TRANSFUSION AND CARDIAC OUTCOMES

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ACUITY: Major bleeding predicts mortality

ACUITY: Predictors of major bleeding

N = 13,819 with ACS

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 years</td>
<td>3.21 (2.17-4.76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.24 (1.37-3.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.44 (1.10-1.91)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.28 (1.10-1.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No prior PCI</td>
<td>1.91 (1.10-3.31)</td>
<td>0.057</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.05 (1.27-3.29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.08 (1.35-3.22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline ST-segment deviation ≥1mm</td>
<td>1.66 (1.19-2.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline cardiac biomarker elevation</td>
<td>1.34 (1.06-1.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heparin plus GPI vs bivalirudin monotherapy</td>
<td>2.23 (1.38-3.62)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Predictors of Postoperative Bleeding: CT surgery

1) Advanced age
2) Small body size or preoperative anemia (low RBC volume)
3) Antiplatelet, antithrombotic drugs
4) Prolonged operation (CPB time) – high correlation with OR type.
5) Emergency operation
6) Other co-morbidities (CHF, COPD, HTN, PVD, renal failure)


BLOOD PRODUCTS

- Whole blood, RBCs
- Platelets
- FFP, cryoprecipitate
- Immunoglobulins
- Fibrin glue

BLOOD PRODUCTS

- Humoral and cellular components
- Typed to major RBC antigens
- Transfusions pose potential risks
**SHOT Report 1996/97 - 2000/01**

- Human error = 51%
- 61% ATR
- 13% DTR
- 12% PTP
- 6% TRALI
- 6% TA-GVHD
- 3% TTI
- 1% Unclass

**Average RBC Age in Days - 2001**


**What is the RBC storage lesion?**

As RBCs are stored *ex vivo* they undergo a series of biochemical, metabolic, structural, inflammatory and physiologic changes.

- 2,3-DPG is depleted during storage by day 14
  - Its decline is mirrored by an increase in Hb oxygen saturation as hemoglobin affinity for O₂ increases
  - 2,3-DPG is restored 24-72 hours after transfusion

- Stored RBCs undergo shape changes
  - Normal morphology is maintained until severe drops in intracellular ATP occur

**RBC shape change**

- The heme chain of oxygenated Hb binds S-nitrosothiols (SNO)
  - Under hypoxic conditions the oxygen and SNO are released
  - SNO causes vasodilatation thus permitting greater blood flow to hypoxic areas
  - Stored RBCs rapidly lose SNO

**Nitric Oxide**

- Not clear if SNO is the biologically important form of NO.
Are All Stored Red Cells the Same? (Shorter vs. Longer Storage Age)

- RBC transfusion is an independent marker for worse outcome since “sicker” patients need more blood.
- Patients who receive more blood are more likely to get older units.
- Retrospective/observational studies cannot completely account for confounding factors.
- No science to support different definitions of storage duration.
- Leukoreduced vs non leukoreduced: ? Relevance
- Primary endpoint and secondary analyses should be defined a priori. Post hoc analyses should be identified as such.

Koch NEJM 2008;358:1229-1239

Considerations for Evaluating Clinical Studies of Red Cell Storage

- RBC transfusion is an independent marker for worse outcome since “sicker” patients need more blood.
- Patients who receive more blood are more likely to get older units.
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Koch NEJM 2008;358:1229-1239

Does Storage Age Affect Patient Outcome?

- Retrospective review of 6000 cardiac surgery pts
  - 2872 pts received 8802 units ≤14 days old (median 11 days)
  - 3130 pts received 10,782 units >14 days old (median 19 days)

Koch NEJM 2008;358:1229-1239

Cleveland Clinic: Large, retrospective study on age of RBCs in cardiac surgery patients

- A large study of CABG or valve surgery patients was performed.
- RBC age: ≤14 days vs. >14 days.
- Patients who received a mix of “fresher” and “older” blood were excluded.
- Composite endpoint:
  - in-hospital death, myocardial infarction, asystole, ventricular tachycardia or fibrillation, tamponade, femoral or aortic dissection, renal failure, sepsis, respiratory insufficiency, pulmonary embolism, pneumonia, cerebral vascular accident, coma, deep or superficial sternal wound infection, prolonged postoperative ventilation (>72 hours), multiorgan failure, and acute limb ischemia.

Koch et al. NEJM 2008

There were important differences in the cohorts

- NYHA grades differed significantly between the 2 groups
- Significant differences in ABO groups of RBCs
- Trend towards older patients in >14 day old blood group

Blood use in each group

- 2872 patients in Newer group, 3130 patients in Older group
- Same median number of RBCs transfused: 2
- Massive transfusion (10 or more units) more likely in the older blood group

Koch et al. NEJM 2008
Outcome measures

<table>
<thead>
<tr>
<th>Complication</th>
<th>Patients receiving younger blood</th>
<th>Patients receiving older blood</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death</td>
<td>98 (1.7)</td>
<td>98 (2.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13 (0.3)</td>
<td>16 (0.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>Ventricular tachyarrhythmia</td>
<td>133 (5.4)</td>
<td>175 (7.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>93 (3.3)</td>
<td>31 (0.8)</td>
<td>0.046</td>
</tr>
<tr>
<td>Cardiac arrest or asystole</td>
<td>47 (1.6)</td>
<td>94 (3.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>48 (1.7)</td>
<td>47 (1.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>3 (0.1)</td>
<td>2 (0.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>75 (1.4)</td>
<td>104 (2.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>81 (2.8)</td>
<td>113 (3.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>5 (0.2)</td>
<td>7 (0.1)</td>
<td>0.87</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>177 (6.5)</td>
<td>278 (8.1)</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Renal failure</td>
<td>45 (1.6)</td>
<td>64 (2.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Major organ failure</td>
<td>2 (0.2)</td>
<td>21 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>442 (29.4)</td>
<td>519 (33.9)</td>
<td></td>
</tr>
</tbody>
</table>

Greater mortality in older blood group; UNADJUSTED!

Issues with Koch study

- Retrospective design
- The 2 cohorts differed in important clinical parameters
- Some of the outcomes had a very low incidence
- Lots of individual measures in the composite outcome
- Chance differences?
- Adjusted analyses were needed
- Hard to imagine that 2 units could be solely responsible

Clinical studies of the effect of red cell storage: cardiac surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Trial Design</th>
<th>Inclusion to Age</th>
<th>Outcomes</th>
<th>Adjusted for Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasser et al. [11]</td>
<td>237</td>
<td>Prospective RCT</td>
<td>&lt;12 h vs 2-5 days</td>
<td>Post-operative bleeding</td>
<td>No</td>
</tr>
<tr>
<td>Vamvakas and Carven [12]</td>
<td>267</td>
<td>Retrospective</td>
<td>Median age</td>
<td>Post-operative infections</td>
<td>Yes</td>
</tr>
<tr>
<td>Vamvakas and Carven [13]</td>
<td>268</td>
<td>Retrospective</td>
<td>Mean age, oldest unit, mean of two oldest units</td>
<td>Hospital and ICU LOS</td>
<td>No</td>
</tr>
<tr>
<td>Leal-Noval et al. [15]</td>
<td>585</td>
<td>Prospective</td>
<td>Mean age</td>
<td>Composite: infection MI, ICU LOS &gt;4 days, MV &gt;1 day</td>
<td>No for most endpoints</td>
</tr>
<tr>
<td>Van de Watering et al. [16]</td>
<td>2732</td>
<td>Retrospective</td>
<td>Mean age, youngest, oldest, &lt;18 vs. &gt;18 days</td>
<td>Hospital and ICU LOS</td>
<td>No in multivar analysis</td>
</tr>
<tr>
<td>Koch et al. [6]</td>
<td>6002</td>
<td>Retrospective</td>
<td>&lt;14 vs &gt;14 days</td>
<td>30 day mortality, Composite of 17 clinical outcomes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yap et al. [17]</td>
<td>670</td>
<td>Retrospective</td>
<td>Median age, oldest, &lt;30 vs. ≥ days</td>
<td>Post-operative mortality, renal failure, pneumonia</td>
<td>No</td>
</tr>
<tr>
<td>Bennett-Guerrero et al. [37]</td>
<td>43</td>
<td>Retrospective RCT</td>
<td>Phase I standard issue vs. &lt;22 days old</td>
<td>Phase II:7 ± 4 vs. 21 ± 4 days</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

Does Storage Age Affect “Outcome”? 20+ major studies show mixed results.

Difficulties in Interpreting Studies

- Single vs. multiple center
- Retrospective vs. prospective
- Population size 15 - 6000+ patients
- Accrual time range 1-14 years
- Divergent patient populations
- Variable RBC processing & storage methods

How generalizable are results of one study to another patient group?
Red Cell Storage Age Study

RECESS

Marie Steiner, Chris Stowell, Steven Sloan, Darrell Triulzi, Eric Gurstenberger, Susan Assmann, Elliott Bennett-Guerrero, Jerrold Levy, Shelley Pulkrabek, Eric Jett, Julie Miller

For the NHLBI Transfusion Medicine and Hemostasis Clinical Trials Network

Transfusion Medicine & Hemostasis Clinical Trials Network

- Multi-center clinical trials network
  - Blood Center of New York
  - Case Western
  - Children’s, Boston
  - Cornell
  - Duke
  - Johns Hopkins
  - Mass General
  - Puget Sound
  - Tufts
  - U of Iowa
  - U of Maryland, Baltimore
  - U of MN
  - UNC, Chapel Hill
  - U of OK HSC (inc UTSW)
  - U of Penn
  - U of Pitt

- Funded by NHLBI (Transfusion Medicine & Cellular Therapeutics branch) in 2002; renewed in 2007
- DCC is New England Research Institutes (NERI)

RECESS: Primary Hypothesis

“There is a clinically important difference between the effect of shorted storage age RBC vs longer storage age RBC on clinical outcome and mortality risk in cardiac surgery patients”

Complications of Transfusion: Effect on Mortality in CABG Patients

Dose-Response for Transfusion and Infection in Cardiac Surgery

Silesty S. Ann Thorac Surg 2000; 70: S12-9


n = 738
Effect of Re-exploration on Mortality

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Patients not Re-explored</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Re-explored Patients</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>0.005</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Infection and Transfusion in Surgical Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No Transfusion</th>
<th>Transfusion</th>
<th>Significant in Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>N=888</td>
<td>N=107</td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>N=343</td>
<td>N=287</td>
<td>*</td>
</tr>
<tr>
<td>Vaginal</td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Cardiac</td>
<td>N=218</td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

LIMITATIONS TO TRANSFUSIONS AND RISKS

- Transfusions should be considered as organ donations
- Leukocytes (PMNs and mononuclear cells are major culprits) for most reactions (except TRALI)
- Transfusions are associated with both risks/costs; availability is issue too
- No one has ever demonstrated efficacy of transfusions, esp FFP

Transfusions are associated with adverse outcomes


Spiess, Royston, Levy et al: Platelet transfusions during CABG surgery are associated with serious adverse outcomes. Transfusion 2004;44:1143

- Data from phase III trials of aprotinin analyzed.
- Adverse outcome data (n = 1720) who received, and did not receive, periop PLT compared.
- Logistic regression analysis used; propensity scoring analysis verified logistic regression.
- PLT Tx pts had longer hospital stays, surgeries, more bleeding, re-op, RBC Tx; less likely full-dose aprot Rx
- Platelet transfusions increased infection, stroke, and death risk
- Propensity scoring analysis confirmed the risk of PLT transfusion.

The Risk Associated with Aprotinin in Cardiac Surgery

We hypothesized that the use of either serine protease inhibitors or lysine analogues in patients with acute coronary syndromes presenting for coronary-surgery surgery is unsafe.

CONCLUSIONS

The association between aprotinin and serious renal-organ damage indicates that the continued use is not prudent. In contrast, the less expensive generic medications argatroban and tranexamic acid are safe alternatives.
Key Study Points

- Observational database from 1996–2000\(^1\)
- 69 Institutions/16 countries\(^2\) with 5,436 pts of 4,374 pt databases available for analysis
- No randomization of therapy to treatment\(^2\)
- “Clinical decisions were not controlled by the study protocol...”\(^2\)
- “The effect of drugs on outcome was assessed with the use of multivariable logistic regression and propensity-score adjustment”\(^2\)


Preoperative Characteristics

<table>
<thead>
<tr>
<th></th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprotinin</td>
<td>11.4</td>
</tr>
<tr>
<td>EACA</td>
<td>5.8</td>
</tr>
<tr>
<td>TXA</td>
<td>4.5</td>
</tr>
<tr>
<td>Control</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Safety of Aprotinin, EACA, TA with Cardiac Surgery

Immunological Reactions

- Acute hemolytic (ABO incompatibility)
- Delayed hemolytic (antibody present)
- Febrile (in 1% of transfusions)
- Transfusion Related Acute Lung Injury (TRALI), antibody in donor plasma against patient’s leukocytes
- Allergic (allergens in donor blood)
- Anaphylactic (possibly IgA related)
- Bacterial (contaminated blood/equipment)

TRANSFUSION REACTIONS

- Febrile reactions
- Alloimmunization, immunosuppression
- GVH reaction (higher in designated donors)
- Hemolytic reactions
- Allergic reactions

COMMON TRANSFUSION REACTIONS

- IgA deficiency
- TRALI
- ABO incompatibility
- Bacterial contamination
- Coincidental drug allergy
TRANSFUSION REACTIONS: TRALI

- Blood from multiparous women contains donor IgG antibodies against neutrophil antigens
- When transfused, Ab bind and aggregate PMNs that are trapped in pulmonary microcirculation

TRANSFUSION REACTIONS: TRALI

- Granulocyte or HLA Ab are found in at least one donor in about 70% of cases.
- HLA class II Ab in donor plasma have been detected against recipient cells, but Ab or Ag involved determined in only a few cases.
  - Yomtovian R: Lancet 1984;1:244.
  - Eastlund T Vox Sang 1989;57:63.

CLINICAL MANIFESTATIONS: TRALI

- Noncardiogenic pulmonary edema
- Dyspnea, fever, chills
- Hypotension, acute RV failure
- Develops within 1-2 hr of transfusion
- Usually present by 4-6 hours
- Difficult to distinguish from ARDS
- Potential role of “priming” event

Neutrophil Activation with TRALI

- Circulating Neutrophil
- Lung Endothelial Cells
- Activated by anti-IgG, cytokines
- Adherent
- CD11b/CD18
- CD11a/CD18
- Penetrating
- Degranulating

Suspected TRALI Fatalities (2003-2005):

- Noncardiogenic pulmonary edema
- Dyspnea, fever, chills
- Hypotension, acute RV failure
- Develops within 1-2 hr of transfusion
- Usually present by 4-6 hours
- Difficult to distinguish from ARDS
- Potential role of “priming” event
**Independent Review of TRALI Fatalities:**

- Representative bar chart showing recipient fatalities with probable TRALI or unrelated to TRALI.

  - Bar colors indicate if an antibody (Ab) was detected and if the donor was a female.

  - Association with leukocyte antibodies: P < 0.001, χ²-test.

**Probable TRALI by Implicated Component:**

- Bar chart for donor fatalities with implicated components.

  - Components include plasma, apheresis platelets, RBCs, RDP, and cryoplatelets.

**Rate of Probable TRALI Fatality per 10⁶ Distributed Units:**

- Graph illustrating the rate of TRALI fatalities by component.

  - Proportion of female donors for each component.

**Strategies to Reduce TRALI:**

- Appropriate use of blood products.
- Selective use of male products.
- Donor history of transfusion or pregnancy.
- Testing for HLA and HNA antibodies.
- Others:
  - Pool & store platelets.
  - Platelet additive solutions.
  - Solvent detergent plasma.

**ETIOLOGIES OF ALLERGIC TRANSFUSION RXNS:**

- Coincidental drug allergy.
- IgA deficiency.
- Transfusion of allergens.
- Transfusion of alloantigens.
- Complement deficiency.

**MECHANISMS OF INJURY WITH TX REACTIONS:**

- Monocytes/macrophages release IL1, chemotactic factors, and express procoag factors (ie, TF).
- CD11b/CD18 expression on PMNs and monocytes facilitate adhesion.
- Activated PMNs secrete leukotrienes, cytokines, proteases, procoagulant factors.
Summary (1)

- Transfusions should be considered as organ donations
- Leukocytes (PMNs and mononuclear cells are major culprits) for most reactions (except TRALI)
- Transfusions are associated with both risks and costs
- Blood conservation is key strategy

Summary (2)

- RBC storage produces measurable changes
- Observational clinical studies have provided inconsistent results and have limitations
- Equipoise remains as to whether or not storage effects impact clinical outcome
- Not prudent to alter tx practice based upon length of storage with current data
- Ongoing RCT such as RECESS and ABLE should provide definitive data

Remember, n=1 is NOT a case series