The Science and Management of Transfusion Therapy

Robert D. Christensen, MD
Declaration of Conflicts of Interest

I have no FDA declaration or financial benefit related to anything I will discuss in today’s lecture.
Outline

1) Differences between banked donor (adult) RBC and a VLBW neonate’s own RBC

2) Associations between “early” RBC transfusion of VLBW infants and development of severe IVH

3) Associations between “liberal” RBC transfusion of VLBW infants and poor neurodevelopmental outcome
Outline

1) Differences between banked donor (adult) RBC and a VLBW neonate’s own RBC

2) Associations between “early” RBC transfusion of VLBW infants and development of severe IVH

3) Associations between “liberal” RBC transfusion of VLBW infants and poor neurodevelopmental outcome
What are the differences between banked donor RBC and a VLBW neonate’s own RBC?
LARGE SIZE of Fetal RBC

McV (fL)

Weeks Gestation

Adult = 88±8fL
LARGE SIZE of Fetal RBC

RBC of VLBW neonates 30-50% larger, and carry 30-50% and more hgb/cell

Adult = 88±8fL
DEFORMABILITY (elasticity) of Fetal RBC. Erythrocytes must change their shape extensively while traversing the microcirculation.
DEFORMABILITY of Fetal RBC. Erythrocytes must change their shape extensively while traversing the microcirculation.

Banked RBC have a time-associated reduction in deformability as part of the “Storage Lesion”
FETAL HEMOGLOBIN. Binds O₂ more tightly, at any physiological pO₂ releases less to tissues.
Dilatation of capillary beds by nitric oxide of VLBW RBC
Nitric Oxide and the RBC Storage Lesion

- Free hemoglobin
- Microparticles
- Hemostatic activation
- Vasoconstriction
- Platelet adhesion and aggregation
- Platelet-neutrophil interactions

Chemical reactions:
- NO → NO$_3^-$
- NO → O$_2^-$

Species:
- Nitric Oxide (NO)
- Nitrate (NO$_3^-$)
- Superoxide (O$_2^-$)
Nitric Oxide and the RBC Storage Lesion

- Increased potassium
- Reduced 2,3 DPG
- Reduced deformability
- Free hemoglobin
- Microparticles
- Reduced NO synthase
- Vasoconstriction/inflammation
Outline

1) Differences between banked donor (adult) RBC and a VLBW neonate’s own RBC

2) Associations between “early” RBC transfusion of VLBW infants and development of severe IVH

3) Associations between “liberal” RBC transfusion of VLBW infants and poor neurodevelopmental outcome
Christensen RD, Lambert DK, Baer VL, Montgomery DP, Barney CK, Coulter DM, Ilstrup S, Bennett ST. Postponing or eliminating RBC transfusions of VLBW neonates by obtaining all baseline laboratory blood tests from otherwise discarded fetal blood in the placenta. Transfusion. 2011 February;51(2):253-8


Baer VL, Lambert DK, Henry E, Snow GL, Christensen RD. RBC transfusion of preterm neonates with a grade 1 IVH is associated with extension to a grade 3 or 4 hemorrhage. Transfusion. 2011 September 51 (9):1933-9.
Intraventricular hemorrhage and periventricular hemorrhagic infarction

- Eight to ten percent of VLBW neonates develop a severe hemorrhage (grade 3 or 4).
- Over 75% of VLBW neonates surviving a grade 3 or 4 hemorrhage develop life-long neurodevelopmental handicaps.
Hypothesis: If the timing of a severe IVH can be approximated by serial ultrasound examination, potentially relevant antecedents can be identified.

Design: Find all cases where one or more cranial US studies showed no hemorrhage, and subsequent scans showed a grade 3 or 4.
The 54 CASES were matched (1:2) with contemporary controls from the same NICUs; demographics and level of illness features.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Gest age (w)</th>
<th>Birth Weight (g)</th>
<th>Gender (% M)</th>
<th>Race (% W)</th>
<th>Surfactant (% yes)</th>
<th>Apgar score @ 5 min</th>
<th>Maternal Steroids (% yes)</th>
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<tbody>
<tr>
<td>CASES</td>
<td>54</td>
<td>26.2±2.0</td>
<td>840±339</td>
<td>56%</td>
<td>93%</td>
<td>98%</td>
<td>6±2</td>
<td>52%</td>
</tr>
<tr>
<td>CONTROLS</td>
<td>101</td>
<td>26.4±2.0</td>
<td>849±304</td>
<td>55%</td>
<td>98%</td>
<td>99%</td>
<td>6±2</td>
<td>50%</td>
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<tr>
<td>P value</td>
<td></td>
<td>0.375</td>
<td>0.866</td>
<td>0.437</td>
<td>0.100</td>
<td>0.457</td>
<td>0.214</td>
<td>0.550</td>
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</table>
BEFORE THE IVH, did the CASES have longer coag times, lower fibrinogen, lower platelets?
<table>
<thead>
<tr>
<th></th>
<th>PT (seconds)</th>
<th>aPTT (seconds)</th>
<th>Fibrinogen (mg/dL)</th>
<th>Platelet count &lt;50K/µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASES</td>
<td>18.7±6.1</td>
<td>57±19</td>
<td>251±155</td>
<td>1/54 (2%)</td>
</tr>
<tr>
<td>CONTROLS</td>
<td>17.9±2.7</td>
<td>60±26</td>
<td>235±134</td>
<td>1/101 (1%)</td>
</tr>
<tr>
<td>P value</td>
<td>0.333</td>
<td>0.440</td>
<td>0.507</td>
<td>0.457</td>
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</table>
Did the CASES have more early-onset infection?
<table>
<thead>
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<th>Neonate begun on Amp/Gent in first 24h</th>
<th>Initial blood culture positive</th>
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<tr>
<td><strong>CASES</strong></td>
<td>54/54 (100%)</td>
<td>3/54 (6%)</td>
</tr>
<tr>
<td><strong>CONTROLS</strong></td>
<td>101/101 (100%)</td>
<td>1/101 (1%)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>1.000</td>
<td>0.122</td>
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Did the CASES have higher NRBC counts at birth, lower cord pH, more vasopressor use in the first 2 days?
Did the CASES have higher NRBC counts at birth, lower cord pH, more vasopressor use in the first 2 days?

<table>
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<tr>
<th></th>
<th>NRBC/100 WBC (mean, median, range)</th>
<th>Cord pH</th>
<th>ET intubation and mechanical ventilation</th>
<th>Vasopressor use in the first 48 h</th>
<th>Expired</th>
</tr>
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<tbody>
<tr>
<td>CASES</td>
<td>76, 18 (0-1096)</td>
<td>7.25±0.14</td>
<td>54/54 (100%)</td>
<td>47/54 (87%)</td>
<td>18/54 (33%)</td>
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<td>CONTROLS</td>
<td>37, 0 (0-585)</td>
<td>7.26±0.15</td>
<td>101/101 (100%)</td>
<td>67/101 (66%)</td>
<td>8/101 (8%)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.005</td>
<td>0.498</td>
<td><strong>1.000</strong></td>
<td>0.004</td>
<td>0.000</td>
</tr>
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</table>

**Logistic Regression**

- For every increase in NRBC by 10/100 WBC, the risk of severe IVH increased by 2%.
- If vasopressors were used in the first 48 hours the risk of IVH increased by 74%.
Did the CASES have more early RBC transfusions? If so why?
Did the CASES receive early RBC transfusions because they had lower hemoglobin concentrations?
Did the CASES receive early RBC transfusions because they had lower hemoglobin concentrations?

Those who developed a severe IVH more likely had an early RBC transfusion but did not have a lower hemoglobin before the transfusion.
The temporal sequence in 94% of the CASES:

1. One or more normal head ultrasound examinations, followed by…

2. RBC transfusion, followed by…

3. Repeat head ultrasound examination showing a severe IVH.
A “Sensitivity Analysis” asks the question, “what is the likelihood that this apparent relationship between RBC transfusion and development of a severe IVH is actually explained by other variables?”
RBC Transfusion

Unknown or unmeasured factors

Severe IVH

R

G
### Results:
Only if unknown factors have a $>0.95$ \( R \) and a $1.00$ \( G \) can such factors explain the apparent association between RBC transfusion and severe IVH.

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<thead>
<tr>
<th>( R )</th>
<th>( 0 )</th>
<th>( 0.2 )</th>
<th>( 0.4 )</th>
<th>( 0.6 )</th>
<th>( 0.8 )</th>
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<td>( 0 )</td>
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<td>( 0.5 )</td>
<td>1.822</td>
<td>1.708</td>
<td>1.602</td>
<td>1.503</td>
<td>1.409</td>
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<td>(1.303,2.64)</td>
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<td>(1.146,2.32)</td>
<td>(1.075,2.18)</td>
<td>(1.008,2.04)</td>
<td>(0.945,1.91)</td>
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<td>( 0.75 )</td>
<td>1.822</td>
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Statistically, it is VERY unlikely that “unknown factors” could explain the relationship between early RBC transfusion and severe IVH.
Why do some grade 1 IVHs extend to become a grade 3 or 4, while others resolve without extending?
METHODS

1. Identify all neonates in the Intermountain data systems with a grade 1 IVH in the 1st week.

2. Identify all where a subsequent ultrasound showed the IVH had extended to a higher grade.

3. Identify antecedents occurring while the hemorrhage was still a grade 1, looking for associations with IVH extension (n=55).
Regression Analysis. (Looking for the most significant statistical association increasing the odds that a grade 1 IVH would extend to a 3 or 4)

Administering a RBC transfusion up to or on the day the grade 1 was detected (OR 2.92, 95% CI, 2.19 – 3.90)
Regression Analysis. (Looking for the most significant statistical association increasing the odds that a grade 1 IVH would extend to a 3 or 4)

Administering a RBC transfusion up to or on the day the grade 1 was detected (OR 2.92, 95% CI, 2.19 – 3.90)

This association was completely independent of hemoglobin, gestational age, birth weight, and whether or not the transfusion was compliant with the guidelines.
In VLBW neonates an “association” exists between early RBC transfusion and the subsequent development of an IVH.

Is there any biologically plausible explanation?
Capillaries in the germinal matrix of the VLBW brain are particularly susceptible to rupture, as then lack supporting cells (pericytes).
RBC traverse the smallest capillary beds one at a time, in line.
RBC traverse the smallest capillary beds one at a time, in line.

RBC must pass through capillary spaces smaller than themselves. This can occur because; 1) RBC deform, 2) RBC release nitric oxide thereby dilating the capillaries.
RBC DEFORMATION. Erythrocytes must change their shape extensively while traversing the microcirculation.
Banked RBC (even after a few days) develop a “storage lesion”. This involves; 1) less deformability and 2) depletion of nitric oxide synthase.
Transfused RBC (poor deformability and lacking nitric oxide synthase) can clog capillaries, paradoxically leading to DECREASED tissue oxygenation.
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If transfused RBC clog capillary flow, pressure can increase upstream leading to capillary rupture.
Capillaries in the germinal matrix of the VLWB brain are particularly susceptible to rupture, as they lack supporting cells (pericytes).
Hypothesis: If early RBC transfusions play a role in the pathogenesis of IVH, successful efforts to limit early RBC transfusion might diminish the incidence or severity of IVH.

Limit early RBC transfusion by:
1. Delayed clamping of the umbilical cord.
2. Stripping (milking) of the umbilical cord.
3. Drawing all baseline NICU blood tests from fetal blood in the umbilical vein on the placenta, thus initially drawing no blood from the neonate.
Immediate vs. Delayed Cord Clamping

INITIAL STUDY. Delayed cord clamping in very preterm infants reduces the incidence of IVH. *Pediatrics*. 2006;117:1235-42.

N=72, <32 wks, randomized to immediate vs. delayed cord clamping (30-45 seconds). About 40% IVH (immediate) vs. about 10% delayed (more prominent effect in males).


Regression model controlling for gestational age, IVH, BPD, sepsis and male gender suggested higher motor scores of male infants with delayed cord clamping.
Umbilical cord “milking” reduces the need for red cell transfusions in VLBW neonates. *Tokyo, 2008*
Umbilical cord “milking” reduces the need for red cell transfusions in VLBW neonates.

Tokyo, 2008

In the delivery of VLBW neonates, clamping (30 sec) and “milking” are equivalent.

Bristol, 2011
Either delayed clamping or milking results in higher hemoglobin, fewer early transfusions, lower prevalence of IVH
Hypothesis: If early RBC transfusions play a role in the pathogenesis of IVH, successful efforts to limit early RBC transfusion might diminish the incidence or severity of IVH.

Limit early RBC transfusion by:
1. Delayed clamping of the umbilical cord.
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3. Drawing all baseline NICU blood tests from fetal blood in the umbilical vein on the placenta, thus initially drawing no blood from the neonate.
Blood tests drawn from a neonate on NICU admission
Another way to obtain fetal blood for NICU admission laboratory tests
PROSPECTIVE STUDY: All baseline blood tests obtained from the umbilical vein in 200 VLBW neonates, matched with 200 drawn in the standard way (from the neonate).
Higher hemoglobin 24 hrs after birth (2.5±0.4 g/dL, \( p=0.000 \))
Fewer RBC transfusions during the first three days ($p=0.04$).
Fewer RBC transfusion during the first five days ($p=0.000$).
Fewer RBC transfusions during the first week ($p=0.000$).
Lower prevalence of grade 3 and 4 IVH ($p=0.001$)
With delayed cord clamping OR cord stripping, an adequate volume of fetal blood remains in the VLBW placenta for all needed base-line blood tests.
Neonatal Intraventricular Hemorrhage Model in Beagle Puppies

Brain hemorrhage is produced by withdrawing about 20% of blood volume followed by transfusing back 20% of blood volume.
QUESTION: Are we unwittingly increasing the risk of IVH by the practice of large early phlebotomy losses followed by banked donor blood transfusion?
Outline

1) Differences between banked donor (adult) RBC and a VLBW neonate’s own RBC

2) Associations between “early” RBC transfusion of VLBW infants and development of severe IVH

3) Associations between “liberal” RBC transfusion of VLBW infants and poor neurodevelopmental outcome
Is it best practice to give RBC transfusions in the NICU using “liberal” or “restrictive guidelines?"

It’s 2012 already…don’t you guys have this figured out YET?
100 VLBW neonates randomized to “liberal” vs. “restricted” RBC transfusion guidelines

### Transfusion Threshold

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>Liberal</td>
<td>&lt; 46%</td>
<td>&lt; 38%</td>
<td>&lt; 30%</td>
</tr>
<tr>
<td>Restrictive</td>
<td>&lt; 34%</td>
<td>&lt; 28%</td>
<td>&lt; 22%</td>
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</table>

Phase 1 = Mechanical Vent  
Phase 2 = O₂ but no Vent  
Phase 3 = RA
Long-term results
Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion
McCoy, Conrad, Richman, Lindgren, Nopoulos & Bell
Child Neuropsychol 2011;17(4):347-67

Long-term outcome of brain structure in premature infants: effects of liberal vs restricted red blood cell transfusions
Nopoulos, Conrad, Bell, Strauss, Widness, Magnotta, Zimmerman, Georgieff, Lindgren, & Richman

Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion
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Long-term outcome of brain structure in premature infants: effects of liberal vs restricted red blood cell transfusions
Nopoulos, Conrad, Bell, Strauss, Widness, Magnotta, Zimmerman, Georgieff, Lindgren, & Richman

Markedly worse neurodevelopmental outcome, and reduced grey matter volume in those randomized to liberally receive RBC transfusions as neonates.
Are we worried about long-term neurodevelopmental problems after liberal NICU transfusions?
Are we worried about long-term neurodevelopmental problems after liberal NICU transfusions?

YES!
What is the explanation for the poor neurodevelopment after “liberal” NICU RBC transfusions?
1. Exposure to more blood donors?
2. Repeated IV exposures to foreign antigens?
3. Repeatedly shutting off erythropoietin production?
1. Exposure to more blood donors?
2. Repeated IV exposures to foreign antigens?
3. Repeatedly shutting off erythropoietin production?
Epo is a critical neuroprotective & neurodevelopmental factor


During CNS hypoxia:

1. Epo is produced rapidly by microglia and binds to receptors on neurons.
2. Activation of Epo receptors induces antiapoptotic peptides.
3. Inhibiting Epo worsens the CNS damage.
4. Administering rEpo up to 6 hrs after CNS hypoxemia improves CNS outcome.
RBC transfusions shut down Epo production at a critical time for neurodevelopment.
Outline

1) Differences between banked donor (adult) RBC and a VLBW neonate’s own RBC

2) Associations between “early” RBC transfusion of VLBW infants and development of severe IVH

3) Associations between “liberal” RBC transfusion of VLBW infants and poor neurodevelopmental outcome
Which one of the following is the most painful blood sucker?
POST-TEST

Which one of the following is the most painful blood sucker?

A.
Which one of the following is the most painful blood sucker?

A.  

B.  

[Image of a mosquito]
Which one of the following is the most painful blood sucker?

A. B. C.
Which one of the following is the most painful blood sucker?

A.   B.   C.   D.
Everything should be made as simple as possible…but not simpler.

Albert Einstein
Evidence-based NICU Transfusion Practices = Better Outcomes for NICU Patients
Science and Management of Transfusion Therapy
THANKS FOR YOUR KIND ATTENTION