Neonatal Encephalopathy
‘Innovations in diagnosis and management’

Ömer ERDEVE, Professor
Ankara University School of Medicine Children’s Hospital

5th Iranian-Turkish Pediatric Meeting, Antalya (Turkey), 15th November, 2018.
It occurs in approximately 2/1000 live births and is associated with a high risk of death or lifelong disability in contrast to the improved perinatal care.

5th common cause of below 5 years mortality in the world, and 4th leading neonatal mortality in Turkey!
Challenges/questions

✓ Terminologic problems - Are all neonatal encephalopathies related to HIE?
✓ Is diagnosis easy as defined, or more complicated then we think? New approaches?
✓ Why therapeutic hypothermia is effective only in half of the patients?
✓ What about treatment modality differences in western and resource-limited settings?
✓ Are there any other possible treatment options? State-of-the art!
**Terminological passages and fetal response**

Anaerobic metabolism due to energy and oxygen lack

Alarm condition
IMPORTANCE OF PREGNANCY FOLLOW-UP and DELIVERY ROOM MANAGEMENT

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Emergency; what should I do?

Diving seal reflex

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Diving seal reflex

Fetal Circulation vs Neonatal Circulation

Fetal Circulation:
- Foramen ovale: Oxygen rich blood is delivered to the brain
- Ductus arteriosus: Mixed blood flows bypasses the lungs to the rest of the body
- Ductus venosus: Directs half of the oxygenated blood flow directly to the heart

Neonatal Circulation:
- All shunts are closed allowing oxygen rich blood to be delivered throughout the body

Deoxygenated blood is oxygenated in the lungs

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Circulatory response in asphyxia

- Cerebral, coronary, adrenal ↑
- Renal, intestinal, skelatory ↓

Prolonged process
- Bass excess << -12
- pH < 7

HIE
- Cardiac output ↓
- Cerebral blood flow ↓
1. **Phase (Fetal hypoxic phase = Energy depletion phase):**
   - Excitatory neurotransmitters, Ca, Hypoxantine

2. **Phase (Ischemia-reperfusion phase):**
   - Free O₂ radicals, inflammation

3. **Phase (Late damage phase):**
   - Apoptosis and down-regulation of neurotropic growth factors

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**Cellular necrosis**

**Apoptosis**
Neonatal encephalopathy may be due to many causes

- IUGR
- Maternal diseases
- Thrombophilia
- Fetal inflammation, infections
- "HIE"

Differential diagnosis:
- Detailed perinatal history
- Placental pathology (Microvillitis)
- Comprehensive laboratory
- Genetic and genomic investigations
Prolonged hypoxemia, hypercapnia and disturbed gas exchange leading to acidosis
Diagnostic approaches

Imaging
1. TFUSG
2. CT
3. MRI
4. Diffusion weighted MRI

Clinical
1. Diagnostic criteria
2. Sarnat scoring

Neurophysiology
1. EEG
2. aEEG
3. NIRS
4. MR spectroscopy

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aEEG and NIRS are increasingly used as bedside tools in NICUs to monitor brain function.

## aEEG

<table>
<thead>
<tr>
<th>Voltage classification</th>
<th>aEEG trace 6cm/hour</th>
<th>Pattern classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal Trace</strong></td>
<td></td>
<td><strong>CNV</strong></td>
</tr>
<tr>
<td>Normal</td>
<td>Normal lower margin &gt;5μV uppper margin &gt;10μV</td>
<td>Continuous Normal Voltage</td>
</tr>
<tr>
<td><strong>Moderately abnormal</strong></td>
<td></td>
<td><strong>DNV</strong></td>
</tr>
<tr>
<td>Trace</td>
<td>Moderate lower margin ≤5μV upper margin &gt;10μV</td>
<td>Discontinuous Normal Voltage</td>
</tr>
<tr>
<td><strong>Severely abnormal</strong></td>
<td></td>
<td><strong>BS</strong></td>
</tr>
<tr>
<td>Abnormal</td>
<td>Severely lower margin &lt;5μV upper margin &lt;10μV</td>
<td>Burst Suppression</td>
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<tr>
<td></td>
<td></td>
<td><strong>LV</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low Voltage</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>FT</strong></td>
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<td></td>
<td></td>
<td>Flat Trace (isoelectric)</td>
</tr>
</tbody>
</table>

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Limitations in neuroimaging and neurophysiology

Morphological and pathologic changes after biochemical and metabolic processes occur at least 24 h later in the brain.

Imaging techniques can demonstrate the damages generally after 72 h.

MRI is better than CT at early phases but only for minor damages/technical difficulties.

aEEG is sensitive in treatment decision but interpreting is difficult after starting hypothermia.

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Biomarkers

Products secreted to blood and CSF from tissues and organs just after the beginning of neonatal HIE

Level should change proportionally to the damage

Should lead to earlier diagnosis when compared to neuroimaging and neurophysiological methods

Should be helpful in differential diagnosis

Useful in decision of treatment (hypothermia)
Currently used non-specific biomarkers:

- CK-BB
- CK-MB
- Lactic acid
- Uric acid
- LDH
Neonatal HIE biomarkers under research

Markers for nerve cell damage
- NSE, MBP (Miyelin Protein), Protein S-100β, GFAP (Glial Fibrilar Acidic Protein), UCH-L1 (Ubikutin), BDNF (Brain Neurotophic Factor), Tau Protein, MiRNA-21, Activin-A

Markers related to brain vascular and blood-brain-barrier tissues
- MMP-9 (Matrix Metaloproteinase), VEGF

Oxidative stress biomarkers
- SOD, MAD

Inflammatory biomarkers
- HsCRP, IL1β, IL6, IL8, IL10; TNF-α, ICAM-1, Selectins

There are no easily available and specific biomarkers for clinical use

Children 2018, 5, 99; doi:10.3390/children5070099
Clin Chemica Acta 2015; 450: 282

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Perinatal Asphyxia: A Review from a Metabolomics Perspective

Claudia Fattuoni 1*, Francesco Palmas 1, Antonio Noto 2, Vassilios Fanos 2 and Luigi Barberini 3

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Review Article
Metabolomic Profiling in Perinatal Asphyxia: A Promising New Field

Niamh M. Denihan, Geraldine B. Boylan, and Deirdre M. Murray
Neonatal Brain Research Group, Department of Paediatrics and Child Health and the Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork and Cork University Maternity Hospital, Wilton, Cork, Ireland

Correspondence should be addressed to Deirdre M. Murray, d.murray@ucc.ie

Received 17 October 2014; Revised 7 January 2015; Accepted 8 January 2015
Delivery room interventions

Maintaining oxygen and energy supplies to vital organs

- Respiratory support
- Circulatory support
- Oxygen
- Avoid hyperthermia (NRP)
- Avoid hypoglycemia
- Monitorization

Advanced treatments in the NICU
Room air or 100% oxygen for resuscitation of infants with perinatal depression
Vadim S. Ten and Dzmitry Matsukeyich

- Oxygen and energy depletion with ischemia
- Resuscitation with 21% vs. 100% oxygen
- Reperfusion injury (ROS)

- Increasing the oxidative damage vs. any delay in oxygenation
- **Resair 2**: Only 25.7% of patients is changed from room-air 100%
- **Vento**: In 75% of patients with 1 min APGAR 1-7 room-air is sufficient

**SUGGESTION**
- Patients with adequate circulation (HR>60); room-air
- Arrest or depressed (HR<60) patients; higher oxygen

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The only targeted treatment for HIE is therapeutic hypothermia
Free radicals

Cytokins
Excitatory neurotransmitters

Akt
HSP-70
BCL-2
STAT

Inflammatory response
Apoptosis

Metabolic pause
O₂ need decreases

Saved ATP
Decrease in cellular edema

Na/K ATPase

Hypothermia

Ca²⁺
Na⁺

Mitochondrial damage

Free O₂ radicals
NO

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Whole-body cooling or Cool cap

Original Article

Comparison of selective head cooling versus whole-body cooling

Yaşar Celik,1 Aytaç Ataç,1 Selvi Gulassy,1 Çetin Okayaz,2 Khatuna Maharonidze3 and Mehmet Ali Sungur3
1Division of Neonatology, Department of Pediatrics, School of Medicine, Mersin University, 2Department of Pediatric Neurology, and 3Department of Biostatistics, School of Medicine, Mersin University, Mersin, Turkey
Current hypothermia protocols have consistently involved starting treatment within the first 6 h of life, with systemic cooling to either 34.5 ± 0.5°C for head cooling, or 33.5 ± 0.5°C for whole-body cooling and continuing treatment for 48–72 h.
• 11 RCT, 1505 moderate/severe encephalopathy

• TH resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (typical RR 0.75, NNTB 7)

• Cooling resulted in reductions in mortality (typical RR 0.75, NNTB 11) and in neurodevelopmental disability in survivors (typical RR 0.77, NNTB 8).

• Some adverse effects of hypothermia included an increase sinus bradycardia and a significant increase in thrombocytopenia.

AUTHORS' CONCLUSIONS:
• Hypothermia should be instituted in term and late preterm infants (>35 wk) with moderate-to-severe HIE if identified before 6 h of age.
Safety and Short-Term Outcomes of Therapeutic Hypothermia in Preterm Neonates 34–35 Weeks Gestational Age with Hypoxic-Ischemic Encephalopathy

Rakesh Rao, MD*
Assistant Professor of Pediatrics, Division of Newborn-Medicine, Washington University School of Medicine, 660 South Euclid, 8th Floor NWT, Campus Box 8116, St Louis, MO 63110

Results—Thirty-one preterm and 32 term neonates were identified. Therapeutic hypothermia-associated complications were seen in 90% of preterm infants and 81.3% of term infants (p=0.30). In the preterm infants, hyperglycemia (58.1% vs.31.3%, p=0.03) and rewarming before completion of therapeutic hypothermia (19.4% vs. 0.0%, p=0.009) were more likely compared with term infants. All deaths occurred in the preterm group (12.9% vs. 0%, p=0.04). Neuroimaging showed the presence of injury in 80.6% of preterm infants and 59.4% of term infants (p=0.07), with no differences in injury severity. Injury to the white matter was more prevalent in preterm infants compared with term infants (66.7% vs. 25.0%, p=0.001).

Conclusions—Therapeutic hypothermia in infants born at 34–35 weeks gestational age appears feasible. Risks of mortality and side effects warrant caution with use of therapeutic hypothermia in preterm infants.
When to cool?

• Clinical data suggested that asphyxiated infants who were able to be cooled within 3 h of birth had better motor outcomes than when hypothermia was started between 3 and 6 h.

• However, hypothermia was only able to be started in 12% of infants within 4 h of birth in RCTs.

*Neonatology* (2013) **104**:228–33.
CONCLUSIONS AND RELEVANCE  Among term infants with hypoxic-ischemic encephalopathy, hypothermia initiated at 6 to 24 hours after birth compared with noncooling resulted in a 76% probability of any reduction in death or disability, and a 64% probability of at least 2% less death or disability at 18 to 22 months. Hypothermia initiated at 6 to 24 hours after birth may have benefit but there is uncertainty in its effectiveness.
Cooling infants with HIE shortly after birth improves survival and neurodevelopmental outcome.

The optimal way to cool infants during transfer to regional NICUs is unclear.

Data from a regional neonatal transfer team, using first passive and subsequently active cooling for these infants, suggest that active cooling results in improved thermal control and a reduction in stabilization time.
Active vs. passive cooling on transport

Active cooling results in better achieved targeted temperature on arrival to hospital (79% vs. 25%)
Duration and depth of the treatment?

- A recent experimental study extending the duration of cerebral cooling from 3 days until 5 days was not associated with any additional improvement in the recovery of EEG power.

- Consistent with this preclinical evidence, a large RCT of 72 h of hypothermia to 33.5°C compared with either prolonged hypothermia for 120 h or deeper cooling to 32°C, was stopped early because
  - longer duration, lower temperature and the combination of longer duration and lower temperature were associated with a trend toward a higher risk of death in the neonatal period


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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

Seetha Shankaran, MD; Abbot R. Laptook, MD; Athina Pappas, MD; Scott A. McDonald, BS; Abhik Das, PhD; Jon E. Tyson, MD, MPH; Brenda B. Poindexter, MD, MS; Kurt Schibler, MD; Edward F. Bell, MD; Roy J. Heyne, MD; Claudia Pedroza, PhD; Rebecca Bara, RN, BSN; Krisa P. Van Meurs, MD; Carolyn M. Petrie Huijtema, MS, CCRP; Cathy Grisby, BSN, CCRC; Uday Devaskar, MD; Richard A. Ehrenkranz, MD; Heidi M. Harmon, MD, MS; Lina F. Chalak, MD, MSCS; Sara B. DeMauro, MD, MSCE; Meena Garg, MD; Michelle E. Hartley-McAndrew, MD; Amir M. Khan, MD; Michele C. Walsh, MD, MS; Namasivayam Ambalavanan, MD; Jane E. Brumbaugh, MD; Kristi L. Watterberg, MD; Edward G. Shepherd, MD; Shannon E. G. Hamrick, MD; John Barks, MD; C. Michael Cotten, MD, MHS; Howard W. Kilbride, MD; Rosemary D. Higgins, MD; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

CONCLUSIONS AND RELEVANCE Among term neonates with moderate or severe hypoxic-ischemic encephalopathy, cooling for longer than 72 hours, cooling to lower than 33.5°C, or both did not reduce death or moderate or severe disability at 18 months of age. However, the trial may be underpowered, and an interaction was found between longer and deeper cooling. These results support the current regimen of cooling for 72 hours at 33.5°C.
Hypothermia in resource-limited settings

PA occurs at an approximate rate of 10‒20 per 1000 live births in LMIC

Of the one million annual neonatal deaths caused by PA, 99% occur in LMIC.

Benefit of therapeutic hypothermia may be far higher in LMIC than in high-income countries, considering the disease burden.

Adequately powered clinical trials are required to ensure that cooling is indeed safe and effective in LMIC neonatal units (HELIX trial NCT01760629).

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The rate of confirmed sepsis is higher in LMICs

There are often delays in providing care owing to a limited medical and nursing infrastructure

Low- resource or less-experienced centers may be less rigorous in using therapeutic hypothermia according to established protocols

Such countries may not be able to provide adequate neonatal intensive care, including proper monitoring, mechanical ventilation, sedation, and use of oxygen.

LMI countries may be less able to afford approved devices to induce stable hypothermia within targeted goals.
Components of MiraCradle™ - Neonate Cooler

1. Conduction Mattress
2. savE® FS-21
3. savE® FS-29
4. Cradle
Phase Changing Material for Therapeutic Hypothermia in Neonates with Hypoxic Ischemic Encephalopathy - A Multi-centric Study.

Thomas N1, Abiramalatha T2, Bhat V3, Varanattu M4, Rao S5, Wazir S6, Lewis L7, Balakrishnan U8, Murki S9, Mittal J10, Dongara A11, Prashantha YN12, Nimbalkar S13.

+ Author information

Abstract

OBJECTIVE: To assess the feasibility and safety of cooling asphyxiated neonates using phase changing material based device across different neonatal intensive care units in India.

DESIGN: Multi-centric uncontrolled clinical trial.

SETTING: 11 level 3 neonatal units in India from November 2014 to December 2015.

PARTICIPANTS: 103 newborn infants with perinatal asphyxia, satisfying pre-defined criteria for therapeutic hypothermia.

INTERVENTION: Therapeutic hypothermia was provided using phase changing material based device to a target temperature of 33.5±0.5°C, with a standard protocol. Core body temperature was monitored continuously using a rectal probe during the cooling and rewarming phase and for 12 hours after the rewarming was complete.

OUTCOME MEASURES: Feasibility measure - Time taken to reach target temperature, fluctuation of the core body temperature during the cooling phase and proportion of temperature recordings outside the target range. Safety measure - adverse events during cooling.

RESULTS: The median (IQR) of time taken to reach target temperature was 90 (45, 120) minutes. The mean (SD) deviation of temperature during cooling phase was 33.5 (0.39) °C. Temperature readings were outside the target range in 10.8% (5.1% of the readings were <33°C and 5.7% were >34°C). Mean (SD) of rate of rewarming was 0.28 (0.13)°C per hour. The common adverse events were shock/ hypotension (18%), coagulopathy (21.4%), sepsis/probable sepsis (20.4%) and thrombocytopenia (10.7%). Cooling was discontinued before 72 hours in 18 (17.5%) babies due to reasons such as hemodynamic instability/refractory shock, persistent pulmonary hypertension or bleeding. 7 (6.8%) babies died during hospitalization.

CONCLUSIONS: Using phase changing material based cooling device and a standard protocol, it was feasible and safe to provide therapeutic hypothermia to asphyxiated neonates across different neonatal units in India. Maintenance of target temperature was comparable to standard servo-controlled equipment.
Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Studies / Participants</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>5 / 806</td>
<td>4.08 (1.55, 10.74)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8 / 1108</td>
<td>1.03 (0.93, 1.13)</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>7 / 1114</td>
<td>0.96 (0.80, 1.15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 / 638</td>
<td>1.28 (1.07, 1.52)</td>
</tr>
<tr>
<td>Seizure after enrolment</td>
<td>8 / 1102</td>
<td>0.96 (0.86, 1.06)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5 / 310</td>
<td>0.95 (0.53, 1.70)</td>
</tr>
<tr>
<td>Hepatic side effects</td>
<td>5 / 678</td>
<td>0.85 (0.69, 1.04)</td>
</tr>
<tr>
<td>Infection</td>
<td>7 / 544</td>
<td>0.86 (0.40, 1.88)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>5 / 636</td>
<td>1.36 (0.95, 1.96)</td>
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Fig. 4. Safety outcomes.
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 Dilmen¹,³

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

Ahmet Akcay, M.D., Melek Akar, M.D., M. Yekta Oncel, M.D., Avidan Kizilelma, M.D., Omer Erdeve, M.D., S. Suna Oguz, M.D., Nurdan Uras, M.D., and Ugur Dilmen, M.D.

Case Report

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

Erhan Calisici,¹ Mehmet Yekta Oncel,¹ Halil Degirmencioglu,¹ Gonca Sandal,³ Fuat Emre Canpolat,¹ Omer Erdeve,⁴ Serife Suna Oguz,¹ and Ugur Dilmen¹,⁵
Erythematous, bullous, necrotic lesions were detected on the lumbosacral, cervical regions and the auricula of the ears.
Ankara University Children’s Hospital NICU last 5 years series:

• 2012-2017
• 45 patients (24 inborn)
• 6 deaths
• Survival %87
What about hypothermia in patients on ECMO run!
Table 1. Promising therapies in management of HIE by mechanism.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Clinical Trials</th>
<th>Pre-Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous</td>
<td>Erythropoietin, darbepoietin</td>
<td>Remote ischemic postconditioning</td>
</tr>
<tr>
<td></td>
<td>Stem cells</td>
<td>Endocannabinoids</td>
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<td>Melatonin</td>
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<td>Exogenous</td>
<td>Monosialgangliosides</td>
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<td>Allopurinol</td>
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<td>Topiramate</td>
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<td></td>
<td>Magnesium sulfate</td>
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</tbody>
</table>
Potential most effective neurotrophic treatment: Mesenchymal stem cell

• MSC treatment:
  ➢ UCB-MSC: Dalous (2012), Xia (2010)
    ✓ Easily obtained
    ✓ No damage to donor
    ✓ More immature cells
    ✓ No ethical problem and somatic mutation risks
    ✓ Low tumor risk potency
    ✓ Low GVHD risk
• **UCB-MSC:**
  - Allogenic: So Yoon An (2015)
  - Autologous: Cotton (2014)

• **Questions:**
  - Administration way (intraventricular/iv)
  - Dose \((1 \times 10^6 - 5 \times 10^5 \text{ cell})\)
  - Timing (as soon as possible)
  - Long term safety

• **DCC-Milking (?)**

In order to optimize the potential of this treatment, systematic preclinical studies of the mechanisms of action, and clinical studies on optimal dosing and timing, and type of stem cells are now needed.

J Pediatr 2014; 164: 973
Neonatology 2016; 109: 377
✓ Asphyxia is still common, even in developed countries but more in LMICs
✓ Not all encephalopathies after birth are due to PA
✓ Neuroimaging and neurophysiological techniques have limitations and there is no specific biomarker defined
✓ Hypothermia should be started as soon as possible. Think about passive/active cooling on transport!
✓ Therapeutic hypothermia is the only proven treatment but is not a golden bullet. There is a need for adjunctant treatment, preferably a cheap one (erythropoietin ?!)
✓ Mesenchymal stem cell transplantation is a promising future treatment choice for HIE for prevention of CP
✓ Adequate resuscitation, targeted oxygen use, preventing hyperthermia and hypoglycemia, initiating passive/active cooling at referring center, therapeutic hypothermia with servo-controlled device or phase changing materias/frozen gel packs should be main aims in treatment for resource-limited settings