On Beyond Cooling- Review of Neonatal Encephalopathy and Its Treatment Head and Body Cooling

Learning for Babies 2013
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CNS injury
- Mechanisms of injury
- Making the diagnosis
- Neuroprotection-cooling total and selective
- Monitoring-Neonatal Neurointensive care-NIRS, aEEG
- EPO
- Magnesium
- Xenon

Lots of Mechanisms of CNS injury
- Congenital structural
- Global Ischemia
- Focal Ischemia-“stroke”
- Hypoxia-oxygen, anemia
- Hemorrhage/trauma
- Metabolic-drugs, toxins,
- Hypoglycemia
- IEM
- Infections-inflammation!!!!!
Neonatal encephalopathy

- Limited CNS repertoire-
  - Poor feeding
  - Seizures-focal general
  - Hypotonia
  - Hypertonia
  - Apnea
  - Unresponsive
  - "COMA"

Case

- 2 kg infant SVD Apgars 1/1
- Decelerations shortly before delivery
- Seizures shortly after delivery
- Now comatose in your nursery
- Cord pH 7.30
- Initial baby pH 7.4
- Diagnosis in chart “asphyxia”

Myotonic Dystrophy NOT HIE
NEW UNDERSTANDING

- In-utero
  - Injury → Intrapartum → Abnormal baby
- At least 25% are abnormal before labor.
- Isolated intrapartum injury occurs but is not common-debated hotly by lawyers and others
- Injury does not equal malpractice

Causes of neonatal encephalopathy

Acute HIE vs. Neonatal Encephalopathy
- Sudden and recent reduced oxygen delivery to the cells in the brain
- Pure hypoxia (low sats or anemia)- rare
- Ischemia- decreased blood flow
  - More critical than saturation
  - 50% of N.E. is HIE but ONLY 50%
Reminder oxygen delivery

- Oxygen delivery = Cardiac output × Oxygen content
- Cardiac output × (Saturation × Hbg + 0.03
Pao2)

Oxygen needed for efficient chemical energy utilization

Pathogenesis

- Decrease ATP = decrease ENERGY
- One half of all energy used maintains membrane ionic gradients
- Where does an Indian get energy from?
Pathogenesis of Hypoxic Injury

- Decrease brain glycogen
- Increase lactate
- Decrease Phos Creatinine
- Decrease ATP
- Tissue acidosis and leaking membranes

Animal models-Vannucci mouse

- Main post ischemic events include:
  - Propagation of cell injury-death of cells that appear undamaged initially
    - Free radical production
    - Excitatory amino acids
    - Calcium channel leak
  - Apoptosis programmed cell death
Cell Death

- Apoptosis.
- Some cells more sensitive than others.
- Hippocampus
- Some brain damage is not immediate but evolves over days.
- Apoptosis cascade started by membrane disruption

cell death and energy loss
FREE RADICALS

THE BAD GUYS
oxygen is a poison gas!!
O2~ OH~ H2O2

FREE RADICALS

THE GOOD GUYS
SUPEROXIDE DISMUTASE
CATALASE
poor CNS penetration limit trials

EXCITATORY AMINO ACID
Glutamine
Directly toxic to neurons
Blockage prevents cell death
Injection causes HIE
picture
Removal reduces HIE
CALCIUM CHANNEL BLOCKERS

Make good theoretical sense
Animal studies have been split

Cardiac output dependent upon Calcium- be careful !!
Recognizing - Acute Perinatal HIE

You MUST know this….

- Criteria for Diagnosis
  - Abnormal tracing - flat or severe bradycardia
  - Cord pH <7
  - Low apgars 10 minutes
  - Hypotonia
  - Seizures
  - Multiorgan dysfunction
- 1-2/1000 = 4000 infants each year in U.S.

Don’t Put Square (HIE) Peg
In Round Hole-
“Neonatal Encephalopathy”

Cord pH

- .6% of all deliveries pH less than 7
- 50% of these had one minute Apgar <=6
- 17% had five minute <=3
- Only those with both low Apgar and low pH had permanent injury
Apgar Scores

➢ One Minute < =3
  • 4.8% of all infants
  • 0% CP if 5 minute >=4
  • 1.7% CP but eight times normal
  • Kids with CP only 26% had one minute <=3
  • All had 5 minute low apgar scores

Apgar Scores

➢ Five Minute < =3
  • 1% of all normal (longterm) infants
  • If next Apgar >=4 only 1% CP incidence
  • Kids with CP only 15% had five minute <=3

Apgar Scores

➢ 10 Minute < =3
  • <.5% of all infants
  • 34% died
  • 16.7% CP in survivors 80 time normal
  • If normal at 15 minutes risk is 4.7%
Apgar Scores

- 15-20 Minute $\leq 3$
  - <.1% of all infants
  - Over 50% died
  - 36% and 57% CP

Timing of HIE

- Frequent medical legal question.
- In term infants
  - 20% antepartum
  - 35% intrapartum
  - 35% both
- More importantly therapeutic question

MRI good but not within first hours
Acute Perinatal HIE versus Neonatal encephalopathy

- Many babies recover without permanent disability
- Isolated Diseases NOT caused by HIE
  - Mental Retardation
  - Epilepsy
- "Must" have CP since motor areas more vulnerable
- Rare exceptions

Predicting adverse outcome of acute Perinatal HIE

- 226 Infants age 3 -1985
  - Mild 0 / 79
  - Moderate 31 / 119
  - Severe 28 / 28
- Thompson Score or Sarnat Score
Is there a window of opportunity to decrease brain injury POST event?

- 1975 Myers monkeys
- Brain swelling is associated with poor outcomes.
- Babies deteriorate and brain swells therefore decreasing swelling could prevent deterioration.

1975-1990

- I was so smart in 1975!!
- Ischemia causes edema which causes further ischemia
- Cascade of cell death edema related
Edema

- “Treatments” (mannitol, diuresis, fluid restriction, hyperventilation and steroids) aimed at controlling the CNS edema
- Did not improve outcomes.
- We learned that the edema is a result of CNS injury not the cause.

Phenobarb

<table>
<thead>
<tr>
<th>Outcome: Severe neurodevelopmental disability in survivors</th>
<th>Number of studies</th>
<th>Number of infants</th>
<th>Number of cases</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein et al. [8]</td>
<td>1/3</td>
<td>1/3</td>
<td>0.36</td>
<td>0.04 (0.01, 0.84)</td>
</tr>
<tr>
<td>Math et al. [4]</td>
<td>1/3</td>
<td>1/3</td>
<td>1.00 (0.32, 3.24)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1/3</td>
<td>1/3</td>
<td>0.87 (0.47, 1.62)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval.
Treatments failed

“Window of opportunity” energy metabolism preserved

Cold Water Submersion

- SURVIVAL AFTER 40 MINUTES SUBMERSION WITHOUT CEREBRAL SEQUELAE
Hypothermia and resuscitation

- Westin et al 1957 and 1958
- 10 infants resuscitation HR below 100, were immersed in cold water bath until breathing or 27 degrees C.
- 9/10 survived no CP
- Subsequent 52 of 65.
Hypothermia and resuscitation

- Report from Sir John Floyer 1697
- "Sarah Parks... gave still-birth to a baby boy... A young doctor assisting the Parks' regular physician begged for an opportunity to experiment with an idea he had to rouse the lifeless infant. A tub of ice was ordered and the young doctor plunged the baby into it. Out came the screaming little Parks and he was named Gordon after the doctor who prodded him to life."

Warmth and Resuscitation

- Silverman 1958
- Survival of Premies =
  - 83% if warmed
  - 68% if cool

Hypothermia Risks

- Peripheral Vasoconstriction
- Diuresis
- Cardiac Dysfunction
- Arrhythmias
- Coagulopathy
- Leukocyte dysfunction
Keep the baby warm!

HYPOTHERMIA in RATS

- 37 CENTIGRADE: 90%
- 34 CENTIGRADE: 40%
- 31 CENTIGRADE: 0%

Yager JY 93

What does cooling do?

- Decrease metabolic activity
- Reduce fluid loss
- Reduce oxygen consumption
- Reduce shivering
- Reduce protein decomposition
- Reduce thermal irritability
- Reduce infection risk
- Reduce pain
- Reduce mortality
- Reduce metabolic acidosis
- Reduce loss of blood
- Reduce brain swelling
- Reduce fever
- Reduce organ damage
- Reduce stress
- Reduce energy expenditure
When to start? How late is too late?

- Cerebral Hypothermia Is Not Neuroprotective When Started after Postischemic Seizures in Fetal Sheep
- GUNN, ALISTAIR J.;
- 8 hours no effect
- Presently-on-going trial on starting between 6-24 hours

Hypothermia timing

- 90 minutes-5 hours after insult decreases neuronal loss
- Duration 72 hours
- SOONER IS BETTER article by Gunn <2 hours necessary to start in sheep

For how long?

- Twenty-Four Hours of Mild Hypothermia in Unsedated Newborn Pigs Starting after a Severe Global Hypoxic-Ischemic Insult Is Not Neuroprotective
- THORESEN, MARIANNE;
- 48-72 hours necessary
- Adults do 12-24 hours, study on-going for 96 hours
Depth of Cooling

- < 32 degrees rectal worse outcome
- Prolonged QT at 34.5 rectal
- Rectal temperature is 2 degrees C greater than NP temperature
- Can the brain be cooled?
- Differential effects of cooling cortex and deep structures?

**Randomized Trial of Systemic Hypothermia Selectively Protects the Cortex on MRI in Term Hypoxic-Ischemic Encephalopathy**

JOP Dec '04
NDER, TERRIE E, MB, CHB, MD; et al.
Systemic hypothermia 33-34 C
72 hours

A
B

Reduction in death and disability by whole body hypothermia

- 204 infants followed
- **Death/disability**: 45% vs 62% (RR: 0.55-0.93), adjusted: 0.60-0.98
- **Death**: 24% vs 36% not significant

Death/disability: 45% vs 62% (RR: 0.55-0.93), adjusted: 0.60-0.98
Death: 24% vs 36% not significant
Cooling improved intact survival excluding the most abnormal baseline

EEG changes

- Mortality trended down from 39% (control) to 29% (cooled), p < 0.2
- A 58% reduction in motor abnormality in survivors in this sub-group
Therapeutic hypothermia following perinatal asphyxia-Meta Analysis
Edwards and Azzopardi
ADCFN 2006

- Combined three trials data.
- Either method of cooling reduces the combined chance of death or disability.
- Relative risk of death or disability was decreased to 76% of Controls with confidence interval 65-89%.
- Standard of Care in 2013.

We have moved to whole body to enable monitoring of CNS with NIRS and EEG.

- No major difference in complications or outcomes.

Detecting on-going/impending CNS injury?

- aEEG
- Continuous EEG
- MRI
- Physical exam
- NIRS
What is aEEG?

- Single EEG Lead (3 wires)
- Bi-parietal or frontal
- Monitor Global Electro-cortical Activity
- Very Slow, Trend Display

Very Slow, Trend Display
Global Electro cortical Activity

- Limited number of electrodes
- Global activity only
- Will not localize lesion
- May not see some types of focal seizures
- High level = high activity
- Low level = suppression
Sleep/Wake Cycling

Seizures

Moderately Abnormal
Severely Abnormal

Seizures

General Monitoring

- Assist in neurological evaluation on admission (paralysis)
- Alteration related to other conditions (apnea, hypotension)
EEG

Is it a seizure?

- [http://www.youtube.com/watch?v=fuuysAn5QDc](http://www.youtube.com/watch?v=fuuysAn5QDc)
- [http://www.youtube.com/watch?v=dwr4c96Qi9M](http://www.youtube.com/watch?v=dwr4c96Qi9M)
- [http://www.youtube.com/watch?v=LcyxZjm2540&NR=1&feature=endscreen&list=PL20F51849F3416A3D](http://www.youtube.com/watch?v=LcyxZjm2540&NR=1&feature=endscreen&list=PL20F51849F3416A3D)

NIRS- mixed venous saturation
NIRS in premie

NIRS

To assess cerebral autoregulation

Boy of 31 wk 1350 g. intact autowalory ability
Need more data

- Need more data to understand the correlation of NIRS and aEEG with outcomes
Even in HIE - Need more than cooling

- Despite cooling over 40% of infants will die or suffer moderate to severe disabilities including cerebral palsy, intellectual impairment, and epilepsy.

Xenon-noble gas

- The N-Methyl-D-aspartate (NMDA) subtype of the glutamate receptor is the molecular target for xenon.

- Xenon inhibits NMDA receptors by competing with the co-agonist glycine at the glycine-binding site on the GluN1 subunit.
Xenon-glutamate antagonist
RATS

- Noble gas that rapidly reaches equilibrium with the tissues when inhaled.
- Partial pressure in the brain will closely follow that delivered to the lungs.
- Effective anesthetic with a very rapid onset, no metabolism by the body, and no proven adverse neurotoxic side effects.
- Very expensive

Xenon trial underway in Great Brittan
Babies with HIE
Transport Xenon- costs a lot $$$$
$5400 per hour
$8 per hour if recycled

Mg Sulfate
Pediatrics April 6th 2009

- Mg blocks influx Ca
- 40 babies randomized
- 3 doses 250 mg/kg MgSO4

Result-
- 22% vs 56% abnormal short term
Mg Sulfate-Cochrane review

- The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth for the preterm fetus is now established.

- The number of women needed to be treated to benefit one baby by avoiding cerebral palsy is 63 (95% confidence interval 43 to 155).

Mg Sulfate Trial

- In Qatar- no cooling coordinating a multinational trial of 250 mg/kg Mg Sulfate IV over 30 minutes times three.

- Randomized 47 of 200 enrolled to date

EPO

- Exogenous EPO-enhanced revascularization in the ischemic hemisphere correlated with decreased infarct volume and improved neurological outcomes after H/I. In mice....
**HIE and Erythropoietin Stimulating Agents (ESA)**

- ESA work through several important mechanisms in early and later phases following hypoxia ischemia including:
  - limited oxidative stress
  - decreased apoptosis
  - via pro-angiogenic and neurogenic properties

- Darbepoetin (Darbe), an EPO-derived molecule, has extended circulating half life and comparable biological activity to EPO.
EPO Longer window……?

Darbepoetin Administration in Newborns Undergoing Cooling for Encephalopathy

Mariana Baserga, Joanna Beachy, Bob DiGeronimo, Brad Yoder, Bob Ward, Bob Christensen, Robin Ohls, Dennis Mayock, Sunny Juul, Bill Walsh

Screening and Consent

- Must enroll patients and get study drug started within 12 hours of birth
- Multiple trials of EPO on-going
Case

- Term infant mother noted lots of fetal movements and hiccups
- Baby with seizures starting immediately after birth, cord pH normal, Apgars low.
- Glucose, pH and metabolic work-up negative

Non-ketotic hyperglycinemia

- Rare metabolic disorder associated with inability to metabolize amino acid glycine.
- Labs all normal may even have normal serum amino acids, but CSF glycine abnormal. Usually fatal
- gene therapies?
- at least prediction!

Structural defects - Stem cells?
Stem Cells

➢ Some evidence delayed cord clamping beneficial.

➢ Duke doing trial of Cord derived stem cells.

➢ May be reasonable to bank stem cells for future in families with at risk baby.

➢ Collection & Processing $1,695
➢ First Year of Storage $130
➢ One-Step Shipping $170
➢ **Total Price** (One-Time Payment) **$1,995**

➢ An annual storage fee of $130 is charged each year following your baby’s first birthday.
Infections only 2% but impact development

- Viral TORCH infections
- Bacteria GBS, E.Coli, GNR
  - 25% of sepsis has associated meningitis
  - 18% of meningitis negative Blood culture
  - Poor outcomes
- LP indicated if fontanel not bulging. IICP?

Summary

- Know too little about CNS and its repair- I am so dumb in 2013 compared to how much I knew in 1975
- Neonatal neurology will supplant Cardiopulmonary focus in neonatology?
- New monitoring tools and treatments are being developed.

Questions? Time flies…. 
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