Hypothermia: Neuroprotective Treatment of Hypoxic-Ischemic Encephalopathy

Floris Groenendaal
Department of Neonatology

Therapeutic hypothermia

- Background of hypothermia
- Clinical application
- Complications
- Results of trials and outside trials
- Future studies

Serious perinatal asphyxia

- frequency of 1-2 per 1000 live births
  - Netherlands Perinatal Registry: estimated at least 180 per year (170,000 full term births)
- High mortality and morbidity (RCTs hypothermia: 65% 'adverse outcome' without hypothermia)
- Until recently no specific treatment

Does hypothermia work?
Cranio-cerebral hypothermia (CCH) in neonates using tap water

In Russia it does!

Background of neuroprotection

- ‘Secondary energy failure’
- ‘Therapeutic window’ of approximately 6 hours

Does hypothermia provide tissue protection?

- ‘Near-drowning’ with normal outcome
- Cardiac surgery in neonates using deep hypothermia
- Sports injury: cooling of injured joints

Neonatal $^{31}$P-MR Spectroscopy

Full term, severe perinatal asphyxia
31P - MR spectroscopy

After hypoxia

Cady, 1997

冬季 energy failure’ (human)

Wyatt, 1989

冬季 energy failure’ (sheep)

Gunn 2002

冬季 energy failure’ (pig)

Lorek, 1994; Peeters-Scholte C, 2002
**Experimental studies on perinatal asphyxia and hypothermia**

- Many species (pig, sheep, rat, mouse)
- **Authors: Thoresen, Gunn, Fan**
- Hypothermia protects!

**Pathways after hypoxia-ischemia**

- Hypothermia is neuroprotective

**Experimental evidence**

- Hypothermia protects

**PCr/Pi ratio**

- PCr/Pi ratio was significantly decreased at 24h of reperfusion for PLAC…

- PLAC
- ALLO
- DFO
- 2-IB

**Hypoxia-ischemia**

- Reperfusion-reoxygenation
- Hypoxia-ischemia
Clinical application of hypothermia

• Whom?
• When?
• Where?
• How?
• Assessment?
• Follow-up?

The first RCTs with 18 months' follow-up

• Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Gluckman et al, Lancet. 2005


• Cochrane review Summer 2007

It became more and more obvious …

Neonatal Hypothermia:
Head cooling for neonatal encephalopathy: the state of the art

Gunn and Gluckman 2007

Who may benefit from hypothermia?

• Inclusion criteria:
  • >36.0 weeks

• Well documented asphyxia
  • Apgar scores 5 min ≤ 5
  • Resuscitation
  • Prolonged ventilatory support (IPPV)
  • pH < 7.0 and Base Excess
  • Lactate …

• Encephalopathy
Logistics

• Start <6 hours after birth (shorter is better)
• Duration 72 hours
• Target temperature brains 33.5 °C
• Rewarming 0.5 °C per hour

Where should we cool?

• During transport?
• In local hospitals or only in ‘level III’ NICUs?

Hypothermia protocol

• >36.0 weeks
• AND ...
• Apgar 5 min <=5
• resuscitation/ventilation
• pH<7.0 base deficit >16 mmol/L (Umbilical or <1 h after birth)
• lactate > 10.0 mmol/L (arterial or venous <1 h after birth)
• AND ...
• ‘encephalopathy’ (clinically) or aEEG criteria (suppressed background pattern or seizures)
• AND ...
• Time <6 h after birth
• Duration: 72 hours
• Temperature: 33.5 °C

Hypoxic-ischemic encephalopathy (according to Sarnat and Sarnat, 1976)

• Grade I: irritable (hyperalert), crying, hypertonia—no handicaps
• Grade II: seizures, EEG abnormalities, 25% handicaps
• Grade III: stupor/coma, no seizures anymore, >95% handicaps
Other methods of assessing encephalopathy

- OR
- aEEG: DNV or worse with a baseline ≤5 μV OR seizures
Single seizure

Repetitive seizures (RS)

Repetitive seizures (RS)

Status Epilepticus (SE)

Precautions during hypothermia …

Correction of blood gas values – beware of vasoconstriction by low CO₂

Complications Cochrane

- Sinus bradycardia - 14 x/min per degree Celsius
- Thrombocytopenia (<150 x 10⁹/L)
- No effects on potassium, glucose, coagulation, infections, PPHN (Cochrane)

Groenendaal et al. Pediatrics 2009

Jacobs SE et al. Cochrane 2013
Safety of hypothermia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies / number of participants</th>
<th>Relative risk</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anomia</td>
<td>6/406</td>
<td>1.54 (1.51, 1.57)</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>8/338</td>
<td>1.04 (0.95, 1.13)</td>
<td></td>
</tr>
<tr>
<td>Nephropathy</td>
<td>7/323</td>
<td>0.99 (0.95, 1.02)</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>8/330</td>
<td>0.99 (0.95, 1.03)</td>
<td></td>
</tr>
<tr>
<td>Hepatic side effects</td>
<td>5/350</td>
<td>0.89 (0.83, 1.06)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>3/518</td>
<td>0.81 (0.72, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>5/106</td>
<td>1.64 (0.75, 3.56)</td>
<td></td>
</tr>
</tbody>
</table>

Hypoxic-ischemic encephalopathy (Sarnat grade II-III) in the Utrecht level III NICU

- **Before** the era of hypothermia
- In 2004-2006: 128, of whom 38 died (30%), mostly due to redirection of care

Results of hypothermia

Our first patient …
Start cooling:
6 h
phenobarbital at F

15 h

28 h
status epilepticus

Follow-up

- Hyperactive at 2 years?
- At 3.5 years: fearful behaviour (nightly fears)

Phenobarbital at C
'drift of the baseline'
38 h

Begin of
'Sleep-wake-cycling' at
56 h

The Netherlands and Flanders
• Data were collected prospectively
• Clinical data, complications, neurodevelopmental outcome
• N=332, of whom 24 had congenital abnormalities

Number of patients treated with hypothermia per 3-month period.

Clinical data

Table 1. Gestational age, birth weight and Apgar scores of hypothermia in neonates without congenital malformations

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>Died</th>
<th>Significance value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>177 (60.1)</td>
<td>79 (26.8)</td>
<td>0.419</td>
</tr>
<tr>
<td>Flanders</td>
<td>32 (66.3)</td>
<td>19 (36.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>39.5 (5.3)</td>
<td>39.4 (5.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>Birth weight</td>
<td>3,417 (627)</td>
<td>3,367 (628)</td>
<td>0.51</td>
</tr>
<tr>
<td>Lowest pH</td>
<td>6.9 (0.15)</td>
<td>6.8 (0.32)</td>
<td>0.008</td>
</tr>
<tr>
<td>Apgar score 5 min, median (IQR)</td>
<td>7 (1)</td>
<td>7 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Head circumference</td>
<td>36.3 (2.2)</td>
<td>36.3 (2.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Neuraxial analgesia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>NICU admissions</td>
<td>129 (41.3)</td>
<td>79 (26.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Central line</td>
<td>21 (6.8)</td>
<td>21 (6.8)</td>
<td>–</td>
</tr>
<tr>
<td>Death/total day</td>
<td>19 (6.3)</td>
<td>19 (6.3)</td>
<td>–</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>9 (2.8)</td>
<td>9 (2.8)</td>
<td>–</td>
</tr>
<tr>
<td>Unknown follow up</td>
<td>22 (7.1)</td>
<td>22 (7.1)</td>
<td>–</td>
</tr>
</tbody>
</table>
The range of gestational age was 35.0–42.6 weeks, birth weight ranged from 1,900 to 5,200 g, and age at start of hypothermia ranged from 45 min to 8 h.

In 16 neonates, hypothermia was started later than 6 h after birth.

Protocol violations: GA, start time hypothermia, ...

- subcutaneous fat necrosis (n = 2)
- overcooling (temperature <33 C; n = 5)
- thrombosis of a subclavian vein (n = 1)

Death: 31.8%

Cerebral palsy in 6.8%, delayed development of more than 3 months in 6.2%, and severe hearing loss in 0.6%.

Milder abnormalities were hemianopia in 1 patient (0.3%), and Erb’s paresis in 3 patients (0.9%).
Comparison with trial data

Table 2. Outcome of hyperthermia in the Netherlands and Flanders compared to data of large randomized trials of therapeutic hyperthermia in preterm infants

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Hyperthermia</th>
<th>Adverse outcome in survivors</th>
<th>Mortality</th>
<th>Combined adverse outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>593</td>
<td>24 [29.4; 26.9]</td>
<td>34 [29.4; 26.9]</td>
<td>34 [29.4; 26.9]</td>
<td>34 [29.4; 26.9]</td>
</tr>
</tbody>
</table>

Adverse outcome in survivors (%)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Hyperthermia</th>
<th>Adverse outcome in survivors</th>
<th>Mortality</th>
<th>Combined adverse outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>593</td>
<td>24 [29.4; 26.9]</td>
<td>34 [29.4; 26.9]</td>
<td>34 [29.4; 26.9]</td>
<td>34 [29.4; 26.9]</td>
</tr>
</tbody>
</table>

Mortality and morbidity in trials

Table 1. Patient characteristics and neurodevelopmental follow-up across the three centers

<table>
<thead>
<tr>
<th>UCSF</th>
<th>WKZ</th>
<th>UCHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>67</td>
<td>58</td>
</tr>
<tr>
<td>Birthweight (grams)</td>
<td>3220 [490]</td>
<td>3220 [490]</td>
</tr>
<tr>
<td>UA or First Blood Gas pH</td>
<td>6.96 [0.023]</td>
<td>6.97 [0.116]</td>
</tr>
<tr>
<td>UA or First Blood Gas Base Deficit</td>
<td>14.8 [3.74]</td>
<td>15.1 [3.65]</td>
</tr>
<tr>
<td>Received Aldrenalin at Birth</td>
<td>2477 [331]</td>
<td>8366 [421]</td>
</tr>
<tr>
<td>Age achieved goal temperature (hours)</td>
<td>5.1 [2.02]</td>
<td>4.1 [2.13]</td>
</tr>
<tr>
<td>PVL, IVH, and Abnormal PVE at 24 hrs</td>
<td>16 [22]</td>
<td>21 [33]</td>
</tr>
<tr>
<td>Age at MRI (days)</td>
<td>5.4 [4.2]</td>
<td>5.4 [4.2]</td>
</tr>
</tbody>
</table>


Mortality (%)

Data presented as N (%), mean ± (SD), median (p25, p75)
Measures of outcome

- Clinical assessment
- aEEG
- MRI, proton MR spectroscopy
- Follow-up (Griffiths DQ, BSITD-III, …)

Limited value of clinical assessment

- Hypothermia did *not* affect severity of encephalopathy at day 4
- Infants with moderate encephalopathy at day 4 treated with hypothermia had a higher rate of favourable outcome than those treated with standard care

Gunn AJ et al. J.Pediatr 2008

Prediction using clinical assessment and aEEG

- Far more difficult during hypothermia!
- Hypothermia improves outcome
Effect of Hypothermia on Amplitude-Integrated Electroencephalogram in Infants With Asphyxia.

Pediatrics 2010, e131-e139

Normalization of an infant's aEEG while being cooled occurs later:
“… a hypothermia-treated infant could still develop normally as long as the aEEG recovered before 48 hours”

So …

• No longer redirection of care in case of poor aEEG background pattern and hypothermia <36 hours after birth.

PPV of abnormal aEEG background (BS, CLV, or FT) to predict ‘poor outcome’

©2013 by American Academy of Pediatrics

How about MRI and MRS?

… MRI in the neonatal period is qualified as a biomarker of disease and treatment response … Rutherford M et al. Lancet Neurol. 2010

… deep gray matter proton MRS is the most accurate quantitative MR biomarker for prediction of neurodevelopmental outcome after NE … Thayyil S et al. Pediatrics 2010
Severe perinatal asphyxia, day 4

1H-MR Spectroscopy and DW-MRI

Diffusion weighted MRI and Apparent Diffusion Coefficient (of water)

Normal diffusion of water oedema

Cytotoxic

Changes over time

Rutherford et al. 2004, Alderliesten et al. 2011
Diffusion weighted MRI and hypothermia

Aldriesten et al. Radiology 2011

$^{1}$H-MRS: severe encephalopathy

Hypothermia and prediction

- $^{1}$H-MRS was useful for prediction of neurodevelopmental outcome after perinatal asphyxia and hypothermia

- Lac/NAA was significantly higher at 24h of reperfusion for PLAC...
How about pharmacokinetics?

Effects of Hypothermia on Pharmacokinetics and Pharmacodynamics
A Systematic Review of Preclinical and Clinical Studies
Masol P H van den Broek, Flora Groenendaal, Armin C G Everts, and Corin M A Bakker

Still unanswered questions

- Earlier rewarming when (a)EEG is normal?
- Rewarming for ECMO? → Trial
- Cooling when 1st ultrasound shows abnormalities?
- When perform MRI? → day 4-7 (DWI)

Further studies

- Hypothermia Plus (Xenon, EPO, topiramate, stem cells...)
- Pharmacokinetics/pharmacodynamics? → PharmaCool study
- Length of ‘Therapeutic window’? → Late hypothermia
- Optimal temperature? Duration of hypothermia?
- Preterm hypothermia?
In summary

- Hypothermia is neuroprotective in full term neonates with hypoxic-ischemic encephalopathy (NTT 7)
- Hypothermia has few negative side effects
- Adverse outcome after hypothermia remains substantial (45%)
- Future studies are needed to improve the effects of hypothermia

Many thanks to …

- UMCU:
  - Linda de Vries
  - Manon Benders
  - Frank van Bel
  - Mieke Brouwer
  - Karin Rademaker
  - Mona Toet
  - Rutger-Jan Nievelstein
- NIDOD lab
- National and International collaborators
- UMCU Follow-up team:
  - Inge-Lot van Haastert
  - Rian Eijsermans
  - Corine Koopmans
  - Petra Lemmers
- PhD students
- Post-docs
- MR technicians