Trauma & Transfusion Ratios: What’s the Evidence?

Rachael Callcut, MD, MSPH
Assistant Professor of Surgery
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Fast Moving Field

- 7223 articles ‘trauma transfusion’
- 642 since last year’s conference
- What’s new?
  - RCT of ratio
  - Tranexamic Acid
  - Prothrombin Complex Concentrate
  - Functional testing guided resuscitations (Thromboelastography/ROTEM)
  - ? Whole Blood Resuscitation

The Old Days...

<table>
<thead>
<tr>
<th>Blood Loss (ml)</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ml</td>
<td>&lt;750</td>
<td>751-1500</td>
<td>1501-2000</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>% Blood Vol</td>
<td>&lt;15%</td>
<td>15-30%</td>
<td>30-40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>&gt;120</td>
<td>&gt;140</td>
</tr>
<tr>
<td>BP</td>
<td>nl</td>
<td>nl</td>
<td>decreased</td>
<td>decreased</td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td>nl</td>
<td>decreased</td>
<td>decreased</td>
<td>decreased</td>
</tr>
<tr>
<td>RR</td>
<td>14-20</td>
<td>20-30</td>
<td>30-40</td>
<td>&gt;35</td>
</tr>
<tr>
<td>UOP</td>
<td>&gt;30cc/hr</td>
<td>20-30</td>
<td>5-15</td>
<td>negligible</td>
</tr>
<tr>
<td>CNS</td>
<td>nl</td>
<td>anxious</td>
<td>confused</td>
<td>lethargic</td>
</tr>
<tr>
<td>Fluid Choice</td>
<td>crystalloid</td>
<td>crystalloid</td>
<td>crystalloid</td>
<td>crystalloid</td>
</tr>
</tbody>
</table>

Standard Resuscitation Paradigm

Crystalloid 3:1 Ratio

- Goal: “To restore intravascular volume & VS back to normal as quickly as possible to restore vital organ perfusion.”
- Blood
- FFP
- 6-10 u PRBC

Transient or no response
**Standard Resuscitation**

  - No evidence to support large-volume I.V. fluid resuscitation

**But is it harmful?**

**Lung Histology**

- Sham
- LR
- WB

Makley et al, J Trauma 2010

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**Understanding the Impact of the Lethal Triad**

What is predictive of death?

- Acidosis (Base deficit \( \geq 6 \))
- Coagulopathy (INR > 1.5)
- Hypothermia (Temp \(<35\,\text{C}\))
- Hypotension (SBP <90 vs <110)
- Anemia (Hgb <11)
What Resuscitation Strategy for the Severely Injured?

What are our goals?

• Restore volume
• Correct acidosis
• Avoid coagulopathy
• Avoid hypothermia
• Blunt anemia

Goal is to avoid exsanguination and coagulopathy
Uses pRBCs and FFP + platelets
Preliminary data from OIF/OEF
Civilian data compelling to make this Standard of Care

Key Concepts of DCR

• Recognize Shock
  — Identify the critical 10%
• Resuscitate Immediately
  — Devote attention to Hemostatic resuscitation
  • Provide volume that also restores the hemostatic cascade
  • Minimize crystalloid
  • Stop the bleeding
  • Stay out of trouble
How do we do it?

Component Therapy

What Transfusion Ratio??

• Median ratio of FFP:RBC was 1:1.7 in survivors compared to 1:1 in non-survivors (p<0.001).

Can we apply this to the Civilian Trauma Patient?

Civilian Literature (2008)

2746 pts needing operative intervention, 4yr retrospective study

16 Trauma centers pooled their one year experience with transfusion of trauma patients

Survivors vs. Non-Survivors

- FFP:PRBC ratios
  - Plasma rich (≥1u FFP : 1.5u PRBCs)
  - Plasma poor (< 1u FFP : 1.5u PRBCs)
  - OR death (multivariate logistic regression)

<table>
<thead>
<tr>
<th>Product Ratio</th>
<th>Mean ± SD</th>
<th>OR death (poor vs. rich)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC</td>
<td>9.8 units ± 11.7</td>
<td>3.57 (95% CI 1.02 – 12.5)</td>
</tr>
<tr>
<td>FFP:PRBC</td>
<td>8 units ± 7.6</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Plasma rich (survival)</td>
<td>84%</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Plasma poor (survival)</td>
<td>60%</td>
<td>p=0.04</td>
</tr>
</tbody>
</table>
Is all 1:1 the same?

- pRBC
- FFP
- pRBC
- FFP
- pRBC
- FFP
- pRBC
- FFP
- FFP
- FFP
- FFP
- FFP

5 pRBC, 5 FFP

5 pRBC, 5 FFP

How do we answer this question?

Early Aggressive Use of Fresh Frozen Plasma Does Not Improve Outcome in Critically Injured Trauma Patients

Thomas M. Scalea, MD, Keith M. Boachie-Adjei, RN, BSN, MS, Kim Lampl, MD, John R. Hess, MD, MPH, Richard Doty, MD, Anne Pyle, RN, BSN, MS, and Grant V. Boachie-Adjei, MD, MPH

Additionally, we studied patients who survived to get to the ICU. One might theorize that patients who would have benefited from a one to one RBC:FFP resuscitation scheme simply did not survive to be entered into our study. During resuscitation, it is not uncommon to stop when your patient looks well. However, it may not be clear when your patient is hemodynamically stable. There is no question in my mind that a 1:1 resuscitation is wise in some patients, but we have not yet defined who those patients are. There is also no question in my mind that the most important principle in hemostasis after trauma is rapid identification and treatment of the bleeding sites. No

In addition, the timing of transfusion needs may be more important than the total number of units given. For instance, receiving 10 U of blood over the first 12 hours of hospitalization is far different than requiring 10 U of blood over the first 90 minutes of resuscitation. Conversely, patients that arrive with a mortality in excess of 90% are unlikely to survive, no matter what resuscitation strategy is employed.

(Don Surg 2008;249: 578 - 584)
Is 1:1 the correct ratio?

- Phase III clinical trial
- Investigating 1:1:1 plasma:platelet:pRBC vs. 1:1:2
- 12 US trauma centers
- Enrolled 680 MT patients prospectively
- Outcome 24 hr & 30 d mortality
WHICH RATIO?????

Results anticipated soon...

Other Patient Population Who MAY Also Benefit?

**Known**
- Trauma patients requiring <10 units PRBCs (Sub MT)
- Ruptured AAA
- Emergency general surgery patients

**Theoretic**
- Massive GI bleed
- Cardiac Surgery
- Major Orthopedic Cases
- Vascular elective surgery
- OB

### Table

<table>
<thead>
<tr>
<th>Site</th>
<th>Actual Enrollment Date</th>
<th>Number Subjects Enrolled *</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT-Memphis</td>
<td>8/5/2012</td>
<td>149</td>
</tr>
<tr>
<td>UC-SF</td>
<td>6/16/2012</td>
<td>47</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>8/3/2012</td>
<td>66</td>
</tr>
<tr>
<td>Toronto</td>
<td>9/3/2012</td>
<td>26</td>
</tr>
<tr>
<td>Maryland</td>
<td>1/22/2013</td>
<td>50</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>1/18/2013</td>
<td>42</td>
</tr>
<tr>
<td>Oregon</td>
<td>8/22/2012</td>
<td>31</td>
</tr>
<tr>
<td>Alabama</td>
<td>1/9/2013</td>
<td>35</td>
</tr>
<tr>
<td>Arizona</td>
<td>11/1/2012</td>
<td>42</td>
</tr>
<tr>
<td>UCI-LA</td>
<td>10/29/2012</td>
<td>56</td>
</tr>
<tr>
<td>UT-Memphis</td>
<td>9/5/2012</td>
<td>43</td>
</tr>
<tr>
<td>Washington</td>
<td>11/7/2012</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Based on eCRF data entry</td>
</tr>
</tbody>
</table>

Effect of early plasma transfusion on mortality in patients with ruptured abdominal aortic aneurysm


Table III: Multivariable analysis of factors influencing 30-day mortality

<table>
<thead>
<tr>
<th>Effect</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 35</td>
<td>6.64</td>
<td>1.70-25.15</td>
<td>&lt;.007</td>
</tr>
<tr>
<td>Pre-operative tachycardia</td>
<td>1.63</td>
<td>1.21-2.16</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Urine output&lt;100 mL/m2</td>
<td>1.64</td>
<td>1.22-2.19</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Low FFP</td>
<td>2.68</td>
<td>1.25-4.40</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

*OR is for each 10 beats per minute (bpm) increase in heart rate above 100 bpm.
**OR is for each 100 mL of decreased urine output; LOW FFP: PRBC(HDF;2:1)
The Future is Here...

• Adjuncts to balanced resuscitation are coming...

What is TXA?

• Trauma patients quickly fibrinogen deplete
• Inexpensive
• Oral or IV formulations
• Many uses outside of trauma

What is TXA?

• Antifibrinolytic
• Synthetic derivative of the amino acid lysine
• Binds to plasminogen and blocking the interaction with fibrin
• Prevents dissolution of the fibrin clot

CRASH-2

• “Aim to assess effect of Tranexamic acid on death in trauma patients with significant hemorrhage.”
• RCT double blind placebo controlled
• 20,211 pts in 274 hospitals in 40 countries
• Adult patients with or at risk of major hemorrhage
  – 1 gm over 10 minute loading dose
  – 1 gm infusion over 8 hours
### Table 2: Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment

<table>
<thead>
<tr>
<th>Time to Treatment (h)</th>
<th>N</th>
<th>All Causes of Death</th>
<th>Bleeding Death</th>
<th>Non-Bleeding Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>20427</td>
<td>0.81 (0.75-0.87)</td>
<td>0.86 (0.76-0.96)</td>
<td>0.94 (0.86-1.02)</td>
</tr>
<tr>
<td>≥0</td>
<td>7433</td>
<td>0.82 (0.76-0.89)</td>
<td>0.68 (0.62-0.72)</td>
<td>1.04 (0.83-1.21)</td>
</tr>
<tr>
<td>&gt;1-3</td>
<td>6013</td>
<td>0.87 (0.77-0.97)</td>
<td>0.79 (0.64-0.97)</td>
<td>0.91 (0.78-1.06)</td>
</tr>
<tr>
<td>≥4</td>
<td>6614</td>
<td>1.00 (0.90-1.13)</td>
<td>1.44 (1.12-1.84)</td>
<td>0.89 (0.78-1.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p</em> test of homogeneity</td>
<td></td>
<td>4.41 (p=0.13)</td>
<td>235.06 (p=0.0005)</td>
<td>2557 (p=0.03)</td>
</tr>
</tbody>
</table>

### So why not for all?
- Controversial study
- 34 articles in last 1 year
- Multiple on-going US pre-hospital trials just underway

### Prothrombin Complex Concentrate
- 24 articles 2012
- 63 articles Jan 2013 to May 2014
- PCC (Prothrombin Complex Concentration)
- Factor IX complex
  - Vitamin K dependent factors (II, VII, IX, X)
  - Originally used for rapid Coumadin reversal
- Many uses outside TRAUMA
Different formulations
- All given with Vit K
- 3 factor has to be generally given with 1 or 2 units FFP
- Relatively inexpensive ($500-1000)
  - Standard dose – 25 units per kg
  - Factor VII – very expensive ($3k to 12K per patient)

Reduction in RBC & FFP needs

Thromboelastography (TEG)
Example of TEG Guided Resuscitation

But...

Much Interest & Promise in Lab Studies

Summary

- Fast moving field
- Prospective observational data supports more balance plasma to PRBC to platelets improves survival
- RCT is forthcoming for optimum ratio
- Overall number of units utilized is decreasing
- Many analogous hemorrhaging ICU patient populations that may also benefit
- New adjuncts gaining steam that may augment our ratios...
Questions?