Whole Blood vs. Components For Hemorrhagic Shock

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St Louis Children’s Hospital
Disclosures

- **Consultant**
  - US Army Blood Research Program
  - Norwegian Navy Blood Research Program
  - TerumoBCT
  - Entegrion

- **Research Support**
  - Haemonetics
  - Diapharma
Objectives

- History of WB to components
- Data comparing WB to components
- Rationale of benefits of WB for HS
- Planned trial of WB vs. components for hemorrhagic shock
My Background

- 12 years Active Duty Army
- 1 year – Baghdad, 2004-2005
- Fresh Whole Blood Program Development
  - Transfusion approach to hemorrhagic shock
  - RBC storage lesion
  - Coagulation monitoring
  - Adults and Children
Transfusion History

- First Transfusion
- Lamb’s blood to human
  - June 15, 1667
  - Dr Jean-Baptiste Denis
Optimal resuscitative product for life threatening bleeding:

- High efficacy in reversing/treating shock and coagulopathy
- Does not promote dilution coagulopathy
- Reduced storage duration that may effect efficacy and safety
- Does not exacerbate immune, coagulation, endothelial dysfunction.
- Limited amount of processing
- Logistically feasible to provide and use.
Transfusion History

- Transition from
  - Whole blood
  - Modified whole blood
  - Single Component Therapy

- Whole blood now only
  - Austere settings
  - 15% of children’s hospitals surveyed in US

1 Spinella PC. Survey of Pediatric Transfusion Policies in the US and Canada. Transfusion 2010
What Influenced Transition?

- Primary customer: Oncology patients
  - Single deficits
  - More efficient/economical to use components

- Belief that bleeding patient
  - 30% coagulation factors for hemostasis
  - Platelets not needed early

- Fluids and RBCs adequate for early resuscitation of severe bleeding
Data to Support Transition in Severely Bleeding Patients?

- Whole Blood to Components – None
What do we Transfuse Today?

- RBC Units
  - Stored at 2-6 degrees C
  - 42 days

- FDA Criteria for RBC Storage Solutions
  - 70% survival and recovery 24 hours post Tx
    - Hemolysis, ATP and 2,3 DPG informally
RBC Storage

- NO DATA - RBCs stored > 7-14 days
  - Efficacious
    - Improve oxygen utilization
  - Safe (except infectious data)
- Storage solutions - “Grandfathered” by FDA
Changes in Red Cells and Physiologic Effects Associated with Storage Process

- **Storage Lesion**
  - Oxidative Injury
  - Microparticles
    - Bioactive Lipids
  - Immune Modulation
    - ↑ Inflammation
    - ↑ Infection
    - ↑ Hypercoagulability
    - ↑ Endothelial Injury
  - ↓ Microvascular Perfusion
    - ↔ ↓ O₂ Consumption
      - ↓ MOF
        - ↑ Death

- ↓ 2,3 DPG
- ↓ Deformability
- ↓ N.O.
- ↑ RBC Aggregation & Adhesion

Adapted from Spinella PC, Crit Care Med 2007
Preferential use of Older RBCs in Sickest

- Standard approach is to give the oldest RBC in inventory to minimize waste
- Sickest patients get the oldest blood since they use the most
- Sickest patients in shock and coagulopathy need efficient/safe product immediately
RBC age and severity of illness
(two hit hypothesis)

- Relationship between RBC age and outcomes with the degree of critical illness important to understand

- Post-op ortho (<1% mortality)
- Post-op cardiac (3-5%)
- ARDS (20-40%)
- Severe Trauma (20-40%)
- Severe Sepsis (40%)

Increased risk of old RBC with increased critical illness
Plasma Requirements

● Stored frozen for one year
  – 80% of coagulation factors

● 30-50% of coagulation factor activity needed for hemostasis
  – NOT SUPPORTED in TRAUMA PATIENTS
  – Derived: Patients w/ congenital factor deficiencies
Plasma Storage Requirements

- Is 80% enough?
- Are other proteins in plasma more important?
- Plasma much more than coagulation factors
- Thawed plasma
  - More available
  - At what cost?
Platelet Storage History

- 1970 Murphy Data
- Platelets at 4C
  - Activated but cleared from circulation quick
- Platelets at 22C
  - Remain in circulation but not active

- How do you define function?
- Different patients – Different needs
Toward a definition of “fresh” whole blood: an in vitro characterization of coagulation properties in refrigerated whole blood for transfusion

TRANSFUSION Volume 51, January 2011

David Jobes, Yanika Wolfe, Daniel O’Neill, Jennifer Calder, Lisa Jones, Deborah Sesok-Pizzini, and X. Long Zheng
Average ± SEM ADP-, collagen-, ASPI-, and TRAP-6-stimulated aggregation in WB stored at 4°C versus 22°C (p<0.001 for all four agonists by repeated measures ANOVA).

Pidcoke, H.F., Transfusion. 51(3S): Suppl (Abstract #SP8).
Platelet Storage

● In vivo studies needed
  – Cold vs room temp storage

● There is an FDA licensed product with platelets stored at 2-6 C.
Whole Blood – Licensed FDA

- **Civilian**
  - Cold - 2-6 degrees C
  - Fresh if < 48 hrs
  - Licensed for 21 days

- **Military**
  - Warm - 20-24 degrees C
  - Fresh if < 24 hours
  - Not formal TTD testing (rapid tests)
Transfusion Approach to Hemorrhagic Shock

- CONTROVERSIAL – NO RCT data
  - High Ratios of FFP:RBC and PLT:RBCs
    - 1:2 or 1:1 ratios
  - BASED on WHOLE BLOOD Resuscitation
  - TEG/ROTEM Guided Hemostatic Resuscitation
    - After initial volume replacement
The Coagulopathy of Trauma: A Review of Mechanisms

John R. Hess, MD, MPH, FACP, FAAAS, Karim Brohi, MD, Richard P. Dutton, MD, MBA, Carl J. Hauser, MD, FACS, FCCM, John B. Holcomb, MD, FACS, Yoram Kluger, MD, Kevin Mackway-Jones, MD, FRCP, FRCS, FCEM, Michael J. Parr, MB, BS, FRCP, FRCA, FANZCA, FJJFCM, Sandro B. Rizoli, MD, PhD, FRCSC, Tetsuo Yukioka, MD, David B. Hoyt, MD, FACS, and Bertil Bouillon, MD
Is WB better than components for HS?

If it is

How can it be made more available?
Potential FWB Benefits

● FWB Vs. Stored Components
  – **Less dilutional** effect
    • Increased anti-coagulants and preservatives in stored components ¹
  – **More functional** fresh product ²
  – **Less storage lesion (adverse effects)** of aged products

1 Spinella PC, J Trauma. 2009;66:S69-76
**Volume and Concentrations Between Component Therapy vs Warm Whole Blood**

**Component Therapy:**
- 1U PRBC + 1U PLT + 1U FFP + 1 U cryo
- 680 COLD mL
  - Hct 29%
  - Plt 80K
  - Coag factors 65% of initial concentration
  - 1000 mg Fibrinogen

**FWB:**
- 500 mL
- Hct: 38-50%
- Plt: 150-400K
- Coag concentration 100%
- 1000 mg Fibrinogen

Standard Amounts of Anti-coagulants and Additives in Reconstituted Whole Blood vs Whole Blood

<table>
<thead>
<tr>
<th>Component Therapy per Unit:</th>
<th>Whole Blood per Unit:</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 X RBC (AS-5) 6 X 120 ml = 720 ml</td>
<td>6 X 63ml = 378ml</td>
</tr>
<tr>
<td>6 X FFP 6 X 50 ml = 300 ml</td>
<td></td>
</tr>
<tr>
<td>1 X aPLT 1 X 35 ml = 35ml</td>
<td></td>
</tr>
<tr>
<td><strong>Total =1055ml</strong></td>
<td><strong>Total: 378ml</strong></td>
</tr>
</tbody>
</table>

There is 3 times the volume of anticoagulant and additives with reconstituted whole blood from components compared to whole blood

Spinella PC, J Trauma. 2009;66:S69-76
FWB Risks

- Unnecessary exposure to plasma/platelets
- Immune Modulation – WBC exposure
  - Leukoreduction with platelet sparring filters are now available
- Rare Transfusion associated GVHD
  - WBC inactivating methods in development
- Infection – Only in Military Scenarios
What Data is There on FWB vs Components?

- **2 RCT**
  - Pediatric Cardiothoracic Surgery
    - Pump prime only
    - Intra and post op use in ICU

- **3 Retrospective**
  - 2 combat trauma
  - 1 mixed civilian population
Manno - Methods

- Prospective double-blinded study
  - 161 children requiring cardiac surgery
- Patients were randomized to
  - Warm FWB (< 6 hours at 20 degrees C)
  - Cold FWB (24 - 48 hours at 4-6 C)
  - Reconstituted whole blood (1:1:1)
    - (RBCs ≤ 5 days of storage, FFP, and platelets).

Manno - Results

- Patient groups similar
  - Sex and Age
  - Surgical severity score
  - By pass and circulatory arrest time
  - # requiring circulatory arrest
**Manno - Results**

<table>
<thead>
<tr>
<th></th>
<th>Warm FWB</th>
<th>Cold FWB</th>
<th>Recon Blood</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hr blood loss (ml/kg)</td>
<td>50.9 (±9)</td>
<td>44.8 (±6)</td>
<td>74.2 (±9)</td>
<td>0.03∞</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>24 hr blood loss (ml/kg)</td>
<td>52.3 (±11)</td>
<td>51.7 (±7.4)</td>
<td>96.2 (±11)</td>
<td>0.001 §</td>
</tr>
<tr>
<td>&lt; 2 yrs</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTT (30 min)</td>
<td>38.2 (±1.1)</td>
<td>39.7 (±3.4)</td>
<td>43.3 (±1.8)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>202 (±5.4)</td>
<td>195 (±5.6)</td>
<td>184 (±4.8)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT aggregation (30 min)</td>
<td>most reduced</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

∞ cold vs recon
§ warm and cold vs recon

Impact of the Duration of Platelet Storage in Critically Ill Trauma Patients

(J Trauma. 2011;71: 1766–1774)

Kenji Inaba, MD, FRCSC, FACS, Bernardino C. Branco, MD, Peter Rhee, MD, MPH, FACS, Lorne H. Blackbourne, MD, FACS, John B. Holcomb, MD, FACS, Philip C. Spinella, MD, FACS, Ira Shulman, MD, Janice Nelson, MD, and Demetrios Demetriades, MD, PhD, FACS

![Diagram showing the impact of platelet storage duration on overall complications. The diagram indicates that the odds ratio (OR) for complications decreases with shorter storage times. OR=2.4, p=0.007* for aPLT ≤ 3 days compared to aPLT 5 days. OR=1.6, p=0.220 for aPLT 4 days compared to aPLT 5 days. The overall complication rates are 13.3%, 19.3%, and 26.4% for aPLT ≤ 3 days, aPLT 4 days, and aPLT 5 days, respectively.]
Fresh Whole Blood versus Reconstituted Blood for Pump Priming in Heart Surgery in Infants

Warm Fresh Whole Blood Is Independently Associated With Improved Survival for Patients With Combat-Related Traumatic Injuries

Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Alec C. Beekley, MD, and John B. Holcomb, MD

968 patients in database

614 excluded

354 (37%) patients included

254 (72%) CT patients

100 (28%) FWB patients

530 neither WB/PLT

84 both WB/PLT

30% total blood volume = WFWB
Survival

Spinella PC, J Trauma. 2009;66:S69-76
Multi-variate Logistic Regression for 30 day survival – Patient study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95.% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFWB group*</td>
<td>15.4 (2.3 – 106)</td>
<td>0.005</td>
</tr>
<tr>
<td>Plasma:RBC ratio</td>
<td>10.3 (2.3 - 45.)</td>
<td>0.002</td>
</tr>
<tr>
<td>ISS</td>
<td>0.94 (0.91 - 0.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>GCS eyes (normal)</td>
<td>3.91 (1.5 - 10.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Base deficit</td>
<td>0.88 (0.82 – 0.95)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Referent group were CT patients
AUC (95% CI) = 0.9 (0.85-0.95)
Multi-variate Logistic Regression for 30 day survival – individual blood product amounts

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95.0% C.I.)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFWB (U)</td>
<td>2.15 (1.21-3.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>Plasma (U)</td>
<td>1.09 (1.02-1.18)</td>
<td>0.019</td>
</tr>
<tr>
<td>RBC (U)</td>
<td>0.91 (0.85-0.97)</td>
<td>0.003</td>
</tr>
<tr>
<td>Base Deficit</td>
<td>0.91 (0.84-0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>GCS eyes (normal)</td>
<td>3.8 (1.4-10.2)</td>
<td>0.009</td>
</tr>
<tr>
<td>ISS</td>
<td>0.94 (0.91-0.98)</td>
<td>0.001</td>
</tr>
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</table>

AUC (95% CI) = 0.9 (0.86 – 0.95)

Spinella PC, J Trauma. 2009;66:S69-76
Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients

**TRANSFUSION** 2011;51:242-252.

US and Foreign Nationals – Massive transfusion only
- 40% are US patients
- High rate of censoring prior to 30 day survival
  • 245/369 (66%) still available at 30 days
- Different use of personal protective gear

Fig. 2. Unadjusted Kaplan-Meier survival curves comparing FWB to aPLT groups.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Logistic regression for mortality at 24 hr*</th>
<th>Cox regression for mortality at 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>aPLT group†</td>
<td>3.38 (0.96-11.87)</td>
<td>1.38 (0.77-2.47)</td>
</tr>
<tr>
<td>US nationality</td>
<td>0.35 (0.12-1.02)</td>
<td>0.33 (0.18-0.59)</td>
</tr>
<tr>
<td>TRISS</td>
<td>0.57 (0.44-0.74)</td>
<td>0.71 (0.64-0.79)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>0.69 (0.48-1.01)</td>
<td>1.00 (0.84-1.21)</td>
</tr>
<tr>
<td>PLT count (1 x 10⁹/L)</td>
<td>1.00 (0.99-1.01)</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td>INR</td>
<td>1.45 (0.97-2.16)</td>
<td>1.21 (1.01-1.45)</td>
</tr>
<tr>
<td>Base deficit (mEq/L)</td>
<td>1.05 (0.98-1.13)</td>
<td>1.02 (0.99-1.06)</td>
</tr>
<tr>
<td>Total RBC units‡</td>
<td>1.06 (1.02-1.11)</td>
<td>1.02 (0.99-1.04)</td>
</tr>
<tr>
<td>Plasma ratio (%)§</td>
<td>0.94 (0.92-0.97)</td>
<td>0.99 (0.98-0.999)</td>
</tr>
<tr>
<td>rFVIIa usage</td>
<td>0.86 (0.29-2.57)</td>
<td>1.05 (0.61-1.83)</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>&lt;0.001</td>
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<td></td>
<td>p value</td>
<td>&lt;0.001</td>
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<td></td>
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<td>0.96</td>
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<tr>
<td></td>
<td>p value</td>
<td>&lt;0.13</td>
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<tr>
<td></td>
<td>p value</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.23</td>
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<tr>
<td></td>
<td>p value</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.85</td>
</tr>
</tbody>
</table>
Factors associated with acute lung injury in combat casualties receiving massive blood transfusions: A retrospective analysis

Chee M. Chan MD, MPH\textsuperscript{a,\#}, Andrew F. Shorr MD, MPH\textsuperscript{a}, Jeremy G. Perkins MD, FACP\textsuperscript{b}

\textsuperscript{a}Pulmonary and Critical Care Department, Washington Hospital Center, Georgetown University Medical Center, Washington, DC 20010, USA
\textsuperscript{b}Hematology and Oncology Department, Walter Reed Army Medical Center, Washington, DC, USA

\begin{table}
\centering
\begin{tabular}{llll}
\hline
        & AOR & 95\% CI & \textit{P} \\
\hline
Whole fresh warm blood & 1.06 & 1.00-1.13 & .04 \\
Wound, blunt           & 3.54 & 1.61-7.77 & .002 \\
Crystalloids           & 1.05 & 1.00-1.10 & .04 \\
FFP                   & 0.99 & 0.96-1.03 & .83 \\
TRISS                 & 1.03 & 0.89-1.18 & .71 \\
\hline
\end{tabular}
\caption{Independent factors associated with the development of ALI}
\end{table}

An AOR greater than 1 signified a higher risk for ALI. Thus, WFWB, crystalloid therapy, and blunt trauma wounds were associated with ALI. 

\textsuperscript{\#}Hosmer-Lemeshow test (\textit{P} = .201).
Whole Blood Availability

- Currently
  - Not Leukoreduced
  - Whole blood < 48 hrs at 4C in clinical use
    - FDA approved for 21 days at 4C
- Leukoreduction possible – platelet sparing
- Use past 2 days of storage at 2-6 C
Platelet Sparing Leukoreduction

● Imuflex®
  – FDA licensed: survival and recovery data
  – NO PLT function testing

● In vitro testing of PLT function at 4 and 22 C
  – Underway
  – Storage up to 10 days
  – Including with rapid infuser
In Vivo Study

- To determine if platelet function in WB stored at 4C for 10 days is equivalent to components for hemorrhagic shock
- Would extend clinical use of WB
  - From 2 to 10 days
- Increase Availability

Children's Hospital · St. Louis
Washington University in St. Louis
School of Medicine
Pilot RCT study - for feasibility

● Patient Cohort
  – 20 Liver transplant patients with Hepatitis C
    • Type A or O
  – 78% patients require 1 - 20 units.
  – Median RBC: 11 units (IQ range 5-19)
● 39 patients eligible per year
● Co-PI: Sara Cheng and Phil Spinella
● R34 application for funding
Methods

● Randomize patients to receive
  – LR-WB (Imuflex)
  – CT in a 1:1:1 ratio (leukoreduced)

● CT in 1:1:1 ratio is defined as
  – 5 units of LR RBCs
  – 5 units fresh frozen plasma (FFP)
  – 1 unit LR apheresis platelets
Methods

- Standardized transfusion algorithm
- 20 units of WB will need to be made available on a 24/7 basis
  - Type O and A only
  - WB will be leukoreduced using Imuflex® WB-SP leukoreduction filter blood bag system
- 10 patients randomized to each arm
Outcomes

● Primary outcome
  • Feasibility to provide either treatment during surgery.
  • This will be measured by compliance rate
    • Proportion of patients in each arm who received all blood products per protocol.
Secondary Outcomes

● Efficiency of FWB use
  • Incidence of FWB and components wasted during the time period of the study protocol.

● Hemostatic and oxygenation function
  • TEG, WB aggregometry
  • INR, PTT, thrombin generation, fibrinogen
  • Tissue oxygen saturation (NIRS)
  • Immune and Endothelial function
Secondary Outcomes

- Total intraoperative blood use
- Morbidity and Mortality 24 hour and 30 day
- Citrate toxicity
  - ionized calcium levels, calcium use
- Donor exposure
- Transfusion reactions
  - TRALI and TACO
Pilot Study Summary

- NHLBI Transfusion Branch support
- Significant
  - Need to know which blood product approach
  - Reduce shock/coagulopathy and therefore outcomes
- Innovative
  - No RCTs of WB vs components in adults
- Methods
- Environment
Summary

• Whole blood provides balanced product
  – Reverse both Shock and Coagulopathy
  – Optimal vs 1:1:1 approach?

• Needs to be analyzed

• Possible
  – PLT sparring LR Filter
  – Cold Storage
Optimal resuscitative product for life threatening bleeding:

- High efficacy in reversing/treating shock and coagulopathy
- Does not promote dilution coagulopathy
- Reduced storage duration that may effect efficacy and safety
- Does not increase risk of exacerbating immune, coagulation, endothelial dysfunction.
- Limited amount of processing
- Simple and easy to make available and transfuse or logistically feasible to provide and use
Reconstructing Deconstructed Blood for Trauma

I hear the train a comin’
—Johnny Cash, Folsom Prison Blues, 1956

Military medicine has been, and continues to be, at the forefront of many important medical developments and innovations, especially in the area of the care of traumatic injury. The advances made for combat casualty care have had important and lasting impacts on the care of civilian trauma. Included in these have been the treatment of hemorrhagic shock, fluid resuscitation, and transfusion of blood and blood components. In this issue of Anesthesiology, Ho et al. examined the evidence for the increased use of plasma in treating major hemorrhage, a practice that began in the U.S. military and that has been embraced in U.S. civilian practice, as well.

The ability to separate whole blood into components began with Cohn’s separation of plasma into fractions (“fractionation”) and his suggestion that they be received as not needed, withdrawing them for patients need them. Although this has been successful for circumstances of a deficiency of specific component, the efficacy of this strategy for needing more than one components of blood, is questionable and untested. The ubiquitous separation of collected in the United Canada, and Europe into and plasma (for freezing or fractionation) proceeded beyond Cohn’s original suggested abetted by the development of regional blood centers, ratl individual hospitals, as well as collectors of blood. The objected cited the additive effort to transfuse both packed red cells (PR) to those in need of whole blood especially for massive hemorrhage, implying that agencies were motivated other than clinical care. The need for whole blood was lensed as unsupported by

“The logical question that should arise is that if a ratio of transfused red cells to plasma of 1:1 is beneficial, then why not transfuse whole blood, thus reducing substantially recipient exposure to donors?”
Johnny Cash heard the train coming (note the trauma described in the second verse)\(^1\); others (Bryan Cotton, verbal and written communication, August 2011),\(^{36}\) and I can see it, as well. The blood banking community is likely to get on board only if they are convinced by data, surgeons, anesthesiologists, intensivists, and other clinicians caring for trauma patients.

Richard B. Weiskopf, M.D., Department of Anesthesia, University of California, San Francisco, San Francisco, California. rbw@itsa.ucsf.edu
Thank you

Spinella_p@kids.wustl.edu
Warm storage of whole blood for 72 hours

Transfusion; 47: 2050-2056

J.D. Hughes, V.W. Macdonald, and J.R. Hess

Fig. 2. In vitro assays of plasma stability derived from 10 split whole-blood units stored at 19°C (◇) or 25°C (●). Assays revealed a significant increase in (A) PT but no significant changes in (B) PTT, (C) fibrinogen, or (C) thrombin time. A slight, nonsignificant decrease was observed in (D) FV and (E) FVIII activity. Activity of (F) FVII and (H) FX as well as FII, F IX, FXI, and FXII (data not shown) showed no changes in activity. Error bars, 1 SD.

Fig. 4. Thromboelastograph results revealed no significant changes in time to onset of clotting, TEG R (A); rate of clot growth, α (B); or maximum clot strength, MA (C) in whole-blood units stored both 19°C (◇) and 25°C (●). Error bars, 1 SD.
Manno - Discussion

- Exclusive use of either FWB or components both intra-operatively and post-operatively
- Multivariate linear regression to determine if other factors influenced their results.
- Powered for blood loss and not survival.
- Limited by randomization that was dependent upon FWB availability.

Mou - Methods

● RCT of cold stored FWB to reconstituted blood (RBCs and FFP) in the pump prime
● 200 pediatric cardiac surgery patients less than one year of age.
● No FWB post-operatively in the ICU where outcomes were measured.
● The primary outcome of this study was a composite score for survival and ICU LOS.
Mou - Results

- No difference in groups compared
  - Age, sex
  - Illness severity score, diagnoses
  - CPB or CA times

- Post-op no difference in
  - Composite score between study groups
  - Transfusion requirement
  - Chest tube output

Mou – Results/Discussion

● Secondary outcome
  – Increased in FWB group
    • ICU LOS - 97 hrs vs. 70 hrs, (p=0.04)
    • Total fluid requirement

● Not adjusted for potential confounders
  – Use of extracorporeal membrane oxygenation
  – ECMO 6 vs 2 in FWB vs Recon blood group
    • Increase risk of ICU LOS and fluid requirements.

Methods

- Retrospective study
  - January 2004 and October 2007
- Database of transfused combat casualties at US Army Institute Surgical Research
  - US patients only
  - 1 or more units of RBCs
  - Iraq and Afghanistan

Spinella PC, J Trauma. 2009;66:S69-76
Methods

- 2 groups of patients were compared
  - WFWB: Warm Fresh Whole Blood
    - WFWB, RBCs and plasma - but not aPLT
  - CT: Component Therapy
    - RBC, plasma, and aPLT - but not WFWB.
- Patients were excluded if
  - Both WFWB & aPLTs
  - Neither WFWB nor aPLTs.
## Comparison between study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>WFWB (n=100)</th>
<th>CT (n=254)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>24 (21-29)</td>
<td>23 (21-28)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>97.6 (96.4-98.2)</td>
<td>98.5 (97.4-99.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>112 (95-136)</td>
<td>115 (91-138)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td>110 (80-122)</td>
<td>109 (80-130)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>GCS eye</strong></td>
<td>4 (2-4)</td>
<td>4 (1-4)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>GCS verbal</strong></td>
<td>5 (1-5)</td>
<td>5 (1-5)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>GCS motor</strong></td>
<td>6 (3-6)</td>
<td>6 (1-6)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>11.6 (10-14)</td>
<td>11.8 (9.8-13.4)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Base Deficit</strong></td>
<td>6 (4-10)</td>
<td>6 (3-11)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>1.4 (1.1-1.6)</td>
<td>1.4 (1.2-1.8)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>ISS</strong></td>
<td>18 (10-26)</td>
<td>18 (10-26)</td>
<td>0.74</td>
</tr>
</tbody>
</table>
Comparison of adverse events between study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>WFWB (n=100)</th>
<th>CT (n=254)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Embolism</td>
<td>7 (7%)</td>
<td>11 (4%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cerebral Stroke</td>
<td>0 (0%)</td>
<td>5 (2%)</td>
<td>0.33</td>
</tr>
<tr>
<td>ARDS</td>
<td>7 (7%)</td>
<td>7 (3%)</td>
<td>0.08</td>
</tr>
<tr>
<td>DVT</td>
<td>15 (15%)</td>
<td>21 (8%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>8 (8%)</td>
<td>7 (3%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Patient Characteristics

- US and Foreign Nationals
- Massive Transfusion Only
  $\geq 10$ U RBC in 24 hrs
Patient Characteristics

- FWB patients sicker
  - ISS, Base deficit, Platelet count, temperature
- PLT group
  - More FFP:RBC, rFVIIa, cryoprecipitate
Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries

Philip C Spinella\textsuperscript{1,2}, Christopher L Carroll\textsuperscript{1}, Ilene Staff\textsuperscript{3}, Ronald Gross\textsuperscript{4}, Jacqueline Mc Quay\textsuperscript{4}, Lauren Keibel\textsuperscript{1}, Charles E Wade\textsuperscript{2} and John B Holcomb\textsuperscript{5}

Kaplan Meier Curve of trauma associated survival over 180 days for patients transfused fresh and old RBCs. RBC: red blood cells.
600 trauma patients transfused > 2 units

Compared exclusive receipt of
- RBCs > and < 14 days
- No Difference in RBC volume between groups
  - 6.1 vs 5.5 units

Old vs Fresh RBC group
- Mortality: 27% vs 20% (p=.08)
- Adjusted OR Mortality: 1.57 (1.14-2.15)
WB in vitro PLT Function Study

● Primary Aim
  – To determine if platelet function is maintained when filtered with Imuflex Leukoreduction filter

● Secondary Aims
  – Assess the effect on platelet function
    • Storage temperature
      – 2-6 vs 20-24 degrees C
    • Storage duration
      – 10 days
Methods

10 blood donors

WB collected – 500ml

Non-Leukoreduced WB
- Stored at 22°C
  - Time 0
  - Time 24 hr
  - Time 72 hr
  - Time 5 day
  - Time 10 day
- Stored at 4°C
  - Time 0
  - Time 24 hr
  - Time 72 hr
  - Time 5 day
  - Time 10 day

WB LR with Terumo Imuflex ® WB SP filter
- Stored at 22°C
  - Time 0
  - Time 24 hr
  - Time 72 hr
  - Time 5 day
  - Time 10 day
- Stored at 4°C
  - Time 0
  - Time 24 hr
  - Time 72 hr
  - Time 5 day
  - Time 10 day

25 ml sampled at each time point with 20 time points = 500ml collection
Outcomes

- **Platelet function**
  - Multiplate whole blood aggregometry
  - TEG parameters
- **Coagulation parameters**
  - Platelet count, INR, aPTT, fibrinogen
  - Pro and anti-coagulant factors
  - Thrombin generation assays