TREATMENT OF HYPOXIC ISCHEMIC ENCEPALOPATHY AND CEREBRAL HYPOTHERMIA

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Disclosure statement

- I declare that I do not have any relevant financial interest or other relationship with a commercial entity.
- I will not discuss any unlabeled use of a commercial product in this presentation
- I will share some of the results of 'Mag-Cool Study' which preliminary results are sent to a Journal to be published.

Treatment of hypoxic ischemic encephalopathy

Following initial resuscitation and stabilization, treatment of hypoxic-ischemic encephalopathy (HIE) is largely supportive and should focus on adequate ventilation and perfusion, careful fluid management, avoidance of hypoglycemia and hyperglycemia and treatment of seizures.

Perfusion and Blood Pressure Management

a) Studies indicate that a mean blood pressure (BP) above 35-40 mm Hg is necessary to avoid decreased cerebral perfusion.
b) Hypotension is common in infants with severe hypoxic-ischemic encephalopathy and is due to myocardial dysfunction, capillary leak syndrome, and hypovolemia; hypotension should be promptly treated.
c) Dopamine or dobutamine can be used to achieve adequate cardiac output in these patients.
d) Avoiding iatrogenic hypertensive episodes is also important.

Fluid and Electrolytes Management

a) Because of the concern for acute tubular necrosis (ATN) and syndrome of inappropriate antidiuretic hormone (SIADH) secretion, fluid restriction is typically recommended for these infants until renal function and urine output can be evaluated. However, this recommendation is not based on evidence from randomized controlled trials.

b) Therefore, fluid and electrolyte management must be individualized on the basis of clinical course, changes in weight, urine output, and the results of serum electrolyte and renal function studies.

Prophylactic theophylline

- The role of prophylactic theophylline, given early after birth, in reducing renal dysfunction after hypoxic-ischemic encephalopathy has been evaluated in 3 small randomized controlled trials. In these studies, a single dose of theophylline (5-8 mg/kg) given within 1 hour of birth resulted in (1) decreased severe renal dysfunction (defined as creatinine level >1.5 mg/dL for 2 consecutive days); (2) increased creatine clearance; (3) increased glomerular filtration rate (GFR); and (4) decreased b2 microglobulin excretion. The clinical significance of these findings remains unclear.
- Larger studies are warranted to confirm the safety of adenosine inhibitor use following hypoxic-ischemic encephalopathy.

Fluid and Electrolytes Management

a) Fluid and glucose homeostasis should be achieved.
b) Avoid hypoglycemia and hyperglycemia because both may accentuate brain damage.
c) Hypoglycemia in particular should be avoided. In a retrospective study, initial hypoglycemia (< 40 mg/dL) is significantly associated with adverse neurological outcomes.

Treatment of Seizures

- Hypoxic-ischemic encephalopathy is the most common cause of seizures in the neonatal period. Seizures are generally self-limited to the first days of life but may significantly compromise other body functions, such as maintenance of ventilation, oxygenation, and blood pressure.
- Additionally, studies suggest that seizures, including asymptomatic electrographic seizures, may contribute to brain injury and increase the risk of subsequent epilepsy.
- Current therapies available to treat neonates with seizures include phenobarbital, phenytoin, and benzodiazepines. Phenobarbital has been shown to be effective in only 29-50% of cases, Phenytoin only offers an additional 15% efficacy.

Mechanisms of Action of Hypothermia (HT)

Neuroprotection

Experimental and clinical evidence have confirmed the neuroprotective effects of hypothermia. The mechanism(s) underlying the beneficial properties of HT are multifactorial and include reductions in the cerebral metabolism of glucose and oxygen consumption; pathways mediating accumulation of excito-toxic neurotransmitters, intracellular acidosis, and the influx of intracellular calcium and oxygen free radical production;-alterations in the expression of "cold shock proteins"; reduction in brain edema; minimizing the risk of thrombosis; and reducing the risk of epileptic activities through electrical stabilizing properties.

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. Liu L, Yenari MA. Therapeutic hypothermia: neuroprotective mechanisms Front Biosci 2007;12:816–825.

Hypothermia Therapy

Extensive experimental data suggest that mild hypothermia (3-4°C below baseline temperature) applied within a few hours (no later than 6 h) of injury is neuroprotective.

The neuroprotective mechanisms are not completely understood. Possible mechanisms include

(1) reduced metabolic rate and energy depletion;

(2) decreased excitatory transmitter release;

(3) reduced alterations in ion flux;

(4) reduced apoptosis due to hypoxic-ischemic encephalopathy; and

(5) reduced vascular permeability, edema, and disruptions of blood-brain barrier functions.

Hypothermia inclusion criteria

- Near-term infants born at 36 weeks' gestation or more with birth weight of 1800-2000 g or more, younger than 6 hours at admission
- Evidence of acute event around the time of birth - Apgar score of 5 or less at 10 minutes after birth (In the study by Shankaran et al, this needed to be in conjunction with either evidence of acute perinatal event or need for assisted ventilation for at least 10 min.), severe acidosis, defined as pH level of less than 7 or base deficit of 16 mmol/L or less (cord blood or any blood gas obtained within 1 h of birth), continued need for resuscitation at 10 minutes after birth
- Evidence of moderate to severe encephalopathy at birth - Clinically determined (at least 2 of the following: lethargy, stupor, or coma; abnormal tone or posture; abnormal reflexes [suck, grasp, Moro, gag, stretch reflexes]; decreased or absent spontaneous activity; autonomic dysfunction [including bradycardia, abnormal pupils, apneas]; and clinical evidence of seizures), moderately or severely abnormal amplitude-integrated electroencephalography (aEEG) background or seizures (CoolCap and TOBY)

Inclusion criteria

Study	Enrollment criteria	Method	Duration of cooling	N	Time of Follow-up	Results
Gluckman et al (2005)	< 6h pH<7.0, BE≥16 Apgar≤5 @ 10′ Encephalopathyby aEEG	Head cooling	72h 34-35°C Rectal	110 (H) 108 (N)	18 mth	No effect in most severe aEEG Death or severe disabilty: 66% (N) vs 48% (H) *; NNT= 6 Severe neuromotor disability: 28% (N) vs. 12% (H) * MDI: 77 (N) vs. 85 (H) * PDI: 85 (N) vs. 90 (H) *
Eicher et al (2005)	< 6h pH<7.0, BE≥14 Apgar≤5 @ 10′ Clinical enceph	Whole body cooling	48h 33-33.5°C Rectal	32 (H) 33 (N)	12 mth	Death or mod/severe disability: 84% (N) vs. 52% (H) * PDI <70: 64% (N) vs 24% (H) * Mortality: 42% (N) vs 31% (H)
Shankaran et al (2005)	< 6h pH<7.0, BE>16 Clinical enceph	Whole body cooling	72h 33-33.5°C Esophageal	102 (H) 106 (N)	18 mth	Death or mod/severe disability: 62%(N) vs. 45%(H) ** NNT=6 Mortality: 36% (N) vs. 24%(H)

H= hypothermia group, N= normothermia group

* p<0.05 vs. N; ** p<0.01 vs. N

The Goals of Hypothermia Therapy

- Reduce the risk for disability and death in affected term babies
- Reduce brain damage in surviving babies

Passive Cooling Safety

- Passive Cooling during transport of asphyxiated term newborns
  - 3 year retrospective study to evaluate efficacy and safety of passive cooling during transport
  - n=43, 27=passive cooling
  - Results: Passively cooled infants reached target temperature for cooling significantly earlier than those not passively cooled.
  - Only 1 infant was overly cold, after prolonged resuscitation and 2 emergent procedures prior to transport

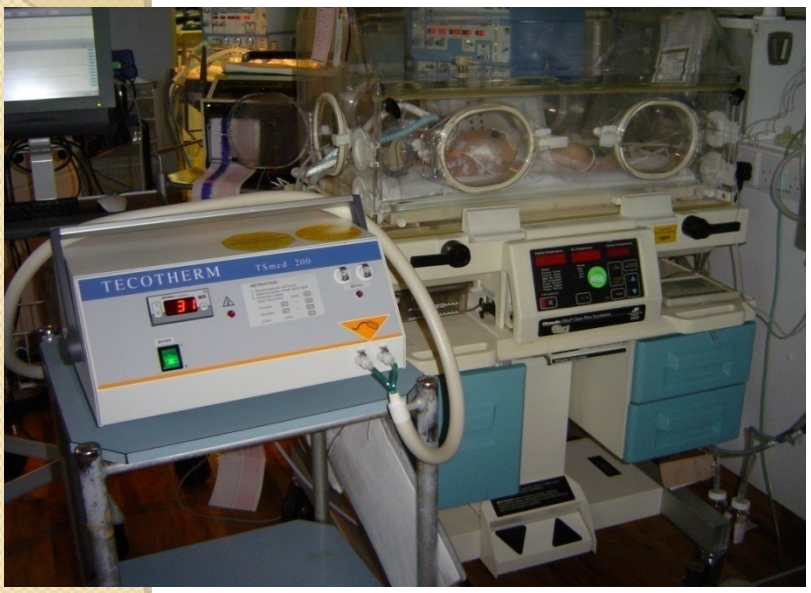
Initiating Passive cooling

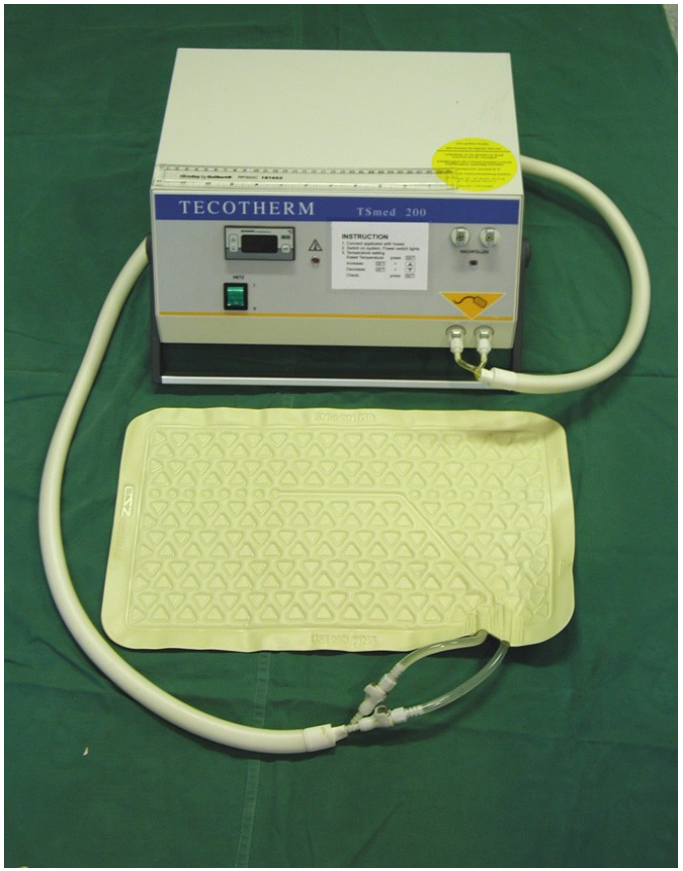
- In the Delivery Room
- Upon tertiary center's request
  - Turn heat source off
  - Monitor temperature q15min
  - Avoid TOO low of a temp<34°C (93.2°F)
  - Avoid HYPERthermia >36.5°C (97.7°F)
    - Worsened outcomes
- Establish IV access
- Observe for seizures
- Obtain blood gas

Total Body Cooling

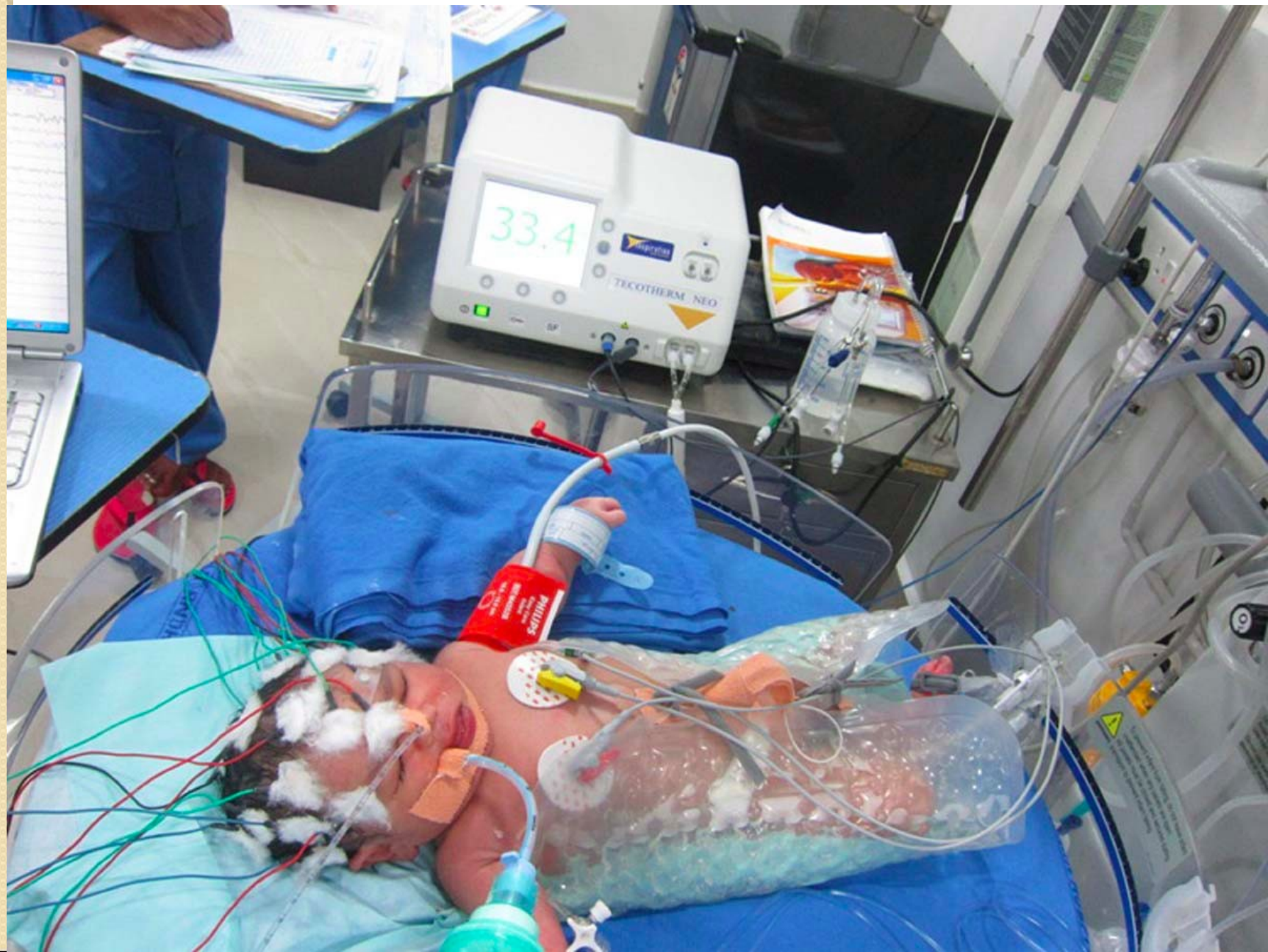
- Cooling Blanket
- Cooling Wrap
- Monitoring Goals
  - Core Temperature goal = 33-34C*
  - 72 hours of cooling
  - Slow Re-warming
    - Over 6 to 12 Hours

Whole body cooling using a manually controlled cooling blanket





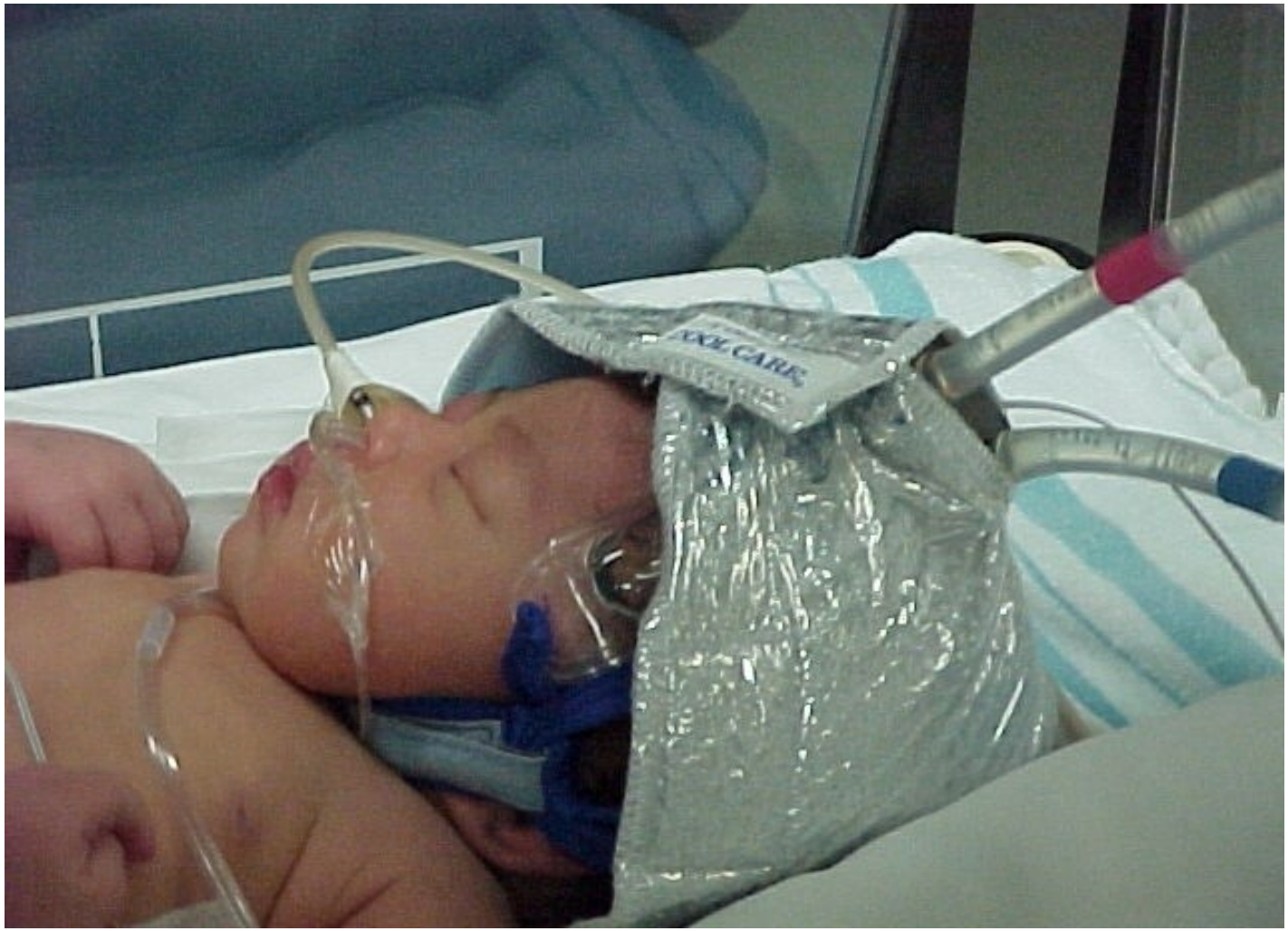
Whole body cooling using a servo-controlled device



Head Cooling

- FDA approved for treatment of HIE
- Neuroprotection while minimizing side-effects of hypothermia

The 'CoolCap'



CoolCap

- Cooling cap with circulating water placed on head for 72 hours
- Reduced brain temperature
- Decreased secondary injury
- Body maintained at defined temp
- Instituting by 6 hours is important

What is the optimal timing of initiation of hypothermia therapy?

Cooling must begin early, within 6 hours of injury. However, experimental evidence strongly suggest that the earlier the better.

Reports on the feasibility and safety of cooling on transport indicate that initiation of hypothermia therapy at referring centers is possible, provided that ongoing education is in place. The recently published ICE trial confirmed that a simplified method using widely available icepacks is an effective way to provide hypothermia therapy in referring centers while awaiting transfer to a tertiary NICU.

On the other hand, a favorable outcome may be possible if the cooling begins beyond 6 hours after injury. A current National Institute of Child Health and Human Development (NICHD) study is evaluating the efficacy of delayed hypothermia therapy for infants presenting at referral centers beyond 6 hours of life or with evolving encephalopathy.

Original Paper

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Time Is Brain: Starting Therapeutic Hypothermia within Three Hours after Birth Improves Motor Outcome in Asphyxiated Newborns

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Conclusion:

Starting cooling before 3 h of age in surviving asphyxiated newborns is safe and significantly improves motor outcome.

Cooling should be initiated as soon as possible after birth in eligible infants.

PDI 90 vs 78.

What is the optimal duration of hypothermia therapy?

a) The greater the severity of the initial injury, the longer the duration of hypothermia needed for optimal neuroprotection.
b) The optimal duration of brain cooling in the human newborn has not been established.
c) 72 hours duration is widely used and almost a standart of care.

What is the best method?

- Two methods have been used in clinical trials: selective head cooling and whole body cooling.
- In selective head cooling, a cap (CoolCap) with channels for circulating cold water is placed over the infant's head, and a pumping device facilitates continuous circulation of cold water. Nasopharyngeal or rectal temperature is then maintained at 34-35°C for 72 hours.
- In whole body hypothermia, the infant is placed on a commercially available cooling blanket, through which circulating cold water flows, so that the desired level of hypothermia is reached quickly and maintained for 72 hours.
- The relative merits and limitations of these 2 methods have not been established.

A Comparison of Cooling Methods Used in Therapeutic Hypothermia for Perinatal Asphyxia

WHAT'S KNOWN ON THIS SUBJECT: Large clinical trials have shown the benefit of hypothermia for neonatal encephalopathy. A number of methods are used to cool infants, but it is unclear whether there are differences in temperature and hemodynamic stability between methods.

WHAT THIS STUDY ADDS: Whole-body cooling by using a servo-controlled system virtually eliminated overshoot at the onset of cooling and maintained core temperature within a narrow range during treatment and rewarming. None of the methods studied had an adverse effect on hemodynamic parameters.

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KEY WORDS
newborn, perinatal asphyxia, therapeutic hypothermia, cooling method, rewarming, cardiovascular

ABBREVIATIONS
TH—therapeutic hypothermia
Trec—rectal temperature
MABP—mean arterial blood pressure
HR—heart rate
SHC—selective head cooling
WBCmc—manually controlled whole-body cooling
WBCsc—servo-controlled whole-body cooling
bpm—beats per minute

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abstract

OBJECTIVE: The objective of this study was to compare cooling methods during therapeutic hypothermia (TH) for moderate or severe perinatal asphyxia with regard to temperature and hemodynamic stability.

CONCLUSIONS: Manually controlled cooling systems are associated with greater variability in Trec compared with servo-controlled systems. A manual mattress often causes initial overcooling. It is unknown whether large variation in temperature adversely affects the neuroprotection of TH. Pediatrics 2010;126:e124–e130

Distribution and severity of hypoxic–ischaemic lesions on brain MRI following therapeutic cooling: selective head versus whole body cooling

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ABSTRACT

Background Whole body cooling (WBC) cools different parts of the brain uniformly, and selective head cooling (SHC) cools the superficial brain more than the deeper brain structures. In this study, the authors hypothesised that the hypoxic–ischaemic lesions on brain MRI following cooling would differ between modalities of cooling.

Aim To compare the frequency, distribution and severity of hypoxic–ischaemic lesions on brain MRI between SHC or WBC.

Methods In a single centre retrospective study, 83 infants consecutively cooled using either SHC (n=34) or WBC (n=49) underwent brain MRI. MRI images were evaluated by a neuroradiologist, who was masked to clinical parameters and outcomes, using a basal ganglia/watershed (BG/W) scoring system. Higher scores (on a

What is known

Whole body cooling uniformly cools the brain, whereas selective head cooling cools the superficial brain more than the deeper brain structures.

What this study adds

Hypoxic–ischaemic lesions on brain MRI were more frequent and more severe in neonates treated with selective head cooling, compared with whole body cooling.

Conclusions Hypoxic–ischaemic lesions on brain MRI following therapeutic cooling were more frequent and more severe with SHC compared with WBC.

Effects of therapeutic hypothermia on multiorgan dysfunction in asphyxiated newborns: wholebody cooling versus selective head cooling.

Multiorgan system dysfunction in asphyxiated newborns during cooling remains similar for both cooling methods. Concerns regarding a differential effect of WBC versus SHC on multiorgan dysfunction, other than of the brain, should not be a consideration in selecting a method to produce therapeutic hypothermia.

J Perinatol 2009 Aug;29(8):558-63. doi: 10.1038/jp.2009.37.

- **What is the optimal rewarming method**?
- Rewarming is a critical period. In clinical trials, rewarming was carried out gradually, over 6-8 hours.
- **Can the use of aEEG improve candidates selection?**
- Predefined subgroup analysis in the CoolCap trial suggested that head cooling had no effect in infants with the most severe aEEG changes.
- The findings were beneficial only in infants with less severe aEEG changes.
- Cooling makes delay on recovery of aEEG abnormalities

Long term benefit? Cochrane results

- 11 randomised controlled trials in this updated review, comprising 1505 term and late preterm infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia.
- Therapeutic hypothermia resulted in a **statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability** to 18 months of age number needed to treat for an additional beneficial outcome (NNTB) 7 (95% CI 5 to 10) (8 studies, 1344 infants).
- Cooling also resulted in statistically **significant reductions in mortality** NNTB 11 (95% CI 8 to 25) (11 studies, 1468 infants)
- Neurodevelopmental disability in survivors NNTB 8 (95% CI 5 to 14) (8 studies, 917 infants).
- Some adverse effects of hypothermia included an increase sinus bradycardia and a significant increase in thrombocytopenia.

Future Neuroprotective Strategies

Strategies	Interventions
↓ cerebral metabolic rate	Hypothermia is now standart of care
Block NMDA receptor channel	Magnesium
↓ glutamate release	Adenosine Adenosine agonists Adenosine uptake inhibitors
Inhibit voltage-sensitive Ca++ channels	Calcium channel blockers
↓ free radical reactions	Free radical scavengers Allopurinol Vitamin C, E Super oxide dismutase (SOD)
Prevent free radical formation	Indomethacin Iron chelators Allopurinol NOS inhibitors
↓ inflammatory response	Allopurinol Inflammatory antagonists (blocking IL-1 and TNF-α, steroids)
Attenuate apoptosis pathway	Caspase inhibitors

Prophylactic barbiturates

- In a small randomized trial, high-dose phenobarbital (40 mg/kg) was given over 1 hour to infants with severe hypoxic-ischemic encephalopathy. Treated infants had fewer seizures (9 of 15) than untreated control infants (14 of 16). Treated infants also had fewer neurological deficits at age 3 years (4 of 15) than untreated infants (13 of 16). In another small study, thiopental given within 2 hours and over 24 hours, did not result in improved rate of seizures or neurodevelopmental outcomes at 12 months.
- Hypotension was more common in infants who received thiopental.
- Thus, the role of prophylactic barbiturate remains unclear. Further studies are needed.

Erythropoietin:

- In a recent study, low-dose erythropoietin (300-500 U/kg) administered for 2 weeks starting in the first 48 hours of life decreased the incidence of death or moderate and severe disability at age 18 months (43.8% vs 24.6%; $P < 0.05$) in infants with moderate-to-severe hypoxic-ischemic encephalopathy.
- Subgroup analysis indicated that only infants with moderate disability benefited from this therapy.

Future Neuroprotective Strategies

- Allopurinol: Slight improvements in survival and cerebral blood flow (CBF) were noted in a small group of infants tested with this free-radical scavenger in one clinical trial.[94]
- Excitatory amino acid (EAA) antagonists: MK-801, an EAA antagonist, has shown promising results in experimental animals and in a limited number of adult trials. However, this drug has serious cardiovascular adverse effects.

New protocols (cochrane)

- **Interventions to reduce the severity of hypoxic-ischemic encephalopathy (4)**
- **Erythropoetin for preterm infants with hypoxic isch**

  (protocol stage)
- **Hyperbaric oxygen for term newborns with hypoxi**

  (protocol stage)
- **Erythropoietin for term and late preterm infants w**

  (protocol stage)
- **Magnesium sulfate for term infants following perina**

  (protocol stage)

Our experiences

Çocuk Sağlığı ve Hastalıkları Dergisi 2012; 55: 96-99 *Derleme*

Perinatal asfikside hipotermi tedavisi ve pasif soğutma uygulamaları

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SUMMARY: Öncel MY, Akar M, Erdeve Ö, Dilmen U. (Dr. Zekai Tahir Burak Women's Health Research and Training Hospital, Ankara, Turkey). Hypothermia treatment in perinatal asphyxia and passive cooling applications. Çocuk Sağlığı ve Hastalıkları Dergisi 2012; 55: 96-99.

Despite advances in neonatal intensive care, hypoxic ischemic encephalopathy remains an important cause of permanent injury to the central nervous system resulting in neonatal death, cerebral palsy and several developmental disorders in later life. One of the most effective treatment modalities used to decrease morbidity and mortality due to hypoxic ischemic encephalopathy is hypothermia. The efficacy and success of hypothermia is directly correlated with the early initiation of treatment (0-6 hours). The scarcity of hypothermia centers in Turkey requires the consideration of important issues such as patient transport and early initiation of passive cooling. The goal of this report was to highlight the significance of developing protocols in Turkey regarding the practice of passive cooling at the hospitals of birth and also during ambulance transport.

Key words: hypothermia, passive cooling, perinatal asphyxia, neonatal transport.

Our experiences

DOI: 10.4274/tpa.552

Tüm vücut soğutma yöntemi ile hipotermi uygulanan hipoksik iskemik ansefalopatili yenidoğanların değerlendirilmesi

Evaluation of whole body hypothermia on term neonates with hypoxic ischemic encepholopathy

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Özet

Amaç: Bu çalışmada hipoksik iskemik ansefalopatili zamanında doğmuş yenidoğanlara tüm vücut soğutma yöntemi ile uygulanan hipotermi tedavisinin hem doğum sonrası erken sorunlara hem de uzun dönem nörogelişimsel sonuçlara olan etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya perinatal asfiksi ve hipoksik iskemik ansefalopati evre 2-3 tanılı yenidoğan bebekler alındı. Olgular ilk altı saatteki amplitüt entegre elektroansefalogram (aEEG) bulgularına göre iki gruba ayrıldı; Grup 1: aEEG bulguları anormal olan veya klinik nöbet gözlenen ve hipotermi tedavisi uygulananlar, Grup 2: aEEG bulguları normal olan ve hipotermi tedavisi uygulanmayanlar. Yaşayan olguların 18. ayda Bayley Gelişim Ölçeği-2 kullanılarak mental gelişim indeksi ve psikomotor gelişim indeksi puanları hesaplandı. Çalışma için yerel etik kuruldan onay alındı (Onay no:8).

Bulgular: Toplam 35 hasta (Kız=18, Erkek=17) çalışmaya alındı. On sekiz olguya (%51) hipotermi tedavisi uygulandı. Grup 1'deki olguların %44,4'ünde, grup 2'deki olguların ise %5,9'unda bradikardi saptandı (p=0,04). Diğer klinik bozuklukların görülme sıklığı bakımından gruplar arasında önemli bir fark yoktu. Grup 1'deki olguların ölüm oranı grup 2'den yüksekti (p=0,03). Grup 1'deki olguların %70'i; grup 2'deki olguların ise %86'sı nörogelişimsel açıdan değerlendirilebildi. Hipotermi uygulanan olguların nörogelişimsel değerlendirme sonuçları diğer gruba göre daha iyi olmakla birlikte aradaki fark istatistiksel olarak anlamlı değildi.

Our experiences

Case Report

A Neonate with Subcutaneous Fat Necrosis after Passive Cooling: Does Polycythemia Have an Effect?

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Subcutaneous fat necrosis (SCFN) is an inflammatory disorder of adipose tissue. The main risk factors for the development of SCFN are perinatal asphyxia and hypothermia. Presented here is a case of a newborn who developed SCFN in association with polycythemia and hypocalcemia following treatment by passive cooling. Neonates who undergo passive or whole body cooling therapy should be closely monitored for any signs of SCFN.

Our experiences

Pediatric Dermatology Vol. 30 No. 1 120–123, 2013

Hypercalcemia Due to Subcutaneous Fat Necrosis in a Newborn After Total Body Cooling

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Abstract: Subcutaneous fat necrosis is an inflammatory disorder of adipose tissue. Although patients need long-term follow-up to prevent hypercalcemia, the prognosis is generally favorable. We herein present a case of a newborn who developed subcutaneous fat necrosis–related hypercalcemia after hypothermia treatment for hypoxic ischemic encephalopathy. Widespread use of hypothermia treatment for hypoxic ischemic encephalopathy in the neonatal intensive care unit may increase the risk of developing subcutaneous fat necrosis and subsequently hypercalcemia. Great care should be taken to recognize skin findings early in newborns receiving hypothermia treatment, and those diagnosed with subcutaneous fat necrosis require close follow-up because they are at risk for developing hypercalcemia.

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DOI: 10.3109/08880018.2013.771240

informa
healthcare

Our experiences

HEMATOLOGY IN INFANTS

The Effect of Whole-Body Cooling on Hematological and Coagulation Parameters in Asphyxic Newborns

Mehmet Yekta Oncel,[1] Omer Erdeve,[2] Erhan Calisici,[1] Serife Suna Oguz,[1] Fuat Emre Canpolat,[1] Nurdan Uras,[1] and Ugur Dilmen[1,3]

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PA results in significant reductions in levels of factors of the extrinsic pathway and has been associated with thrombocytopenia and disseminated intravascular coagulation. Hypothermia may actually improve the clinical picture in such patients rather than aggravating the hemostatic disturbance,particularly with the implementation of supportive treatment.

Our experiences -*The Mag Cool Study*

Multicenter Randomized Controlled Trial of Therapeutic Hypothermia plus Magnesium Sulphate ($MgSO_4$) vs. Therapeutic Hypothermia plus Placebo in the Management of Term and Near Term babies with Hypoxic Ischemic Encephalopathy (*The Mag Cool Study*) - A preliminary safety analysis

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The Mag Cool Study Methodology

Term and near term babies (≥35 weeks) with a clinical diagnosis of moderate and severe HIE were randomized to either Arm A (Therapeutic Hypothermia plus MgSO4) or Arm B (therapeutic Hypothermia plus placebo) using a net based randomization system. Both groups received, within six hours of birth, standard hypothermia therapy (72 hours of cooling to 33.5^{0}C followed by slow rewarming over a period of eight hours). The groups were compared for short term pre-discharge adverse outcomes.

The Mag Cool Study Results

A total of 60 patients (now 77) were randomized (29 in Arm A and 31 in Arm B). Both groups had similar baseline characteristics ($p>0.05$) including severity of HIE.

There was no difference in the short term adverse outcomes (death, seizures, thrombocytopenia, coagulopathy, renal failure, raised LFT's, hypotension, intracranial hemorrhage, necrotizing enterocolitis, pulmonary hemorrhage, pulmonary hypertension and pulmonary air leak syndromes) between the two groups ($p>0.05$).

The Mag Cool Study Conclusions

The combined use of therapeutic hypothermia and MgSO4 appears to be safe particularly with respect to maintaining blood pressure and coagulopathy.

Long term survival and neurodevelopmental outcomes remain to be evaluated (MagCool-2)

Neonatal encephalopathy – potential future treatments

- Erythropoietin
- Melatonin
- Topiramate
- Acetylcysteine
- Xenon
- ……

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2	Recruiting	Safety and Efficacy of Topiramate in Neonates With Hypoxic Hypothermia	**Condition:** Hypoxic Ischemic Encephalopathy **Intervention:** Drug: Topiramate in newborns with h hypothermia
3	Recruiting	Late Hypothermia for Hypoxic-Ischemic Encephalopathy	**Conditions:** Infant, Newborn; Hypoxia, Brain; Hy Ischemic; Hypoxic-Ischemic Encepha **Interventions:** Procedure: Hypothermia; Procedure
4	Not yet recruiting	Preemie Hypothermia for Neonatal Encephalopathy	**Conditions:** Infant, Newborn; Hypoxia, Brain; Hy Ischemic; Hypoxic-Ischemic Encepha **Interventions:** Procedure: Hypothermia; Procedure
	Recruiting	Efficacy Study of Hypothermia Plus Magnesium Sulphate(MgSO4) in Babies With Hypoxic Ischemic Encephalopathy	**Conditions:** Severe Hypoxic Ischemic Encephalopathy; M **Interventions:** Drug: Magnesium Sulphate; Drug: Placebo


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Thanks!