Transfusion Ratios: What’s the Evidence?

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Assistant Professor of Surgery, UCSF

Civilian Trauma Mortality

Hemorrhage COD in 30-40% of early deaths

The Old Days...

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

Standard Resuscitation Paradigm

Crystalloid 3:1 Ratio

Blood 6-10 u PRBC

Goal: “To restore intravascular volume & VS back to normal as quickly as possible to restore vital organ perfusion.”
Military Resuscitation

<table>
<thead>
<tr>
<th>Era</th>
<th>Focus</th>
<th>Resuscitation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>World War I</td>
<td>Wound toxins</td>
<td>None</td>
<td>Early death</td>
</tr>
<tr>
<td>World War II</td>
<td>Intravascular</td>
<td>Colloids, blood</td>
<td>Early survival</td>
</tr>
<tr>
<td>Korean War</td>
<td>Repulsion</td>
<td></td>
<td>ARF → death</td>
</tr>
<tr>
<td>Vietnam war</td>
<td>Intravascular and extravascular fluid resuscitation</td>
<td>Crystalloids, banked blood</td>
<td>Early survival</td>
</tr>
<tr>
<td>1970s–80s</td>
<td>ICUs, organ failure, metabolic support</td>
<td>PA catheters, endpoints of resuscitation</td>
<td>ARF, ARDS, MOF, MOF deaths</td>
</tr>
<tr>
<td>1980s–present</td>
<td>Trauma centres, trauma systems</td>
<td>Rapid triage, damage control, shock and trauma ICUs</td>
<td>Early survival, ARDS, MOF, MOF deaths</td>
</tr>
</tbody>
</table>

ARF=acute renal failure, ARDS=adult respiratory distress syndrome, MOF=multi organ failure.

Standard Resuscitation

• Cochrane Review (2003)
  • No evidence to support large-volume I.V. fluid resuscitation

But is it harmful?

• Harmful effects:
  – Increased BP accelerates rate of bleeding which can dislodge a soft early clot
  – Dilutes RBCs therefore reduces oxygen delivery despite an increased CO
  – Reduced hct and clotting factors inhibit new clot formation
  – Resuscitative fluids are harmful themselves
    • Acidic
    • Pro-inflammatory
    • Abdominal Compartment Syndrome

The consequence...
Lung Histology

Makley et al., J Trauma 2010

Lethal Triad


Increased Mortality Associated With the Early Coagulopathy of Trauma in Combat Casualties

Sarah E. Yoo, MD, MPH, Daniel T. McGough, MD, Jensen G. Perkins, MD, Charles E. Wade, PhD, Tsao-Chung Li, PhD, Philip C. Spinella, MD, and John B. Holcomb, MD

Base Deficit

Fig. 2. Prevalence of coagulopathy by ISS and BD in patients requiring a blood transfusion.

Hypothermia

The impact of hypothermia on trauma care at the 31st combat support hospital

Zachary Arthurs, M.D.*, Daniel Cieslak, M.D., Alex Reckley, M.D., Kurt Garshwold, M.D., Jeremy Perkins, M.D., Robert Rish, M.D., James Sehota, M.D.

Table 5

Independent predictors of mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia (&lt;36°C)</td>
<td>3.8 (2.1-6.9)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>GCS &lt; 8</td>
<td>23 (14.8-35.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Shock (MAP &lt; 50 mm Hg)</td>
<td>8.1 (5.1-12.1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ISS &gt; 25</td>
<td>13.9 (7.3-26)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

- 18% arrive cold (<36°F)
- 100% mortality < 34°C

What Resuscitation Strategy for the Severely Injured?

What are our goals?

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

What is the solution?

Warm Fresh Whole Blood

- Restore volume
- Reverse acidosis
- Avoid coagulopathy
- Avoid hypothermia
- Blunt anemia
How about reconstituted whole blood?

- Restore volume
- Reverse acidosis
- Avoid coagulopathy
- Avoid hypothermia
- Blunt anemia

Component Therapy vs. Fresh Whole Blood

Component Therapy
1U PRBC + 1U PLT + 1U FFP + 10 pk Cryo =

660 COLD mL
- Hct 29%
- Plt 87K
- Coag activity 65%
- 750 mg fibrinogen

Damage Control Resuscitation

- Concept from Damage Control Surgery
  - "Staying out of trouble rather than getting out of trouble"
- Aggressive hemostatic resuscitation techniques should be performed in parallel with equally aggressive surgical control of bleeding

Hemostatic (Damage Control) Resuscitation

- 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??

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The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

- Median ratio of FFP: RBC was \(1.17\) in survivors compared to \(1.3\) in non-survivors (\(p<0.001\)).
Civilian Literature (2008)

Review of Current Blood Transfusion Strategies in a Mature Level I Trauma Center: Were We Wrong for the Last 40 Years?

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

<table>
<thead>
<tr>
<th></th>
<th>PRBC (mean +/- sd)</th>
<th>FFP (mean +/- sd)</th>
<th>FFP:PRBC (mean)</th>
<th>Plasma rich (survival)</th>
<th>Plasma poor (survival)</th>
<th>OR death (poor vs. rich)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC</td>
<td>9.8 units +/- 11.7</td>
<td>8 units +/- 7.6</td>
<td>1 : 1.26</td>
<td>84%</td>
<td>60%</td>
<td>3.57 (95% CI 1.02 – 12.5)</td>
</tr>
</tbody>
</table>

Multicenter, retrospective 466 pts.

Table 3: Mortality differences and respiratory outcome based on the ratio of blood products

<table>
<thead>
<tr>
<th>Product ratio Measure</th>
<th>0.14</th>
<th>0.4-1.1</th>
<th>≥1 : 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP:PRBC 6 hour mortality %</td>
<td>37.3*</td>
<td>15.2*</td>
<td>2.0* &lt; 0.001</td>
</tr>
<tr>
<td>In-hospital mortality %</td>
<td>54.9*</td>
<td>41.1*</td>
<td>25.5* &lt; 0.04</td>
</tr>
<tr>
<td>Ventilator free days*</td>
<td>9</td>
<td>7.9</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Multicenter, retrospective 466 pts.

A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study

Karen A. Zink, M.D., Oltra N. Sambasivan, M.D., John B. Holcomb, M.D., Gay Chichilnisky, Ph.D., Martin A. Schreiber, M.D.*

Department of Surgery, Trauma/Critical Care Section, Oregon Health & Science University, 3181 SW Sam Jackson Road (L210), Portland, OR 97239, USA.

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Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients


Platelets: RBCs

Multicenter, prospective 214 MT pts.
Trauma centers pooled their one year experience with transfusion of trauma patients
Is all 1:1 the same?

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

5 pRBC, 5 FFP
5 pRBC, 5 FFP

Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

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

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

5 pRBC, 5 FFP
5 pRBC, 5 FFP

PROMMT
Prospective Observatinal Multicenter Major Trauma Transfusion Study

- 10 Level 1 trauma centers
- July 2009-October 2010
- Primary objective:
  - Investigate in hospital mortality in all patients surviving at least 30 minutes after ED admission
  - Minute to minute tracking until resuscitation complete
  - Followed until hospital discharge

5/30/2013

5 pRBC, 5 FFP

5/30/2013
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

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

**Method**

- **Table III:** Multivariate analysis of factors influencing 30-day mortality

**Results**

- **Pre-operative tachycardia**
  - OR: 1.63
  - 95% CI: 1.21-2.16
  - P value: 0.005

**Analysis**

- **PRBCs/FFP ratio:**
  - OR: 4.25
  - 95% CI: 1.25-14.49
  - P value: 0.018

**Notes**

- OR is for each 10 units reduction in PRBCs/FFP ratio.
- *P* values are derived from multivariate analysis.
- The study suggests a potential benefit for a more standardized protocol of initial resuscitation for these patients, and prospective studies are warranted to determine the optimal PRBC/FFP ratio in AAA patients.
Is 1:1 the correct ratio?

Figure 1:. MIP-2 Levels after resuscitation. P<0.05 vs all other groups

Figure 2:. MIP-1α Levels after resuscitation. P<0.05 vs plasma and pRBCs alone

Figure 4:. Evan’s blue levels in the colon after resuscitation.

Figure 5:. Evan’s blue levels after resuscitation in the lung. P<0.05 vs pRBCs alone

Makley et al, manuscript 2011

PROPR - Pragmatic, Randomized Optimal Platelet and Plasma Ratios

PROPR is a multi-center, prospective, randomized trial that will compare different ratios of blood products given to trauma patients who are predicted to require massive transfusions (greater than 10 units of PRBC’s within the first 24 hours).

http://cetir-tmc.org/research/propr

Summary

- Phase III clinical trial
- Investigating 1:1:1 plasma:platelet:pRBC vs. 1:1:2
- 12 US trauma centers
- Enroll 580 MT patients prospectively
- Outcome 24 hr & 30 d mortality

- Prospective Observational data supports prior retrospective data that more balance plasma to PRBC to platelets improves survival in massively hemorrhaging trauma patients.
- RCT is forthcoming for optimum ratio.
- Overall number of units utilized is decreasing.
- Many analogous hemorrhaging ICU patient populations that may also benefit.
Acknowledgements

- PROMMTT Investigators
  - Univ of Cincinnati Department of Surgery
  - Univ of Texas – Houston
  - UCSF
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- Cohen Research Staff
- 24/7 Staff
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