns was worsened by hypothermia.

Glucose and Electrolytes

Glycemic control and electrolytes particularly magnesium should be maintained within the normal ranges. Hypo or hyperglycemia may affect neuroprotection. Magnesium can increase the threshold for shivering. There is experimental evidence for the neuroprotective effect of magnesium [45]. Postnatal magnesium sulphate infusion in asphyxiated newborn infants maintaining Mg ≥ 1.2mmol/L improved the short term outcome [46]. In adults, Mg > 1mmol/L have been shown to reduce shivering during HT. We suggest to keep plasma Mg~ 1mmol/L. However supranormal levels (> 2.5 mmol/L) can lead to unacceptable hypotension and respiratory depression [47].

Clotting/bleeding disorder

Asphyxiated neonates often have abnormal clotting. Ideally one would like to correct this first and then cool, however the therapeutic time window for cooling will be lost. Although it is a fact that hypothermia prolongs bleeding time, there was no difference between normothermic and hypothermic infants in the trials regarding the complication related to abnormal coagulation. Nonetheless, clinical increased bleeding tendency should be treated as soon as possible, before any clotting results are available to avoid treatment delay.

Hypothermia in Low Resourced Settings

In low resourced settings, there are many ethical issues to be considered. It is argued that evidence for hypothermia comes from countries who can afford decent health care and extrapolating the evidence may not be appropriate. The patient population is very likely to differ with either more of severely asphyxiated infants or their early demise, can leave a population of moderately asphyxiated infants. Most of these infants are naturally hypothermic which may offer natural neuroprotection. Some argue that infants in low resource settings should be maintained normothermic and hypothermia is still experimental, which is ethically debatable. Though cooling can be achieved with many low cost techniques, there should be adequate counseling of parents of the long term outcome, where the burden of looking after infants with disabilities is unaffordable and one often visits the question of acting in the best interest of the infant and the risk benefit balance. The ongoing trials in the low resource settings must take this into account during the informed consenting process. There was a trend of increased poor outcome in the cooled group in the two pilot studies undertaken in Uganda [48] and India.

Future of Neuroprotection in Asphyxiated Infants

NNT of 9 is a fantastic result for the three first ever large trials in newborns with perinatal asphyxia. It is likely that the effectiveness of hypothermia could be improved by improved protocols and intensive care. Many research groups study HT combined with other drugs. Inhaling the inert gas Xenon while hypothermic doubles the neuroprotection in both small [49] and large animal model [50]. Anticonvulsants [51, 52] and erythropoietin [53] have yielded neuroprotection in animal and human studies. However, there is a lack of data on combination of these with optimum duration of HT. Entering data locally as well as internationally like the Vermont Oxford Network is important to document outcome in the clinical setting. This part of the journey may be less exciting than the previous one but equally important. The outcome after specialist treatment improves with experience and patient volume in the treating institutions [21]. To develop and validate a new treatment and improve protocols rigorous documentation and follow up is needed. While it is advisable to centralise the management of medically very sick infants in cooling centres, it is equally important to educate all hospitals with obstetric and newborn care, the entry criteria for cooling therapy, diagnostic evaluation and the initiation of early cooling before transport team arrives.

References

1. Finer NN, Robertson CM, Richards RT et al. Hypoxic-ischemic encephalopathy in term neonates: perinatal factors and outcome. The Journal of pediatrics. 1981;98:112-117 PMID: 7452386

2. Robertson CM, Finer NN. Long-term follow-up of term neonates with perinatal asphyxia. Clinics in perinatology. 1993;20:483-500 . PMID: 7689432

3. Gunn AJ. Cerebral hypothermia for prevention of brain injury following perinatal asphyxia. Curr Opin Pediatr. 2000;12:111-115PMID: 10763759

4. Iwata O, Iwata S, Thornton JS et al. "Therapeutic time window" duration decreases with increasing severity of cerebral hypoxia-ischaemia under normothermia and delayed hypothermia in newborn piglets. Brain Res. 2007;1154:173-180 .PMID: 17475224

5. Gunn AJ, Thoresen M. Hypothermic neuroprotection. NeuroRx. 2006;3:154-169 PMID: 16554254

6. Thoresen M. Cooling the newborn after asphyxia - physiological and experimental background and its clinical use. Semin Neonatol. 2000;5:61-73 PMID:10802751

7. Thoresen M, Penrice J, Lorek A et al. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. Pediatric Research. 1995;37:667-670 PMID:7603788

8. Bona E, Hagberg H, Loberg EM et al. Protective effects of moderate hypothermia after neonatal hypoxia-ischemia: short- and long-term outcome. Pediatric Research. 1998;43:738-745 PMID:9621982

9. Tooley JR, Satas S, Porter H et al. Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. Annals of neurology. 2003;53:65-72. PMID:12509849

10. Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in Mammalian central nervous system. J Cereb Blood Flow Metab. 2003;23:513-530 PMID:12771566

11. Thoresen M, Satas S, Puka-Sundvall M et al. Post-hypoxic hypothermia reduces cerebrocortical release of NO and excitotoxins. Neuroreport. 1997;8:3359-3362 PMID:9351672

12. Edwards AD, Yue X, Squier MV et al. Specific inhibition of apoptosis after cerebral hypoxia-ischaemia by moderate post-insult hypothermia. Biochem Biophys Res Commun. 1995;217:1193-1199. PMID:8554576

13. Northington FJ, Graham EM, Martin LJ. Apoptosis in perinatal hypoxic-ischemic brain injury: how important is it and should it be inhibited? Brain research. 2005;50:244-257 PMID:16216332

14. Jacobs S, Stewart M, Inder T et al. ICE: the Australian cooling trial for hypoxic-ischemic encephalopathy-in hospital outcomes. Proceedings of the Hot Topics in Neonatology Conference. Washington DC, 2008

15. Simbruner G, Mittal R, Rohlman F, Muche R. European nEURO.network trial. Proceedings of the Hot Topics in Neonatology Conference. Washington DC, 2008

16. Gluckman PD, Wyatt JS, Azzopardi D et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005;365:663-670 PMID:15721471

17. Gunn AJ, Gluckman P, Wyatt JS et al. Selective head cooling after neonatal encephalopathy - author's reply. The Lancet. 2005;365:1619-1620

18. Shankaran S, Laptook AR, Ehrenkranz RA et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. The New England journal of medicine. 2005;353:1574-1584 PMID:16221780

19. Azzopardi DV, Strohm B, Edwards AD et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. The New England journal of medicine. 2009;361:1349-1358 PMID:19797281

20. Edwards AD, Brocklehurst P, Gunn AJ et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ (Clinical research ed. 2010;340:c363.PMID:20144981

21. Thoresen M, Westaas L, Liu X, DeVries L. Amplitude integrated EEG and onset of sleep wake cycling is not predictive during hypothermia. Pediatrics. 2010:(in press)

22. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. Pediatrics. 1999;103:1263-1271.PMID:10353940

23. Toet MC, Hellstrom-Westas L, Groenendaal F et al. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. Archives of disease in childhood. 1999;81:F19-

23 PMID:10375357

24. Thoresen M. Supportive care during neuroprotective hypothermia in the term newborn: adverse effects and their prevention. Clinics in perinatology. 2008;35:749-763, vii. PMID:19026338

25. Robertson NJ, Kendall GS, Thayyil S. Techniques for therapeutic hypothermia during transport and in hospital for perinatal asphyxial encephalopathy. Semin Fetal Neonatal Med. 2010. PMID:20399718

26. Hoque N, Chakkarapani E, Liu X, Thoresen M. A Comparison of Cooling Methods used in Therapeutic Hypothermia for Perinatal Asphyxia. Pediatrics. 2010;press. PMID:20530071

27. Gunn AJ, Gunn TR, Gunning MI et al. Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep. Pediatrics. 1998;102:1098-1106. PMID:9794940

28. Enomoto S, Hindman BJ, Dexter F et al. Rapid rewarming causes an increase in the cerebral metabolic rate for oxygen that is temporarily unmatched by cerebral blood flow. A study during cardiopulmonary bypass in rabbits. Anesthesiology. 1996;84:1392-1400. PMID:8669681

29. Maxwell WL, Watson A, Queen R et al. Slow, medium, or fast re-warming following post-traumatic hypothermia therapy? An ultrastructural perspective. Journal of Neurotrauma. 2005;22:873-884. PMID:16083354

30. Laptook A, Tyson J, Shankaran S et al. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics. 2008;122:491-499. PMID:18762517

31. Wyatt JS, Gluckman PD, Liu PY et al. Determinants of outcomes after head cooling for neonatal encephalopathy. Pediatrics. 2007;119:912-921 . PMID:17473091

32. Greisen G, Munck H, Lou H. Severe hypocarbia in preterm infants and neurodevelopmental deficit. Acta paediatrica Scandinavica. 1987;76:401-404 . PMID:2440226

33. Ikonen RS, Janas MO, Koivikko MJ et al. Hyperbilirubinemia, hypocarbia and periventricular leukomalacia in preterm infants: relationship to cerebral palsy. Acta Paediatr. 1992;81:802-807 . PMID:1421887

34. Engle WD, Laptook AR, Perlman JM. Acute changes in arterial carbon dioxide tension and acid-base status and early neurologic characteristics in term infants following perinatal asphyxia. Resuscitation. 1999;42:11-17 . PMID:10524727

35. Klinger G, Beyene J, Shah P, Perlman M. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? Archives of disease in childhood. 2005;90:F49-52 PMID:15613575

36. Sarkar S, Barks JD, Bhagat I et al. Pulmonary dysfunction and therapeutic hypothermia in asphyxiated newborns: whole body versus selective head cooling. American Journal of Perinatology. 2009;26:265-270. PMID:19021092

37. Bradley AF, Severinghaus JW, Stupfel M. Effect of temperature on PCO2 and PO2 of blood in vitro. Journal of applied physiology. 1956;9:201-204. PMID:13376428

38. Leahy FA, Cates D, MacCallum M, Rigatto H. Effect of CO2 and 100% O2 on cerebral blood flow in preterm infants. Journal of applied physiology. 1980;48:468-472. PMID:6768701

39. Schuchmann S, Schmitz D, Rivera C et al. Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis. Nature medicine. 2006;12:817-823. PMID:16819552

40. Fugelseth D, Satas S, Steen PA, Thoresen M. Cardiac output, pulmonary artery pressure, and patent ductus arteriosus during therapeutic cooling after global hypoxia-ischaemia. Archives of disease in childhood. 2003;88:F223-228. PMID:12719397

41. Zhou WH, Shao XM, Zhang XD et al. [Effects of hypothermia on cardiac function in neonates with asphyxia]. Zhonghua er ke za zhi. 2003;41:460-462. PMID:14749008

42. Walsh EP, Saul JP, Sholler GF et al. Evaluation of a staged treatment protocol for rapid automatic junctional tachycardia after operation for congenital heart disease. Journal of the American College of Cardiology. 1997;29:1046-1053 . PMID:9120158

43. Glass HC, Glidden D, Jeremy RJ et al. Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury. The Journal of pediatrics. 2009;155:318-323 . PMID:19540512

44. Bennet L, Dean JM, Wassink G, Gunn AJ. Differential effects of hypothermia on early and late epileptiform events after severe hypoxia in preterm fetal sheep. Journal of neurophysiology. 2007;97:572-578 PMID:17093117

45. Spandou E, Soubasi V, Papoutsopoulou S et al. Neuroprotective effect of long-term MgSO4 administration after cerebral hypoxia-ischemia in newborn rats is related to the severity of brain damage. Reprod Sci . 2007;14:667-677.PMID:18000228

46. Bhat MA, Charoo BA, Bhat JI et al. Magnesium sulfate in severe perinatal asphyxia: a randomized, placebo-controlled trial. Pediatrics. 2009;123:e764-769. PMID:19349375

47. Levene M, Blennow M, Whitelaw A et al. Acute effects of two different doses of magnesium sulphate in

infants with birth asphyxia. Archives of disease in childhood. 1995;73:F174-177. PMID:8535876

48. Robertson NJ, Nakakeeto M, Hagmann C et al. Therapeutic hypothermia for birth asphyxia in low-resource settings: a pilot randomised controlled trial. Lancet. 2008;372:801-803. PMID:18774411

49. Hobbs C, Thoresen M, Tucker A et al. Xenon and hypothermia combine additively offering long term functional and histopathological neuroprotection after neonatal hypoxia-ischemia. Stroke; a journal of cerebral circulation. 2008;39:1307-1313. PMID:18309163

50. Chakkarapani E, Dingley J, Liu X et al. Xenon Enhances Hypothermic Neuroprotection in Asphyxiated Newborn Pigs. Annals of neurology. 2010;(in press). PMID:20658563

51. Liu Y, Barks JD, Xu G, Silverstein FS. Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats. Stroke; a journal of cerebral circulation. 2004;35:1460-1465. PMID:15105511

52. Schubert S, Brandl U, Brodhun M et al. Neuroprotective effects of topiramate after hypoxia-ischemia in newborn piglets. Brain Res. 2005;1058:129-136. PMID:16139822

53. Zhu C, Kang W, Xu F et al. Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. Pediatrics. 2009;124:e218-226.PMID:19651565