CAN WE PREVENT OR REDUCE IVH IN THE VERY PREMATURE?

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OUTLINE

• DEFINITION OF IVH AND PVL

• IVH BY THE NUMBERS - National, Local

• ANATOMY OF THE PRETERM BRAIN AND VULNERABLE AREAS - Basic Science?! yikes…..

• RISK FACTORS FOR IVH/ICH

• THERAPIES OR INTERVENTIONS TO REDUCE IVH/ICH

• FUTURE INTERVENTIONS OR CHANGES FOR TG-NICU
INTRAVENTRICULAR HEMORRHAGE (IVH) AND PERIVENTRICULAR LEUKOMALACIA (PVL)

- IVH is a major complication of prematurity
- Originates in the Germinal Matrix (GM) - a highly vascular mass of neuronal-glial precursor cells
- Cause of IVH - mainly due to inherent fragility of the GM, disturbances in Cerebral Blood Flow (CBF), platelet or coagulation disorder,
- CBF changes, platelet/coag. disorder can possibly be altered by care practices, at this time
EPIDEMIOLOGY OF IVH

• Annually, about 12,000 premature infants in the USA develop IVH

• Highest rates in the most immature neonates

• 500-750 gram patients: 45% develop IVH, 26% will have severe forms (Grade 3, 4)

• 750-1000 gm: 25-30% overall, 12% severe IVH
IVH - WHY?

- PRIMARILY ATTRIBUTED TO:
- INCREASED VASCULAR FRAGILITY
- DISTURBANCES TO CEREBRAL BLOOD FLOW (CBF)
- POSSIBLY, BUT NOT OFTEN DISORDER OF PLATELET COUNT, COAGULATION
Grades of IVH

- Grade I - also called Germinal Matrix Hemorrhage (GMH) - localized to GM
- Grade II - blood ruptures through GM, and extends into the ventricular system
- Grade III - extensive blood into the ventricular system, with associated dilation of ventricles
- Grade IV - extension of the hemorrhage into the adjacent white matter, causing eventual necrosis
**TACOMA GENERAL HOSPITAL-MULTICARE [TACO:178]**

Severe IVH - Yearly

Gestation: All; Birth Weight: <=500g, 501 - 1500g
Patient Status: All; Admit Group: All; Network: High Volume PDX Sites

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<th>Year</th>
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VON - IVH, 2013 at TGH
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IVH - Biology of the VLBW Brain

- Very vascular, vulnerable to bleed
- After 24 weeks, thickness decreases, gone by 36-37 wk
- Hemorrhage in the GM - grade I IVH or, GM Hemorrhage, GMH
ANATOMY OF THE GERMINAL MATRIX
NEUROANATOMY OF THE PREMATURE BRAIN - GERMINAL MATRIX, ETC

- Blood vessels in the brain form a Blood-Brain Barrier - a complex, dynamic interface

- Structures: endothelial tight junctions, basal lamina, pericytes, astrocyte end-feet

- Deficiency in any area weakens the vascular integrity, thus becoming prone to bleeding

- Pericytes are a key component: angiogenesis; position to strengthen vessels
NEUROANATOMY OF THE PREMATURE BRAIN - GERMINAL MATRIX, ETC

• Pericytes are recruited by growth factors; TGF beta and 3 others (Transforming growth factor)

• Reduced Fibronectin in basal lamina

• Reduced GFAP in the astrocyte end feet (glial fibrillary acidic protein)

• Rapid angiogenesis, low TGF-beta, deficient pericytes in an area of fragile blood vessels
CAN WE DEFINE THE CAUSES OF IVH?

- **RISKS** - Vaginal Delivery, low Apgar score, severe RDS, pneumothorax, hypoxia
- Also - hypercapnia, seizures, Patent Ductus arteriosus, infection, lack of intrapartum care
- Others: chorioamnionitis, fluctuating BP, lower birthweight, decreasing Gestational age
- Absence of maternal antenatal Steroids/Glucocorticoids
CUS: GRADE I, IVH
CUS: GRADE II, IVH
CUS: GRADE III, IVH
CUS: GRADE IV, IVH
Germinal Matrix Hemorrhage
Grade II (2) IVH
Grade III (3) IVH
Grade IV (4) IVH
STRATEGIES TO REDUCE IVH

• STABILIZE THE CBF

• STRENGTHEN VASCULATURE OF THE GERMINAL MATRIX

• CORRECT PLATELET OR COAGULATION ABNORMALITIES

• OVERALL IVH REDUCTION “BUNDLE”
Don’t rush to cut the cord
New recommendations call for delaying cord clamping in preterm infants

by Tonse N. K. Raju, M.D., D.C.H., FAAP

The Academy has endorsed a statement from the American College of Obstetricians and Gynecologists that recommends waiting 30-60 seconds when feasible before clamping the umbilical cord in preterm infants (Obstet Gynecol. 2012;120:1522-1526). The College committee opinion was based on studies showing delayed clamping has measurable benefits to the infant with little or no risk to the infant or mother.

The committee did not endorse delayed cord clamping for term infants or for those requiring immediate resuscitation. It stated that “there was insufficient evidence to support or refute the benefit of delayed cord clamping” in such cases. Moreover, there is a small risk of increased need for phototherapy in infants with delayed cord clamping.

In 2009, the World Health Organization (WHO) recommended delaying cord clamping up to 120 seconds in term infants based on studies showing increased infant blood volume, higher iron stores and cental transfusion. A Cochrane systematic review of 15 eligible trials of cord clamping and cord milking with 738 mothers and their preterm infants (24-36 weeks’ gestation) found increased placental transfusion led to robust benefits (Rabe H, et al. Cochrane Database Syst Rev. 2012 Aug 15;8:CD003248) (see table). Six to 15 infants were needed to receive increased placental transfusion, and the risk of anaemia in infants with a total transfusion of 200-250 ml of whole blood was reduced by 53% (95% CI, 10% to 82%).

Future research should focus on optimal time to clamp infants (e.g., infants prone to delayed cord clamping, infants with maternal hemorrage, or those born at lower gestational ages). For now, it appears prudent to delay cord clamping in preterm infants for 30-60 seconds after birth.
DELAYED CORD CLAMPING

- AAP endorsed the ACOG statement recommending delayed umbilical cord clamping
- Obstet Gynecol. 2012; 120:1522-1526
- Obstet Gynecol. 2014; 124 (1); 47-56. Backes
- Measurable benefits to newborn, no risk to mother or baby
- Benefits - reduced IVH all grades, NEC, Sepsis, Mortality
- Reduced need for blood transfusion, BP support
DELAYED CORD CLAMPING

- Cochrane Review 2012: 15 trials, 738 mothers and pre terms (24-36 weeks), cord clamping or cord milking - increased placental transfusion

- Number needed to treat: 6 to 15 neonates to reduce major adverse effects in one patient; 30-60 seconds

- Small risk of increased need for phototherapy

- DCC is performed at TG and Multicare birth centers for EGA < 32 weeks

- Not done if immediate resuscitation is needed, or in multiples
STRATEGIES TO REDUCE IVH - Antenatal

- Maternal Magnesium Sulfate Therapy Before Anticipated Preterm Birth for Neuroprotection - ACOG Committee Opinion No. 455, 2010
- Deliver in a Perinatal-Neonatal Center
THERAPIES AND INTERVENTIONS TO PREVENT IVH

• Prenatal Interventions: Prevention of Prematurity

• Maternal Transport to a Regional Perinatal/Neonatal Center - resuscitation by experienced team of Neos, NNPs, RNs and RRTs

• Prenatal - Administer Betamethasone!!
THERAPIES AND INTERVENTIONS TO PREVENT IVH

- Administration of Maternal Antenatal Steroids:
  - Increases GM Pericyte Coverage
  - Increases GFAP expression in Pericytes
  - Increases Fibronectin in Basal Lamina
Fragility of the germinal matrix vasculature sets the stage for pathologic events.
THERAPIES AND INTERVENTIONS TO PREVENT IVH

- Potential Best Practices (PBPs) ; Carteaux, Cohen et al., PEDIATRICS 2003; 111: e489-e496 - To Prevent Brain Hemorrhage and Ischemic Brain Injury in VLBWs

- Multiple centers grouped together, studied care practices, and devised a list of PBPs

- Ten items were noted: #1 - BETAMETHASONE

- Deliver in Tertiary Center with a NICU, MFM management, antibiotics for Preterm ROM, etc

- Optimal - direct management by Neonatologist
THERAPIES AND INTERVENTIONS TO PREVENT IVH - PBPs

• Use measures to minimize pain and stress - control CBF; noise, handling, light, low dose narcotic only if needed

• Optimal Positioning - head neutral, even when turning; elevate head 30 degrees

• Treatment of Hypotension - treat only overt hypovolemia; fluid bolus over 30 minutes, limit to 2 boluses, then cardio-active drug infusion

• Judicious use of Indomethacin - facilities where still used

• Optimize respiratory management; synchronized
THERAPIES AND INTERVENTIONS TO PREVENT IVH - PBPs

- Optimize Respiratory Management: avoid hypocapnia, no routine Chest PT, avoid routine suctioning of ET tube, also avoid hypercapnia
Delivery and Resuscitation - Can we Improve Gentle Care in the Delivery Room?

Golden Hour of Care

- All sources of sensory stimuli and stress are topics to discuss
- Noise - avoid shouting, use quiet voices.
- Temperature - prewarm room and warmer, thermal pad, warm blankets or bag, hats
- Delayed Cord Clamping - 30 to 60 seconds
- Avoid Oral Suctioning per new AAP guidance - unless it is indicated.
- Prevent hypothermia of the VLBW - place into a “baby bag” even when delaying cord clamping
Gentle Care in the Delivery Room - Golden Hour of Care
Preterms < 31 weeks, < 1500 gms

- Warm room - 76F
- Pulse-ox right wrist; using room air, mask
- Apply Neo-Puff - inflating breath of 5 sec
- Mask CPAP if breathing; assess need for O2
- Maintain CPAP, or Intubate
- Transport to the NICU
- Surfactant: intubate, instill and consider extubation
GOLDEN HOUR OF CARE IN THE DR AND NICU

• Prevent hypothermia - bag, hats, thermal mattress, etc

• Address glucose status, needs right away

• Goal of adequate Blood Pressure (≠ Normal)

• Administer antibiotics within first 60 minutes

• Achieve vascular access in the first hour

• No rapid infusions - meds, volume, blood

• Incubator top down, closed (Admission complete) - 1 hr
Minimal Handling Style of Care - following Golden Hour

• Minimal stimulation or handling: 3 to 5 days (Most IVH occur in first 3 days)

• Head stays in midline (Avoid jugular occlusion?)

• Head of Bed elevated - 15 to 30 degrees (control cerebral blood flow, CBF)

• No early LPs (CBF, agitation)
Minimal Handling Style of Care - following Golden Hour

• Use of Midazolam Sedation? Cochrane Review - March 2012, Ng E., IV Midazolam Infusion for Sedation of Infants in the NICU

• Midazolam was associated with increases in Grade 3 or 4 IVH, PVL, and death

• Insufficient Data to Recommend use of Midazolam as a Sedative for use in the NICU
Minimal Handling Style of Care - following Golden Hour

- Don’t raise the buttocks to change diapers (CBF)
- Assess patient each 6 hours, vital signs by monitor each 3 hrs
- Delay PICC insertion beyond Day 3 (Unless very urgent for vascular access)
Indomethacin and Reduction of IVH

• Early Postnatal use of Indocin helps prevent severe grades of IVH (B. Schmidt, NEJM, 2001)

• A prior study showed the same reduction in IVH compared to controls (L. Ment, Pediatrics, 1994)

• But - the longer term followup showed no difference between treated and control infants on motor deficits (CP), or cognitive delay

• The significant side effects of early indocin (e.g., intestinal perforation) has led our group to stop using this drug
IS IT JUST ABOUT IVH, PVL OR ICH?

• JJ Volpe Pediatric Neurologist, author of Volpe’s Neurology of the Newborn has published new work on a different Neuronal/Axonal Disease

• This frequently accompanies PVL - it is a loss of volume in cerebral white matter, thalamus, basal ganglia, cerebral cortex, brain stem, cerebellum

• “Encephalopathy of Prematurity” - loss of volume on microscopic level, seen better on MRI than US
Volpe and Encephalopathy of Prematurity

• Lancet Neurology; Jan 2009; Brain Injury in premature infants: a complex amalgam of destructive and developmental disturbances

• Brain Injury in Prematures: great public health interest due to larger no. of survivors, disabilities

• Both major cognitive defects and motor disability

• Not just a matter of PVL (Periventricular Leukomalacia)
Encephalopathy of Prematurity: EP

- Gray and white matter lesions in the preterm brain, multifaceted, diffuse
- Reflects acquired insults, altered development trajectories, combined with reparative efforts
- Causes of EP: multifactor, brain hypoxia-ischemia, systemic infection, inflammation, immaturity
- Toxicity to neurons by free radicals, cytokine, etc
- Deficits in executive function, autistic behaviors, cerebral palsy, visual cognitive impairments.
Volpe and Encephalopathy of Prematurity

- PVL - injury to and loss of white matter near ventricles
- Necrosis of neurons
- High risk for motor deficits, Cerebral Palsy
CAN WE PREVENT OR REDUCE IVH IN THE VERY PREMATURE?

Perhaps we can - through a system wide, comprehensive approach that includes OB/MFM, Delivery Room personnel, the post birth Neonatal care team + Parents
IVH Reduction Bundle - Does One Exist?

- Prevent the Premature Birth
- Antenatal Corticosteroids! Yes and Yes
- Deliver in Perinatal/Neonatal Center
- Delayed Cord Clamping
- Careful Delivery Room Management
- Golden First Hour in the NICU
- Avoid BP perturbations, or risk of it (Complications)
- Indocin? Sedation? Developmental Care
IVH Reduction Bundle - Continued

- Ongoing NICU Care -
- Minimal Stimulation and Procedures - head midline and elevated
- Mitigate anything that can cause changes in BP, brain blood flow, hypoxia etc.
- Replace blood products, platelets etc.
- Gentle ventilation, no routing suctioning, SIMV, extubation to CPAP
The Impact of Grade I and Grade II IVH


- 1472 infants, < 27 weeks, Jan 2006-Dec 2008, surviving to 18-22 months for testing

- At 18-22 months, the neurodevelopment outcome of the extremely low Gest. age are not different from those with no IVH
The Impact of Grade I and Grade II IVH


- 471 neonates, < 32 weeks, 1994-2005. Low grade IVH patients had lower cognitive scores, lower psychomotor scores, and higher rates of cerebral palsy and visual impairment

- Perhaps we should continue to urge some caution when discussing these with parents