Clinical Impact of Red-Cell Storage Lesion
A Survey and Possible Consequences

Behrouz Mansouri Taleghani
Center of Transfusion Medicine Bern
Department of Hematology and Central Hematological Laboratory
Inselspital, University of Bern and
Blood Transfusion Service Bern Ltd., Swiss Red Cross

Bern, Switzerland
Duration of Red-Cell Storage and Complications after Cardiac Surgery

Colleen Gorman Koch, M.D., Liang Li, Ph.D., Daniel I. Sessler, M.D., Priscilla Figueroa, M.D., Gerald A. Hoeltge, M.D., Tomislav Mihaljevic, M.D., and Eugene H. Blackstone, M.D.
Storage lesion:
What makes the difference?
(In whom) does it matter?
Consequences?
Changes During RBC Storage

Bennett-Guerrero E. et al. PNAS, 2007;104:17063-17068

5 Days

11.09.2008


Tinmouth et al Transfusion 2006;46:2014-2027


Tinmouth et al Transfusion 2006;46:2014-2027
Changes During RBC Storage

... Responsible for Impaired $O_2$ Delivery

- **Structural**
  - Clumping of RBCs
  - Lose membrane phospholipids
  - Biconcave → spherocyte/shistocyte → impaired rheology

- **Biochemical**
  - ATP depletion
  - 2,3-DPG depletion
  - NO depletion

- **Inflammatory**
  - ↑Inflammatory mediators


11.09.2008
Summary (I)

... Impact of Impaired $O_2$ Delivery

- Transfusion may improve mixed venous oxygen tension

  BUT

- No definite improvement (deterioration?!) in tissue $DO_2$
- Anaerobic glycolysis occurs at higher Hb levels (critical tissue hypoxia at higher Hb)
- Shock develops at higher Hb levels in transfused patients

Storage lesion: what (else) makes the difference?
Hemoglobin

- 4 subunits
- Heme
- Porphyrin ring
- Fe++
- Co-operative O₂ binding
- CO binding
- Binds NO at β-Cys 93

Protein S-nitrosylation: purview and parameters
SNO-Hb in Stored Blood

Reynolds JD et al. 2007. PNAS;104:17058-62
SNO-Hb content and vasodilatory activity of renitrosylated RBCs

Reynolds JD et al. 2007. PNAS;104:17058-62
Summary (II)

... NO in RBC is a further key player in hypoxia

- $O_2$ release is increased via SNO-Hb by
  - vasodilation
  - central stimulation of ventilation
- SNO-Hb decreases in stored blood < 1day
- Currently all RBCs are SNO-Hb depleted
  - Do we suffocate patients by RBC transfusion (microcirculation and central)?
- Renitrosilation of stored blood might be a perspective to overcome the NO-depletion
Storage lesion:
What makes the difference?
(In whom) does it matter?
Consequences?
Duration of Red-Cell Storage and Complications after Cardiac Surgery

Colleen Gorman Koch, M.D., Liang Li, Ph.D., Daniel I. Sessler, M.D., Priscilla Figueroa, M.D., Gerald A. Hoeltge, M.D., Tomislav Mihaljevic, M.D., and Eugene H. Blackstone, M.D.
Consequences of RBC Storage

### TABLE 3. Association of RBC storage with clinical outcomes: observational studies

<table>
<thead>
<tr>
<th>Study: first author, year</th>
<th>Population</th>
<th>Design</th>
<th>Number</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basran, 2006:115</td>
<td>Cardiac surgery</td>
<td>Retrospective cohort</td>
<td>321</td>
<td>Increased mortality associated with mean age of RBC units and age of oldest RBC unit</td>
</tr>
<tr>
<td>Leal-Noval, 2003:104</td>
<td>Cardiac surgery</td>
<td>Prospective cohort</td>
<td>897</td>
<td>Increased pneumonia associated with oldest unit</td>
</tr>
<tr>
<td>Keller, 2002:117</td>
<td>Trauma</td>
<td>Retrospective cohort</td>
<td>86</td>
<td>Increased LOS with number of RBC units &gt;14 days</td>
</tr>
<tr>
<td>Offner, 2002:105</td>
<td>Trauma</td>
<td>Prospective cohort</td>
<td>61</td>
<td>Increased infections with number of units &gt;14 and 21 days</td>
</tr>
<tr>
<td>Vamvakas, 2000:118</td>
<td>Cardiac surgery</td>
<td>Retrospective cohort</td>
<td>268</td>
<td>No change in LOS or mechanical ventilation associated with age of RBC units</td>
</tr>
<tr>
<td>Vamvakas, 1999:103</td>
<td>Cardiac surgery</td>
<td>Retrospective cohort</td>
<td>416</td>
<td>Increased risk of pneumonia with median age of transfused RBC units</td>
</tr>
<tr>
<td>Zallen, 1999:116</td>
<td>Trauma</td>
<td>Prospective cohort</td>
<td>63</td>
<td>Increased multiorgan failure with number of units &gt;14 and 21 days</td>
</tr>
<tr>
<td>Purdy, 1997:114</td>
<td>Septic ICU</td>
<td>Retrospective cohort</td>
<td>31</td>
<td>Increased mortality associated with older median age of RBC units</td>
</tr>
<tr>
<td>Martin 1993:99</td>
<td>ICU</td>
<td>Retrospective cohort</td>
<td>698</td>
<td>Increased LOS with number of units &gt;14 days</td>
</tr>
</tbody>
</table>

n=2841  
Tinmouth et al. Transfusion 2006
Summary (III)

... Storage lesion strongly seems to matter!

- Increasing clinical observations and secondary analyses indicate that transfusion of “older” RBC might be associated with adverse outcome

- Patients with impaired cardiac function seem to be a high risk group for storage related adverse events of RBC transfusion
Storage lesion:
What makes the difference?
(In whom) does it matter?
Consequences?
One of the first documented transfusions, Bellevue Hospital, New York, 1876

Back to the Roots!?
Implications for Research

- Epidemiological and basic research
  - Confirming association of transfusion and adverse outcomes
  - Mechanisms (storage lesion, ....)
- Randomized lower transfusion thresholds
  - Fresh blood vs. older blood
A multicenter, randomized, controlled clinical trial of Transfusion Requirements In Critical Care (TRICC)  

The TRICC Trial

- In critically ill patients a Hb transfusion trigger of 70 g/L compared to a more liberal threshold of 100 g/L
  - could decrease blood usage by more than half
  - shows no change, or even improvement in overall outcome

Summary* (IV)

Table 1. Transfusion Recommendations

<table>
<thead>
<tr>
<th>Variables</th>
<th>Transfusion Trigger, g/L*</th>
<th>Goal, g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>General critically ill (no acute bleeding)</td>
<td>70</td>
<td>70–90</td>
</tr>
<tr>
<td>Critically ill with septic shock (&gt; 6 h)</td>
<td>70</td>
<td>70–90</td>
</tr>
<tr>
<td>Critically ill with septic shock (&lt; 6 h)</td>
<td>80–100</td>
<td>100</td>
</tr>
<tr>
<td>Critically ill with chronic cardiac disease</td>
<td>70</td>
<td>70–90</td>
</tr>
<tr>
<td>Critically ill with acute cardiac disease</td>
<td>80–100</td>
<td>100</td>
</tr>
</tbody>
</table>

* Administer 1 U of RBCs at a time and remeasure hemoglobin concentrations.

* PC Hébert, A Tinmouth, HL Corwin; Chest 2007; 131:1583-1590
Comparison of Transfusion Practise

<table>
<thead>
<tr>
<th>Country</th>
<th>RBCs transfused/year</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>4.3 mio</td>
<td>82 mio</td>
</tr>
<tr>
<td>1 : 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>0.3 mio</td>
<td>7 mio</td>
</tr>
<tr>
<td>1 : 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>0.9 mio</td>
<td>32 mio</td>
</tr>
<tr>
<td>1 : 36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Implementation of transfusion guidelines for red blood cells (RBC) in elective surgery: Impact on RBC utilization and outcome of patients

Stefano Fontana, Behrouz Mansouri Taleghani, Urs Müller

Granted by
Humanitären Stiftung SRK
(Application number 76)
Elective surgery replacement studies
Methods

- Prospective, multi-center before-and-after study in adult elective hip or knee replacement in 10 Swiss hospitals
- Prospective, single-center before-and-after study in major adult cardiac and vascular surgery (valve replacement, coronary bypass [CABG], open abdominal aortic aneurysm procedures)

RBC use, laboratory, and patient outcome

08. 2007 - 02. 2008
1 mth
04. 2008 - 10. 2008
Guideline for the Transfusion of Red Blood Cells (RBC) in elective surgery
This form is part of the medical record

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Hb [g/l]</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent from clinical assessment</td>
<td>&gt; 100</td>
<td>No indication for RBC</td>
</tr>
<tr>
<td>No symptoms, no risk factors, stop of significant blood loss</td>
<td>70 - 100</td>
<td>No indication for RBC</td>
</tr>
<tr>
<td>A: Significant symptoms of anemia¹ or ongoing significant blood loss and / or</td>
<td>70 - 100</td>
<td>Case-to-case decision</td>
</tr>
<tr>
<td>B: Risk factors²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: Independent from clinical assessment</td>
<td>&lt; 70</td>
<td>Consider transfusion of 1-2 RBC</td>
</tr>
</tbody>
</table>

¹ symptoms of anemia
² Risk factors
Elective hip and knee replacement study
Preliminary Results

- 1230 patients (49.7% hip replacements; 45.4% male; mean age m/f = 67/71; median ASA physical status 2)
- 253/1230 (20.6%) received 594 RBC (incl. 34 autologous) with major inter-hospital variation:
  - 5% - 40% of patients;
  - 0.1 - 1.1 RBC per patient
Elective hip and knee replacement study
Preliminary Conclusions

- This first Swiss multicenter study in elective hip and knee replacement revealed a considerable variation of transfusion practice between the hospitals.
- Although we observed a lesser degree than reported for other countries, we expect a further harmonization by the introduction of our guideline.
- Our preliminary data don’t show any correlation between transfusion practice and patient outcome.
“Summary” (V)

“The art of blood transfusion”

"He who feels confident that he has a thorough understanding of platelet transfusion is confused.“


"The sentiment could be equally applied to plasma transfusion therapy with a disturbing degree of accuracy.“

Triulzi DJ. The art of plasma transfusion therapy. Transfusion 2006;46:1268-1270

"The sentiment could be equally applied to all kinds of transfusion therapy with a disturbing degree of accuracy.“

Mansouri Taleghani B: One of my conclusions about confusions while preparing this talk (2008)
Some key Slides are
Provided and Adopted from a Talk of
Andreas Greinacher, Greifswald, Germany

Thank You For Attention!