Clinical Considerations in Neonatal Transfusion: Small patients, big issues

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Disclosure

• I have no financial disclosures or conflicts of interest

• I am not a hematologist.....
Objectives

- Review the unique characteristics of fetal and neonatal circulation and transfusion
- Present current controversies in neonatal transfusion
- Review current approach to neonatal transfusion
- Discuss opportunities for further investigation
What is the impact of this small group of patients?

- For preterm infants <1500 grams
- 80-100 patients per year
- 75-90% get at least one transfusion
- Those transfused receive an average of 3-5 transfusions
- Transfusion volume - 5-30 mls each

- 180-450 transfusions per year on average
Fetal to Neonatal Transitions

Unique considerations
Changes in hemoglobin
Changes in Hemoglobin: Oxygen affinity Fetal vs Adult Hemoglobin

Each transfusion replaces the existing fetal hemoglobin with adult hemoglobin.
Role of the placenta

- The placenta is a unique vascular organ consisting of:
  - (1) the maternal-placental (uteroplacental) blood circulation
  - (2) the fetal-placental (fetoplacental) blood circulation.
  - No intermingling of maternal and fetal blood occurs in the placenta.
- At any one time up to 30% of the fetal blood volume resides in the fetal placental circulation
Baby’s first transfusion
Delayed cord clamping

About 50% emptying in 1 minute, 90% by 3 minutes
In a term baby can be up to 100 cc extra of blood (for a baby with a total blood volume of about 350 ml)
Delayed Cord Clamping:
Proposed Benefits

- **Neonatal**
  - Increased blood volume- up to 30% more blood volume and up to 60% more RBC’s
  - Higher hemoglobin
  - Less iron deficiency anemia as have higher iron stores
  - Better extra-uterine cardiorespiratory transition/adaptation
  - For preterms- better BP, less transfusion requirement, decreased NEC, decreased need for ventilation
Controversies in neonatal transfusion
Who to transfuse? And When?

- Differing considerations
  - Gestational age
    - Preterm
    - Term
  - Illness level
  - Underlying condition
    - Cardiac compromise
    - Respiratory failure
Transfusion of preterm infants

- More studied than other neonatal populations
- Studies have examined numbers and morbidities related to RBC transfusion in those <1500 grams at birth
  - Compared Restrictive (transfuse at lower Hb) vs Liberal (transfuse at higher HB)
  - Early vs late
Transfusion of preterm infants
(Cochrane review September 2011)

- 4 trials
- 614 infants
- Transfusion levels chosen by consensus
  - Stratified by sampling technique, age, ventilation needs

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>Type of sample</th>
<th>Neonates receiving respiratory aid**</th>
<th>Neonates not receiving respiratory aid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>Skin prickle</td>
<td>≤11.5</td>
<td>≤10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤10.4</td>
<td>≤9.0</td>
</tr>
<tr>
<td>8-14</td>
<td>Skin prickle</td>
<td>≤10.0</td>
<td>≤8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤9.0</td>
<td>≤7.7</td>
</tr>
<tr>
<td>≥15</td>
<td>Skin prickle</td>
<td>≤8.5</td>
<td>≤7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤7.7</td>
<td>≤6.8</td>
</tr>
</tbody>
</table>

Modified from Kirpalani et al. 2006\textsuperscript{42}.

* These recommendations are not valid in the case of major surgery, sepsis, shock, haemorrhage or symptoms suggestive of anaemia (tachycardia, tachypnoea).
** Includes assisted ventilation, continuous positive-pressure ventilation, and administration of free-flowing oxygen.
Transfusion of preterm infants

**Review:** Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants

**Comparison:** 1 Transfusion at a restrictive vs a liberal haemoglobin threshold

**Outcome:** 1 Infants transfused once or more

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Restrictive n/N</th>
<th>Liberal n/N</th>
<th>Kisk Kato M-H, Random 35% CI</th>
<th>Weight</th>
<th>Kisk Kato M-H, Random 35% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINT 2006</td>
<td>198/223</td>
<td>217/223</td>
<td></td>
<td>68.5%</td>
<td>0.93 [0.88, 0.99]</td>
</tr>
<tr>
<td>Bell 2005</td>
<td>45/50</td>
<td>47/53</td>
<td></td>
<td>11.7%</td>
<td>1.01 [0.89, 1.16]</td>
</tr>
<tr>
<td>Chen 2009</td>
<td>19/19</td>
<td>17/17</td>
<td></td>
<td>18.8%</td>
<td>1.06 [0.90, 1.11]</td>
</tr>
<tr>
<td>Connelly 1995</td>
<td>9/13</td>
<td>9/11</td>
<td></td>
<td>1.0%</td>
<td>0.85 [0.54, 1.34]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

|                       | 305             | 309         | 100.0%                      | 0.95 [0.91, 1.00] |

*Total events: 271 (Restrictive), 290 (Liberal)*

*Heterogeneity: Tau² = 0.0; Chi² = 2.58, df = 3 (P = 0.45); I² = 0.0%*

*Test for overall effect: Z = 2.04 (P = 0.041)*

*Test for subgroup differences: Not applicable*

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**Review:** Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants

**Comparison:** 1 Transfusion per infant given from study start to study end

**Outcome:** 2 Transfusions per infant given from study start to study end

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Restrictive n</th>
<th>Mean(SD)</th>
<th>Liberal n</th>
<th>Mean(SD)</th>
<th>Mean Difference IV, Random 35% CI</th>
<th>Weight</th>
<th>Mean Difference IV, Random 35% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINT 2006</td>
<td>223</td>
<td>4.3 (4.2)</td>
<td>228</td>
<td>5.7 (5)</td>
<td></td>
<td>41.2%</td>
<td>-0.80 [-1.55, 0.05]</td>
</tr>
<tr>
<td>Bell 2005</td>
<td>50</td>
<td>2.5 (2.4)</td>
<td>53</td>
<td>3.7 (2.6)</td>
<td></td>
<td>33.8%</td>
<td>-1.10 [-2.07, -0.13]</td>
</tr>
<tr>
<td>Chen 2009</td>
<td>19</td>
<td>2.7 (2)</td>
<td>17</td>
<td>3.7 (2.5)</td>
<td></td>
<td>16.1%</td>
<td>-1.00 [-2.49, 0.49]</td>
</tr>
<tr>
<td>Connelly 1995</td>
<td>13</td>
<td>1.3 (1.1)</td>
<td>11</td>
<td>4.4 (3.3)</td>
<td></td>
<td>9.0%</td>
<td>-2.90 [-4.94, -0.86]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

|                       | 305             | 309         | 100.0%                      | -1.12 [-1.75, -0.49] |

*Heterogeneity: Tau² = 0.66; Chi² = 3.48; df = 3 (P = 0.32); I² = 14%*

*Test for overall effect: Z = 3.50 (P = 0.00046)*

*Test for subgroup differences: Not applicable*
Transfusion of preterm infants

Review: Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants

Comparison: 1. Transfusion at a restrictive vs. liberal haemoglobin threshold

Outcome: 6. Death

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Restrictive n/N</th>
<th>Liberal n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prior to first hospital discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PINT 2006</td>
<td>43/223</td>
<td>40/223</td>
<td>1.23 [0.84, 1.79]</td>
<td>1.06 [0.22, 5.01]</td>
</tr>
<tr>
<td>Bell 2005</td>
<td>3/50</td>
<td>3/53</td>
<td>1.79 [0.18, 18.02]</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>Chen 2009</td>
<td>2/19</td>
<td>1/17</td>
<td>0.0 [0.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>Connelly 1999</td>
<td>0/13</td>
<td>0/11</td>
<td>1.23 [0.86, 1.76]</td>
<td>1.09 [0.76, 1.56]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>305</td>
<td>309</td>
<td></td>
<td>1.09 [0.76, 1.56]</td>
</tr>
</tbody>
</table>

Total events: 53 (Restrictive), 44 (Liberal)
Heterogeneity: Tukey = 0.0, Chi² = 0.14, df = 2 (P = 0.93), I² = 0.0%
Test for overall effect: Z = 1.12 (P = 0.26)

2. By 18-21 months follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Restrictive n/N</th>
<th>Liberal n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINT 2006</td>
<td>43/208</td>
<td>45/213</td>
<td>1.09 [0.76, 1.56]</td>
<td>1.09 [0.76, 1.56]</td>
</tr>
</tbody>
</table>

Total events: 48 (Restrictive), 45 (Liberal)
Heterogeneity: not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Transfusion of preterm infants

**Review:** Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants

**Comparison:** 1. Transfusion at a restrictive vs liberal haemoglobin threshold

**Outcome:** 12 Neurosensory impairment at 18–21 months follow-up among survivors

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Restrictive n/N</th>
<th>Liberal n/N</th>
<th>Risk Ratio M 11, Random, 95% CI</th>
<th>Risk Ratio M 11, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive delay MDI &lt; 70</td>
<td>38/156</td>
<td>29/165</td>
<td>1.39 (0.90, 2.13)</td>
<td></td>
</tr>
<tr>
<td>PINT 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Cognitive delay MDI &lt; 85</td>
<td>70/156</td>
<td>56/165</td>
<td>1.32 (1.00, 1.74)</td>
<td></td>
</tr>
<tr>
<td>PINT 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Cerebral palsy</td>
<td>11/182</td>
<td>9/177</td>
<td>1.24 (0.69, 2.22)</td>
<td></td>
</tr>
<tr>
<td>PINT 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Severe visual impairment</td>
<td>2/161</td>
<td>1/173</td>
<td>2.15 (0.20, 23.47)</td>
<td></td>
</tr>
<tr>
<td>PINT 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Severe hearing impairment</td>
<td>4/161</td>
<td>3/173</td>
<td>1.43 (0.33, 6.30)</td>
<td></td>
</tr>
<tr>
<td>PINT 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Any neurosensory impairment</td>
<td>46/160</td>
<td>37/163</td>
<td>1.31 (0.90, 1.90)</td>
<td></td>
</tr>
<tr>
<td>PINT 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagram:**

- Favours Restrictive
- Favours Liberal

- 0.05
- 0.2
- 1
- 5
- 20
Transfusion of preterm infants: So where does this leave us?

- Waiting longer seems to have modest reduction in numbers of infants transfuse and in number of transfusion per baby
- Some concern of long term outcomes when use lower levels
- Continue restrictive approach but don’t go lower
- Need more long term outcome information
Transfusion in term infants

- Less clear guidelines
- Usually based on assessed risk or in otherwise well infants on symptoms
- Cardiac patients with cyanotic lesions a special group – usually aim for Hb > 120 prior to repair
What to transfuse?

- Issues of irradiation and CMV status
  - Dealt with by previous speakers
- How fresh should the blood be?
  - 2012 study- Age of Red Blood Cells in Premature Infants (Canadian trial)
    - 450 infants <1500 grams
    - Fresh 0-7 (mean 5.1) day vs standard 2-42 (mean 14.6) day old blood
    - Looked at standard morbidities of Prematurity
    - No difference was found
Current local approach for RBC transfusion in preterm infants

- Prevention of anemia
  - Cord transfusion (delayed clamping versus milking)
  - Minimize blood letting as prevention
- When transfusion required
  - Use restrictive guideline (but not lower)
  - Consider individual baby condition
- Other considerations:
  - Do another study aimed at examining long term outcomes
  - Multi-packs to minimize door exposure
A word about platelet transfusions

- Even less well studied than RBC transfusions
- Platelet function not always the same as platelet number
- Usual approach is empiric (and then tailored for baby)
  - Well newborn no bleeding - transfuse <50,000
  - Unwell infant (preterm) - transfuse between 50,000-75,000
  - In situations with chronic thrombocytopenia, no bleeding - transfuse <35,000
  - Surgical infants - aime >100,000
Specific platelet issues for the neonatal population

- **Volume of product**
  - For extreme preterm must be super concentrated
    - 500 gram baby (10 cc/kg is only 5 cc)

- **Use for neonatal alloimmune thrombocytopenia (NAIT)**
  - Donor pool
  - Use of IVIG
“A mother’s tears will not save her baby, your blood can.”
-unknown