

Neonatal neuroprotection

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Important?

- 1 million death per year worldwide
- Major cause of CP
- More in developing countries

Treatable?

- Until recently: supportive care
- In the last 10 years: therapeutic hypothermia
- Hypoxia-ischemia leads to a chain of events:
 - Immediate insult
 - Latent interval
 - Neuronal cell death

May be treatable

- Therapeutic hypothermia
- With adjuvant therapies

Clinical signs

- Hyper alertness
- Lethargy
- Somnolence or coma
- Seizures
- Hypotonia
- Poor feeding
- Respiratory problems

Sarnat & Sarnat (Arch Neurol 1976)

- Report of 36 infants, GA > 36 weeks
- Following fetal distress
- N=21
- Three stages:
 - Stage 1: Mild: hyper-alert, normal EEG
 - Stage 2: Moderate: Obtundation, seizures, delta activity on EEG
 - Stage 3: Severe: Stupor, isoelectric/periodic EEG.

prognosis



How good is the Sarnat classification?

- 122 infants followed 2-5 years
- All those with Sarnat stage 1 were normal
- 25% with Sarnat stage 2 died or with disability
- 76% with Sarnat stage 3 died or with disability
- (Levene et al, Lancet 1986)

Hypothermia?

- Used routinely in congenital cardiac anomalies surgery
- In preterm infants: increase death rates
- Basic science showed that **secondary energy failure** is partly responsible for the damage
- Animal studies were promising

What is secondary energy failure?

- Following asphyxia in term infants
 - High energy containing phosphate compounds fall during the initial stages of asphyxia
Insult
 - These rebound after resuscitation when infants are more alert
Grace period
 - They fall again after 8-24 hours permanently
Too late (??) period

Proposed mechanisms for therapeutic hypothermia (in short)

- Decreased metabolic rate
- Decreased O₂ consumption and CO₂ production
- Reduced loss of high energy phosphates
- Reduced excitotoxicity
- Reduced reactive oxygen species production
- Protein synthesis preservation
- Decreased brain edema
- Modulation of the inflammatory cascade
- Change in pro- and anti-apoptotic signaling

3 RCT's published 2005-2009

- **CoolCap trial** (Gluckman et al Lancet 2005)
 - N=234
 - <6 hour
 - Apgar <5 @ 10 min or acidosis + background abnormality on aEEG
 - Selective head cooling 34.5° 72 hrs vs. conventional care
 - Outcome: death or severe disability @ 18 months
 - Results: better outcome if those with severe encephalopathy on aEEG excluded
 - Severe encephalopathy are unresponsive to Rx?

NICHD trial

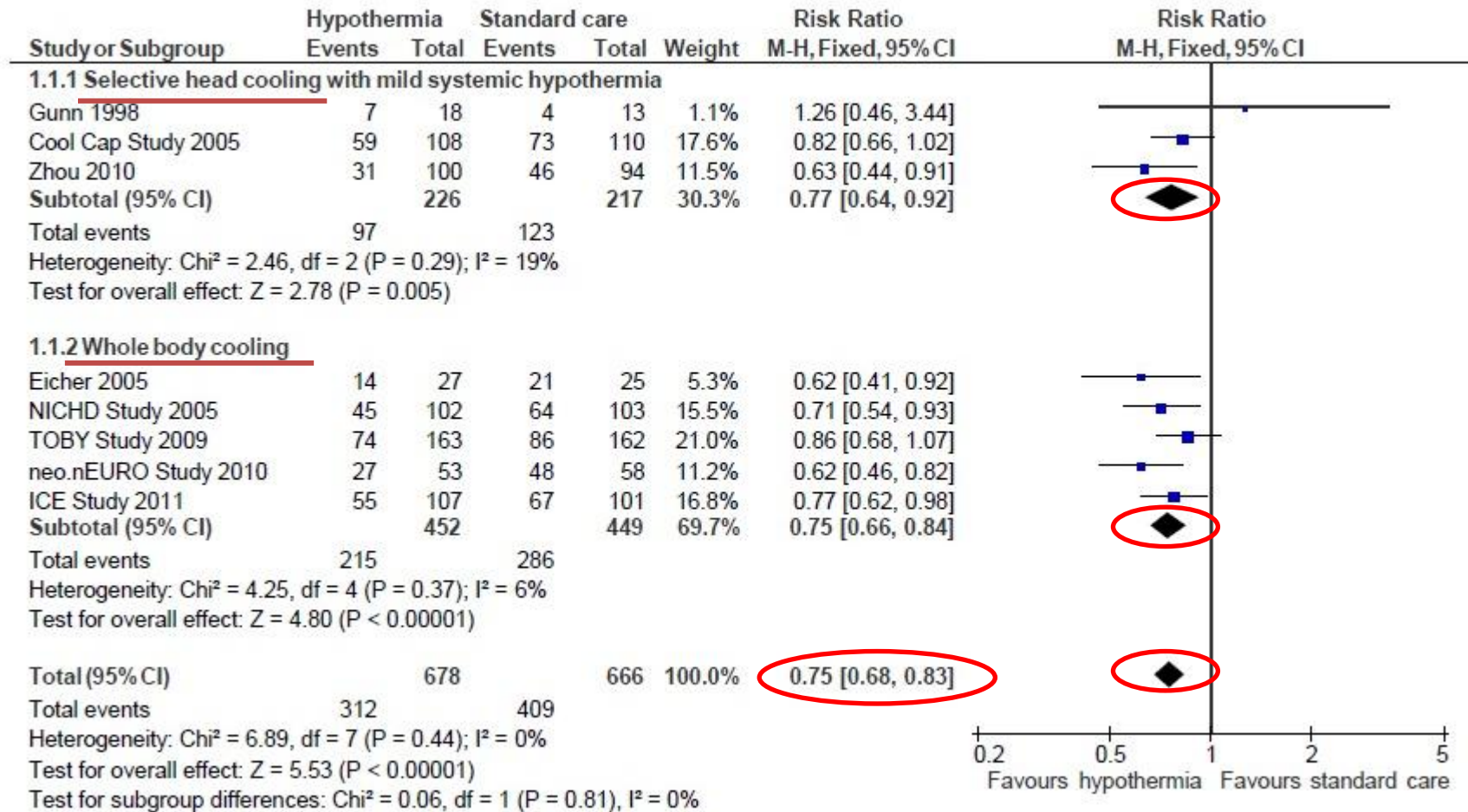
- whole body cooling (Shankaran NEJM 2005)
 - N=208
 - < 6 hrs
 - HIE after asphyxia
 - total body cooling 33.5 ° 72 hrs vs. conventional care
 - Outcome: death or severe disability @ 18 months
 - Results: reduction of death or severe disability from 62 to 44%

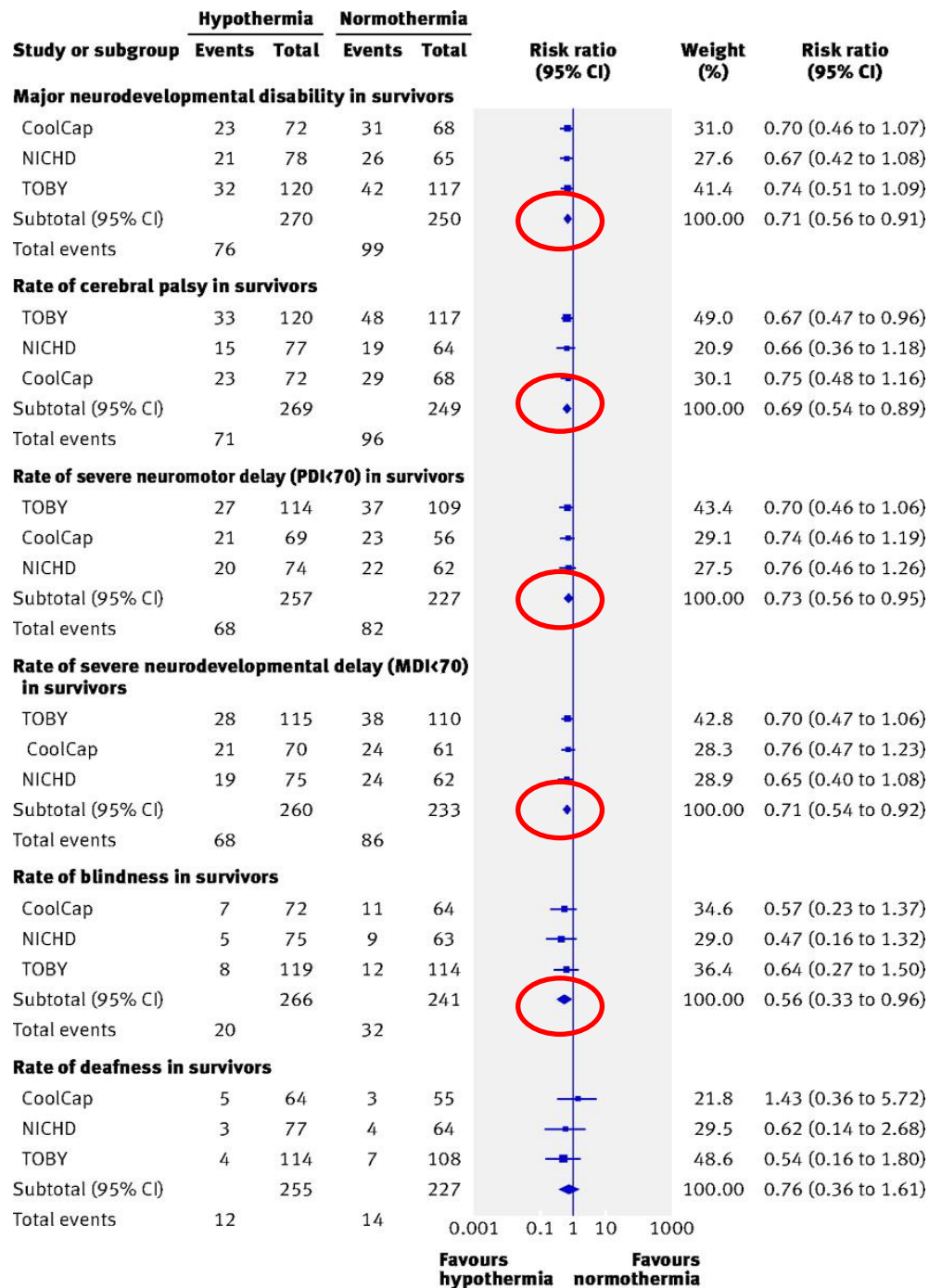
The TOBY trial (Azzopardi et al, NEJM 2009)

- N=325
- <6 hour
- Apgar <5 @ 10 min or acidosis + background abnormality on aEEG
- Whole body cooling 33.5 ° 72 hrs vs. conventional care
- Results: more intact survival 44% vs. 28% ; less CP 33% vs. 48%.

Forest plot of the composite primary outcome of death or major disability in survivors

1.1 Death or major disability in survivors assessed, by method of cooling





Meta-analysis

Cochrane 2012

- There is evidence from the 11 randomized controlled trials included in this systematic review (N = 1505 infants) that therapeutic hypothermia is beneficial in term and late preterm newborns with hypoxic ischemic encephalopathy.
- Cooling reduces mortality and benefits neurodevelopment.
- Hypothermia should be instituted in term and late preterm infants with moderate-to-severe hypoxic ischemic encephalopathy if identified before six hours of age.

Baby B

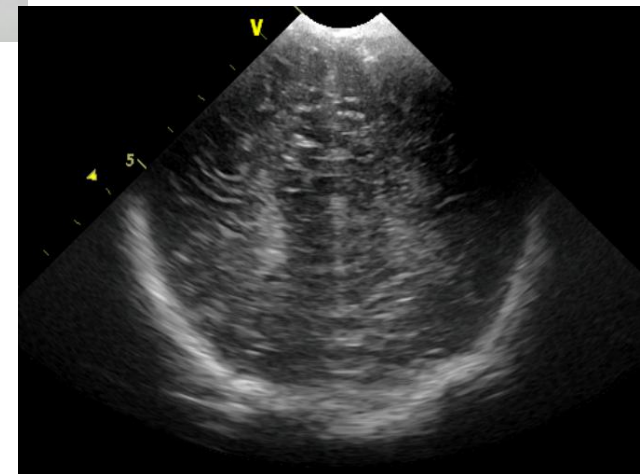
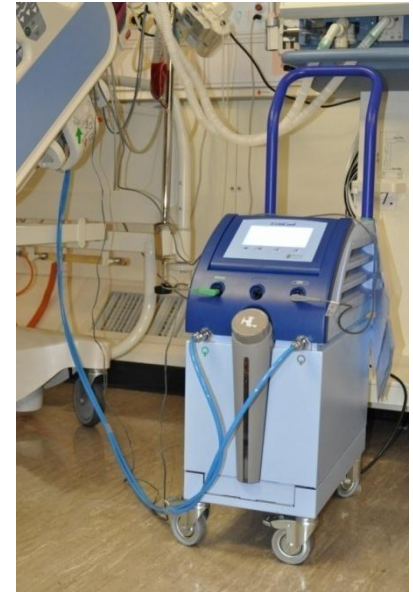
- 40 weeks GA
- Primipara
- After 14 hours in the delivery room: abnormal fetal heart rate
- Trial of vacuum extraction (X2)
- Vaginal delivery
- Cord blood gas: pH=6.86, pCO₂=93, BE=-17

Neonatal course

- Apgar score:
 - 1 min = 1
 - 5 min = 3
 - 10 min = 4
 - 15 min = 4
- Intubation by 3 minutes and PPV
- Physical exam: Hypotonia, reduced movements, no newborn reflexes, encephalopathy
- CFM: Burst suppression

Decision on hypothermia

- 72 hours at 33.5°C using MTRE (Allon) system
- Under CFM with seizure activity: phenobarbital
- Hypertonic upper body with hypotonic lower body
- Severe head lag
- US: hyper-echogenicity, slit-like ventricles (edema), blurring of grey-white matter





Follow-up

- **At discharge:** MRI – within normal limits
- Physical exam @ discharge: Head-lag, partial Moro reflex, no grasp reflex, no stepping and minimal placing reflexes
- EEG: occasional epileptic foci
- **At 2 months:** Moderate axial hypotonia, Head-lag. Physiotherapy
- **At 2 years:** Mild speech delay, NO CP, minimal motor delay

Adjuvant therapies – under clinical trials

- Melatonin:
 - anti oxidant, anti apoptotic, anti inflammatory
- Cannabinoids
 - Modulate intensity of neurotoxic process, and inflammatory response (grey and white matter)
- Erythropoietin
 - Anti apoptotic, anti oxidative, anti inflammatory
 - Repair: stimulates neurogenesis, oligodendrogenesis and angiogenesis

Other studies therapies

- Anticonvulsants:
 - Phenobarbital works in rats
 - Topiramate extends the window of time
- Xenon by inhalation works in piglets
- Nerve growth factor, IGF1, other growth factors (anti apoptotic)
- Stem cells
- All require further studies

What still needs further studies?

- What is the optimal time to initiate hypothermia?
- What is the optimal **duration and depth** of hypothermia?
- Rate of re-warming

A “cool” baby

