HIE – CAN WE DO BETTER?

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Neonatal HI

- 1.2 million perinatal stillbirths
- 0.7 million deaths related to prenatal events
- 1.2 million neonates HI
- 10 million not breathing at birth
- 125 million neonates born
- 0.5 million neurodevelopmental disability

- Most common cause of death & morbidity among human neonates
- 23% infant mortality worldwide
- Even in developed countries, incidence has not decreased in last 2 decades

Lee, Ped Res 2013
Why it’s a problem for us

Every newborn - 2035

Prevention

Lives that could be saved by 2025 with universal coverage of care.
*Lancet* 2014;384(9940):347–70

- 30% reduction in intra-partum related NND following resuscitation training
  *BMC Public Health* 2011;11(3):S12

>90% impact on saving lives
Prevention

HBB – Kenyan rural hospital:
• Quality improvement techniques to reduce HIE rates

• 10 months – HIE ↓53% (14.7/1000 – 7.1/1000 LB)

• Maintained sustained ↓ by:
  ❖ Improving staff communication
  ❖ Ongoing refresher training
  ❖ Retaining trained staff

Hyperthermia, hyperoxia!

- Avoid hyperthermia
  - T \geq 38^\circ C, unfavourable outcomes (CoolCap, nnn-Trial)
  - 3.6-4 fold risk of death/disability for every 1^\circ C \uparrow (NICHD)

- Initial resuscitation with 21\% FiO2
  - Better outcomes - \downarrow mortality, trend \downarrow mod-severe HIE, less oxidative stress (Saugstad, Neonatology 2008)
Current recommendations - Cooling

International consensus – Perlman, Circulation Oct 2015

• Low income/limited resources

• Mod-severe HIE may be treated with TH

• Clearly defined protocols ≈ RCT in developed countries

• Facilities with resources – IV, respiratory support, lab facilities, pulse oximetry, antibiotics, anti-convulsants, multi-disciplinary teams
Benefits of Cooling

• Reduces mortality and neurodevelopmental impairment at 18mo – NNT 6-7

• Advantages persist to 6-7 years (TOBY)
  ✫ more with IQ ≥85
  ✫ less mod-severe disability

• No increase in IQ <70, severe disability, ↓ death at 6-7yrs (NICHD)

• Association between favourable 18/12 and 7-8yr outcomes (CoolCap)
Long term quality of life

“Hypothermia for perinatal asphyxia: trial-based quality of life at 6–7 years” (TOBY children FU)

• Non-significant findings in favour of TH wrt HRQL
  ➢ esp speech

• Similar proportions (TH & control) reported as ‘happy and interested in life’

Campbell H, et al. Arch Dis Child 2018;0:1–6
Simple cooling methods

- Meta-analysis: LTTH + ventilation facilities + intensive monitoring
  - Studies from high & middle income countries
  - Target temperature within 2hrs
  - Mean temps 33.7-33.8°C
  - Significant ↓ in mortality & morbidity in survivors (≈ high tech methods)

Situation in SA in 2012

- Therapeutic hypothermia and hypoxic ischemic encephalopathy: opinion and practice of paediatricians in South Africa *

Start early
“TIME = BRAIN”

- Therapeutic limit – 6 hours
- Start ASAP
- < 3 hours – better motor outcomes
  (Thoresen, Neonatology 2013)

Newborn piglets:

- Latent phase/therapeutic window duration inversely proportional to severity of HI insult

*Iwata O, et al. Brain Res. 2007*
Referred patients

• Transfer
  o ASAP
  o Maintain T 36° C
  o Passive cooling – concerns re excessive/uncontrolled cooling

*Hallberg – Acta Paed 2009; Laptook – Ped 2010*
Outborn infants’ temperatures

USA NICU

TBH NICU

5% ≤ 32°C on admission

★International Consensus 2015: Passive cooling not harmless
- extreme/inappropriate hypothermia

**aEEG – effect of temperature**

- Little change with therapeutic range temperatures

- Flattens with deep hypothermia (<23°C)

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**aEEG related to brain temperature in piglet**

- Normothermia
  - 39°C

- >5°C (<34°C) decrease before significant change in baseline voltage

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Monitoring – NICN prevent 2° injury

Effects of HIE/Cooling

- Renal
- Respiratory
- Pulmonary hypertension
- Myocardial
- Hepatic
- Bone marrow

Multi-organ involvement
Monitoring

aEEG (if available)
• simple, non-EEG experts
• change in neurological status
• sub-clinical seizures
• directing care

Seizures
• >60% likelihood with abn initial aEEG
  (Glass, Neurol 2014)
• Additional brain injury
  (Shah, Arch 2014)
• Worse adverse outcomes
  (Glass, J Ped 2009)
Monitoring – aEEG/EEG

EEG Monitoring Technique Influences the management of Hypoxic-Ischemic Seizures in Neonates Undergoing Therapeutic Hypothermia

Jan s, et al. Dev Neurosci 2017;39:82–88

3 different periods
1. Brief (1 hr) conventional EEG
2. Brief EEG, then aEEG for cooling duration, then brief EEG after re-warming
3. Continuous video EEG (cEEG) during cooling (72h) + 12h during & after re-warming

46% less likelihood of ASD prescription in period 3 cf. period 1
→ Better detection of real seizures, but also less over-treatment
aEEG predictive value affected by TH

- PPV > 90% after 24h

- Abnormal outcome:
  - 50% abn aEEG (BS or worse) 24-48h
  - 100% abn aEEG at 48h

- Continuous/very repetitive seizures
  - usually v suppressed inter-ictal background & poor prognosis

Respiratory mx

- Hypothermia-induced ↓PCO₂ → ↑pH

- Alkalosis
  - ↓Seizure threshold
  - Left shift Hb-dissociation curve → worse tissue hypoxia

- ↑PVR - PPHN
Blood glucose

• Both ↓ and ↑ - adverse outcome


• Likely related to severity of injury vs TH

• Ability to become hyperglycaemic may indicate milder disease (less depleted liver/glycogen stores), but still need to control closely

  ❖ avoid iatrogenic hyperglycaemia while trying to prevent hypoglycaemia
Lab tests

Asphyxia & TH
- ↓Platelets, ↑DIC
- ↑Bleeding time, endothelial dysfunction

Infection risk
- HI → increase immune response
- TH dampens response
  - IL-6, IL-8, IL-10, MCP-1
- Early diagnosis – combination TH & infection → worse outcomes in infection-sensitised animal models
  - Shouldn’t be cooled??
  - Difficulties in diagnosis (TH: ↓WBC markers, del CRP response)
  - Current practice: antibiotics until cultures negative
Drugs

• HI-induced liver and renal injury

• TH-induced ↓ in enzyme kinetics

⇒⇒significant accumulation of drugs
Phenobarbitone

- T-1/2 more than doubled with TH
- Level only starts falling after re-warming
- NB. CYP2C19 function particularly sensitive to liver dysfunction

Other common drugs

• Phase 1 metabolism (hepatic cyt p450)
  - Midazolam, fentanyl, paracetamol, corticosteroids, phenytoin, phenobarbitone
  - **Lignocaine**, clearance ↓ by 24% during TH
    - shorter loading, ff lower weight-based infusion dosing

• Phase 2 (conjugation)
  - Phenobarbitone, paracetamol, Morphine (serum levels ↑42%, and clearance ↓22%)

• Phase 3 (renal excr)
  - ↑ **Gentamicin** trough levels - permanent hearing loss
    - trough levels before every dose, don’t re-dose until level < 2 mg/L
  - **Levetiracetam** largely (66%) excreted unchanged though kidney
    - concern levetiracetam may exacerbate HI injury – TH may protect against this effect - ??

Nutrition – to feed or not?

Survey of nutritional practices during therapeutic hypothermia for hypoxic-ischaemic encephalopathy

Beth Hazeldine,¹ Balamurugan Thyagarajan,¹,² Michellee Grant,¹ Elavazhagan Chakkarapani¹,²

UK units offering TH:

- No consensus re type/vol/frequency/PN
- 31% units – feeding guidelines
- 59% - enteral feeding during TH & re-warming
- 29% - PN; 86% of them feed concurrently
- Lower vols during TH cf after – 7.5ml/kg/d vs 17.5ml/kg/d

*Increasing trend of feeding during TH, primarily breastmilk*
Imaging

Cranial US

- Safe, repeatable, examiner-dependent
- Low predictive accuracy
- **Normal** – reassuring
- BGT, CO – assoc with MRI abnormalities
- Doppler CBF velocities
  - Pre-cooling: RI < 0.55
  - Cooling: PPV 60%, NPV 78%

Imaging - MRI/MRS

- MRI – structural changes after insult
  - support diagnosis of HIE
  - BGT, corticospinal tracts, WM, cortex
  - prognosis
  - assess therapies
  - timing

- MRS – biochemical and metabolic changes
  - ratios of metabolites
MRI injury & outcome

BGT

Mild BGT (28, 22%)
89%: no cerebral palsy
No infants with severe CP

Moderate BGT & equivocal PLIC (13, 10%)
Cerebral palsy: 61%

Moderate BGT & abnormal PLIC (22, 17%)
Cerebral palsy: 73%

Severe BGT (63, 50%)
Cerebral palsy: 98%

Abnormal signal intensity within the PLIC predicts abnormal motor outcome
Sensitivity = 0.9  Specificity = 1.0 *

MRI injury & outcome

**BRAINSTEM**

No brainstem injury (32%)
- No deaths

Moderate brainstem injury (23%)
- 25% died

Severe brainstem injury (45%)
- 50% died

Prediction of outcome

- Repeated & discharge neurological exam – **including HC, feeding**
  
  +

- Neurophysiological tests
  
  +

- Imaging
Conclusion

- Cooling now becoming more established
- Now need to optimise
- Strict monitoring (& follow up) important
- Most efforts - labour/delivery mx, resuscitation
Continuum of care

- "The time has come for these health interventions for newborn babies to be integrated into maternal and child health programmes... The continuum-of-care approach promotes care for mothers and children from pregnancy to delivery, the immediate postnatal period, and childhood, recognising that safe childbirth is critical to the health of both the woman and the newborn child—and that a healthy start in life is an essential step towards a sound childhood and a productive life. Another related continuum is required to link households to hospitals by improving home-based practices, mobilising families to seek the care they need, and increasing access to and quality of care at health facilities."

*The Lancet Neonatal Survival Series, 2005*

- "The right person, at the right time, in the right place, providing the right care."

*Centers for Disease Control/CARE International, 2001*
THANK YOU!