Trauma Induced Coagulopathy: What is it? What can be done about it? What is the future?

5th Annual Major John P. Pryor MD FACS Memorial Lecture
Pennsylvania Trauma Systems Foundation
17th Annual Conference and Meeting
25 October 2013
Donald H. Jenkins MD FACS
Trauma Medical Director Saint Marys Hospital
Mayo Clinic Level I Trauma Center
Background

- Coagulopathy worsens outcomes in casualties with uncontrolled hemorrhage
- Causes of coagulopathy in casualties:
  - Hypothermia (especially in shock)
  - Large volume crystalloid resuscitation
  - Platelet-inhibiting drugs (aspirin and other NSAIDs such as ibuprofen)
  - Acidosis (associated with shock)
  - Intrinsic
  - Protracted scene times (>2 hours)
  - Protracted pre-hospital time (>2 hours)
Pathogenesis of Traumatic Coagulopathy

- Multi-factorial global failure of the coagulation system to sustain adequate hemostasis after major trauma
- Combination of tissue trauma and systemic hypoperfusion cause global anticoagulation and hyperfibrinolysis
- Endothelial activation of Protein C is a central mechanism
Pathogenesis of Traumatic Coagulopathy

• Experimental models show that shock and tissue injury are associated with:
  • Early depletion of Protein C
  • Increased plasma thrombomodulin
  • Low levels of Factor V
• This all suggests the central role of the activation of the Protein C pathway in traumatic coagulopathy
Pathogenesis of Traumatic Coagulopathy

• High levels of Protein C in trauma patients:
  • Reduced clot strength
  • Limited changes in clotting times
  • Increased mortality
  • Greater transfusion requirements

• Normal hemostasis relies on fibrinogen
  • A substrate for clot formation
  • Fibrinogen levels fall rapidly in traumatic coagulopathy
  • Fibrinogen depletion is associated with poor outcomes
  • Fibrinogen replacement corrects coagulopathy (TEG)
Pathogenesis of Traumatic Coagulopathy

- Additional blood loss, hemodilution with crystalloid and/or hypocoagulable blood products, acidemia, consumption of clotting factors and hypothermia all act to exacerbate the deranged coagulation response.

- Functional reduction in clot strength
  - Can be identified by TEG or ROTEM within 5 minutes
  - Predicts need for massive transfusion
Coagulopathy and Trauma

- Derangements in coagulation occur rapidly after trauma
- By the time of arrival at the ED, 28% (2,994 of 10,790) of trauma patients had a detectable coagulopathy that was associated with poor outcome (MacLeod et al., 2003)
- Mortality approaches 50%
- Greater transfusion need
- Higher morbidity: multi-organ failure, sepsis and increased ICU length of stay (Davenport 2013)
Coagulopathy and TBI

• 291% increase – in mortality from blunt head trauma with coagulopathy (Wafaisade)
• 285% increase – in Grade III and IV intracranial hemorrhage with antiplatelet agents (Ivascu)
• 270% increase - in intracranial lesions with ASA or ibuprofen (Fabbri)
• 41% increase – in progression of intracranial hemorrhage with coagulopathy (Allard)
Background

- Hemorrhage is the leading cause of potentially preventable death due to injury
- Coagulopathy increases the risk of hemorrhagic death
- Crystalloids and colloids dilute existing clotting factors in the blood
- Plasma replaces clotting factors lost through hemorrhage: PRBCs do not; crystalloids do not
Background

Brohi K et al. J Trauma, June 2003.

Coagulopathy associated with increased mortality even after adjusting for ISS
Mortality in Trauma

- 600% increase – with coagulopathy in combat casualties requiring a transfusion (Niles)
- 428% increase – remote location vs urban (Fatovich)
- 291% increase – from blunt head trauma with coagulopathy (Wafaisade)
- 245% increase - early deaths with coagulopathy (Mitra)
- 209% increase – more than 1.5 L of crystalloid (Ley)
- 44% increase - IV or IV fluids in shock patients (Haut)
- 29% increase – IV fluids in shock patients (Bickell)
Background

- One of the dramatic advances in the care of trauma patients realized from the U.S. experience in Afghanistan has been the use of higher ratios of plasma to red blood cells in casualties requiring massive transfusions
- This increased emphasis on in-hospital plasma is now the standard of care for the military and is rapidly being adopted by the civilian sector
Fluid Resuscitation: Summary

- Large Volume Crystalloids
  - **Increases** mortality
  - **Worsens** coagulopathy of trauma and TBI
- Hypotensive Resuscitation with Hextend
  - Better logistically (less weight) **BUT**
  - Improved survival over LR not well established
  - Does not treat coagulopathy
- Thawed or liquid plasma
  - The **standard of care** for treating coagulopathy
  - Increases survival as part of Damage Control Resusc
Background 2009

Plasma first used on military transports in 2001 (fixed wing)

but...

To date, no civilian program has described in the literature using thawed plasma on rotary medical transport
Mayo Pre-Hospital Plasma Program: Our Rationale

• Current evidence supports increased ratio of plasma:PRBC and early use of plasma in trauma
• Packed Red Blood Cells (PRBCs) and plasma are optimal resuscitative fluids for patients with serious hemorrhage and/or impairment of coagulation
• Emergency use of Fresh Frozen Plasma is limited by time to thaw (15-30 minutes)
Protocol – ED Phase

• Developed in Feb 2008 with input from:
  - Division of Transfusion Medicine
  - Division of Medical Transport
  - Division of Trauma, Critical Care and General Surgery
• Initial 12 months were restricted to in-hospital Emergency Department use
• Medical and Surgical emergencies
  - Safety concerns
  - Utilization of resources
• Product immediately available in the Trauma Resuscitation Area:
  - 4 units thawed plasma (A+)
  - 4 units PRBCs (0 negative)
• Order of transfusion for trauma patients was:
  • 2 units PRBC
  • 2 units thawed Plasma
  • 2 units PRBC
  • 2 units thawed Plasma
Protocol – Helicopter Phase

Indications for PRBC and Plasma administration in adult trauma patients

**pRBC + Plasma**
1. Hypotension (single reading of systolic blood pressure ≤ 90mmHg)
2. Tachycardia (single reading of heart rate ≥ 120)
3. Penetrating mechanism
4. Point of care lactate ≥ 5.0 mg/dl
5. Point of care INR ≥ 1.5

**Plasma Alone**
1. Point of care INR ≥ 1.5
2. Stable Hemodynamics
Waste Prevention

Division of Transfusion Medicine monitors usage

- Thawed plasma is removed from the satellite blood refrigerator on Day #3 and sent to the Operating Theater for immediate use.
RESULTS

10 TRAUMA PATIENTS TRANSFUSED IN FLIGHT 2/2009 – 9/2010

• 5 for hemorrhage
  • 3 required massive transfusion (> 10 units/24 hours)
• 5 pts transfused for history of trauma and Coumadin use
  • All 4 deaths were in this group
• All pts entered into protocol required ongoing blood product transfusion after arrival to the hospital
<table>
<thead>
<tr>
<th>Trait</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.5 [30-75.3]</td>
</tr>
<tr>
<td>Male</td>
<td>8/10</td>
</tr>
<tr>
<td>ISS</td>
<td>25.5 [16.8-29.3]</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>4.5 [1.8-24.8]</td>
</tr>
<tr>
<td>Mortality</td>
<td>4/10</td>
</tr>
<tr>
<td>Test</td>
<td>Value</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Coumadin</td>
<td>5/10</td>
</tr>
<tr>
<td>Lactate</td>
<td>2.8</td>
</tr>
<tr>
<td>Base</td>
<td>-4.1</td>
</tr>
<tr>
<td>PLT</td>
<td>149</td>
</tr>
<tr>
<td>PTT</td>
<td>30</td>
</tr>
<tr>
<td>HgB</td>
<td>10.8</td>
</tr>
<tr>
<td>Post-Flight INR</td>
<td>1.6</td>
</tr>
<tr>
<td>Pre-Flight INR</td>
<td>2.7</td>
</tr>
</tbody>
</table>
Feasibility

• Excellent utilization
  • No discarded units of plasma to date
• No transfusion reactions documented to date; use of product parallels massive transfusion in the standard setting
Protocol Evolution

• During the study period, total of 771 flights
  • Only two pts received all 4 units of PRBC during transport

• Product Order and Ratio
  • 2009: 2 PRBC, 2 Plasma, 2 PRBC
  • 2010: 2 Plasma, 2 PRBC, 2 PRBC
  • 2011: 3 Plasma, 3 PRBC
## Results

### Feb 2009 – May 2011

<table>
<thead>
<tr>
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<th>PTP (n=9)</th>
<th>Control (n=50)</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>54</td>
<td>41</td>
<td>0.09</td>
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<tr>
<td>Sex (male)</td>
<td>89%</td>
<td>60%</td>
<td>0.07</td>
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<tr>
<td>Penetrating Mech</td>
<td>33%</td>
<td>18%</td>
<td>0.31</td>
</tr>
<tr>
<td>ISS</td>
<td>27</td>
<td>23</td>
<td>0.91</td>
</tr>
<tr>
<td>Warfarin Use</td>
<td>22%</td>
<td>2%</td>
<td>0.04</td>
</tr>
<tr>
<td>TRISS (Ps)</td>
<td>0.24</td>
<td>0.66</td>
<td>0.005</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>56%</td>
<td>18%</td>
<td>0.02</td>
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## Results

### INR

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<td>Pre-hosp INR</td>
<td>2.6</td>
<td>1.5</td>
<td>0.004</td>
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<tr>
<td>Arrival INR</td>
<td>1.6</td>
<td>1.3</td>
<td>&lt;0.001</td>
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<tr>
<td>INR Correction</td>
<td>1.0</td>
<td>0.2</td>
<td>0.08</td>
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# Results

## Time & the ‘Geographic Plasma Deficit’

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<tbody>
<tr>
<td>Facility Transfer</td>
<td>100%</td>
<td>54%</td>
<td>0.002</td>
</tr>
<tr>
<td>Transport → Trauma Ctr (min)</td>
<td>40</td>
<td>39</td>
<td>0.78</td>
</tr>
<tr>
<td>Injury → First Plasma (min)</td>
<td>194</td>
<td>231</td>
<td>0.58</td>
</tr>
<tr>
<td>Trauma Ctr arrival → Plasma (min)</td>
<td>- 34</td>
<td>97</td>
<td>0.013</td>
</tr>
</tbody>
</table>
CONCLUSION

• We successfully implemented pre-hospital thawed plasma use into our rural Level-I trauma system
• Initial results (e.g. feasibility, INR reduction), while not conclusive, are promising
• Protocol has been expanded to other transports in our system
Caveats

- Single institution
- Small numbers
- Differences in trauma system settings may limit the generalizability of our results
Group A Plasma Transfusion

Introduction

• ABO-identical preferred
• Universal plasma donor
  • Group AB
  • Lacks anti-A/anti-B
  • Pan-ABO compatible
  • Rarest blood group

Inaba K et al. Arch Surg 20
Group A Plasma Transfusion
Group AB supply

- Recent safety data
  - ABO incompatible platelets
    - 1 – 2 plasma units
    - 1 in 9000 hemolysis
  - Group O
  - Immunosuppression

Isaak EJ et al. Immunohematology
Josephson CD et al. Transfus Apher Sci
Group A Plasma Transfusion

Methods

• Retrospective review
• Inclusion
  • Trauma patient
  • July 2008 – June 2012
  • ≥ 1 unit emergency release plasma (group A plasma)
• Exclusion
  • death prior to ABO determination
  • < 18 years old
Group A Plasma Transfusion

Methods

• Post hoc ABO compatibility analysis
  • Compatible = groups A and O
  • Incompatible = groups AB and B
• Subgroup
  • Identical – group A
  • Non-identical – groups AB, B, O
• \( P \leq 0.05 \)
Group A Plasma Transfusion Definitions

- **ALI**
  - Bilateral pulmonary infiltrates
  - P:F ≤ 300
  - Lack of CHF
- **Possible TRALI**
  - Within 6 hours
- **ARDS**
  - ALI/possible TRALI
  - P:F ≤ 200
Group A Plasma Transfusion Results

- 10,206 patients over study period
- 258 emergency release plasma (2.5%)
- 4 died prior to blood grouping
Group A Plasma Transfusion Results

- 254 patients
  - 35 ABO Incompatible (14%)
    - 25 group B
    - 10 group AB
  - 219 ABO Compatible (86%)
    - 116 group A
    - 103 group O
### Group A Plasma Transfusion Results

<table>
<thead>
<tr>
<th>Feature</th>
<th>ABO Incompatible n = 35</th>
<th>ABO compatible n = 219</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>56 (39-79)</td>
<td>59 (32-79)</td>
<td>0.944</td>
</tr>
<tr>
<td>Male sex</td>
<td>63%</td>
<td>63%</td>
<td>0.973</td>
</tr>
<tr>
<td>ISS</td>
<td>25 (16-37)</td>
<td>22 (12-30)</td>
<td>0.199</td>
</tr>
<tr>
<td>TRISS</td>
<td>0.86 (0.26-0.97)</td>
<td>0.93 (0.34-0.97)</td>
<td>0.880</td>
</tr>
<tr>
<td>Scene transfer</td>
<td>34%</td>
<td>38%</td>
<td>0.710</td>
</tr>
<tr>
<td>Time from injury to trauma bay admission (mins)</td>
<td>145 (54-185)</td>
<td>172 (92-230)</td>
<td>0.214</td>
</tr>
<tr>
<td>Time in trauma bay (mins)</td>
<td>24 (20-35)</td>
<td>26.5 (20-36)</td>
<td>0.883</td>
</tr>
<tr>
<td>Time at referring hospital</td>
<td>119 (96-144)</td>
<td>121 (70-172)</td>
<td>0.920</td>
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<td>3 (2-8)</td>
<td>0.070</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>4 (1-11)</td>
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<td>0.155</td>
</tr>
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<td>9 (3-24)</td>
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## Group A Plasma Transfusion

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Group A Plasma Transfusion

Results

No hemolytic reactions
## Group A Plasma Transfusion Results

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<tbody>
<tr>
<td>Emergency release plasma (units)</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>0.345</td>
</tr>
<tr>
<td>Total Incompatible Units</td>
<td>3 (2-4)</td>
<td>0 (0-0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total compatible units @ 24 hours</td>
<td>2 (0-6)</td>
<td>3 (2-6)</td>
<td>0.439</td>
</tr>
<tr>
<td>Total plasma @ 24 hours (units)</td>
<td>6 (3-10)</td>
<td>4 (2-7)</td>
<td>0.444</td>
</tr>
<tr>
<td>Total RBC @ 24 hours (units)</td>
<td>5 (0-12)</td>
<td>4 (0-8)</td>
<td>0.472</td>
</tr>
<tr>
<td>Plasma:RBC @ 24 hours</td>
<td>1.3:1</td>
<td>1.1:1</td>
<td>0.155</td>
</tr>
<tr>
<td>Plasma deficit @ 24 hours</td>
<td>2 (0-3)</td>
<td>1 (-1-3)</td>
<td>0.195</td>
</tr>
<tr>
<td>Total Platelet units @ 24 hours</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
<td>0.801</td>
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<td>0.155</td>
</tr>
<tr>
<td>Plasma deficit @ 24 hours</td>
<td>2 (0-3)</td>
<td>1 (1-3)</td>
<td>0.195</td>
</tr>
<tr>
<td>Total Platelet units @ 24 hours</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
<td>0.801</td>
</tr>
</tbody>
</table>
## Group A Plasma Transfusion Results

<table>
<thead>
<tr>
<th>Product</th>
<th>ABO Incompatible N = 35</th>
<th>ABO compatible N = 219</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency release plasma (units)</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>0.345</td>
</tr>
<tr>
<td>Total Incompatible Units</td>
<td>3 (2-4)</td>
<td>0 (0-0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total compatible units @ 24 hours</td>
<td>2 (0-6)</td>
<td>3 (2-6)</td>
<td>0.439</td>
</tr>
<tr>
<td>Total plasma @ 24 hours (units)</td>
<td>6 (3-10)</td>
<td>4 (2-7)</td>
<td>0.444</td>
</tr>
<tr>
<td>Total RBC @ 24 hours (units)</td>
<td>5 (0-12)</td>
<td>4 (0-8)</td>
<td>0.472</td>
</tr>
<tr>
<td>Plasma:RBC @ 24 hours</td>
<td>1.3:1</td>
<td>1.1:1</td>
<td>0.155</td>
</tr>
<tr>
<td>Plasma deficit @ 24 hours</td>
<td>2 (0-3)</td>
<td>1 (0-3)</td>
<td>0.195</td>
</tr>
<tr>
<td>Total Platelet units @ 24 hours</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
<td>0.801</td>
</tr>
</tbody>
</table>
ABO Incompatible Units Transfused

Overall Complication Rate

- 0% N=219
- 25% N=15
- 50% N=13
- 100% N=7

OR 2.4 (0.5-11.0)

OR 1.1 (0.4-3.5)

OR 1.2 (0.4-3.4)

- 32% 0
- 40% 1-2
- 39% 3-4
- 57% 5+

N=219
N=15
N=13
N=7

ABO Incompatible Units Transfused
Group A Plasma Transfusion
Massive Transfusion Results

- 59 patients
  - 12 incompatible plasma (20%)
  - 47 compatible plasma (80%)
- Mortality 8% vs. 40%, p=0.044
- 97.6% reduction in AB plasma use
Group A Plasma Transfusion Discussion

- Emergency plasma use is increasing
- Limited access
- “New” universal donor is needed
Group A Plasma Transfusion Discussion

- Group A plasma has equivalent outcomes to group AB
  - Incompatible transfusions occurred
  - No hemolytic reactions
  - Similar mortality
  - Similar immunogenic complications
Group A Plasma Transfusion
Limitations

- Small comparison group
- Type II error potential
  - Post-hoc analysis
    - All patients at risk
    - Guessed correctly 86%
Group A Plasma Transfusion

Conclusion

- Emergency group A plasma
- Viable alternative to Group AB
  - More common
  - Feasible
  - Safe
- May allow reticent blood banks to incorporate MTPs
Group A Plasma Transfusion

“'I'M SELLING BLOOD TO FUND A PLASMA-TV.'"

Questions?
Any adult injured trauma patient with \( \geq 2 \) of the following plus or active hemorrhage or traumatic brain injury:13, 14, 15

1) Single reading of systolic blood pressure \( \leq 90 \) mm Hg
2) Single reading of heart rate \( \geq 120 \)
3) Penetrating mechanism (i.e. stabbing, gunshot)
4) Positive FAST
5) Point of care lactate \( \geq 5.0 \) mg/dL
6) Point of care INR \( \geq 1.5 \)
7) Warfarin use

**Figure 1.** Indications for pre-hospital plasma transfusion

FAST = Focused Assessment with Ultrasound in Trauma
## Group A Plasma Transfusion

### Results

<table>
<thead>
<tr>
<th></th>
<th>High Plasma:RBC N=31</th>
<th>Low Plasma:RBC N=17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator days</td>
<td>6 (2-13)</td>
<td>7 (5-10)</td>
<td>0.603</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>6 (2-12)</td>
<td>6 (2-13)</td>
<td>0.386</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>15 (2-31)</td>
<td>15 (4-21)</td>
<td>0.363</td>
</tr>
<tr>
<td>Complications</td>
<td>54%</td>
<td>65%</td>
<td>0.579</td>
</tr>
<tr>
<td>ALI</td>
<td>6%</td>
<td>0%</td>
<td>0.285</td>
</tr>
<tr>
<td>Possible TRALI</td>
<td>5%</td>
<td>0%</td>
<td>0.544</td>
</tr>
<tr>
<td>ARDS</td>
<td>7%</td>
<td>0%</td>
<td>0.544</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15%</td>
<td>15%</td>
<td>0.969</td>
</tr>
<tr>
<td>DVT</td>
<td>10%</td>
<td>5%</td>
<td>0.598</td>
</tr>
<tr>
<td>PE</td>
<td>13%</td>
<td>0%</td>
<td>0.156</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0%</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0%</td>
<td>0%</td>
<td>n/a</td>
</tr>
<tr>
<td>Mortality</td>
<td>33%</td>
<td>34%</td>
<td>0.898</td>
</tr>
<tr>
<td>ABO Incompatible plasma</td>
<td>21%</td>
<td>20%</td>
<td>0.963</td>
</tr>
</tbody>
</table>
Hemostatic Resuscitation in Our Trauma Center

- Pre-hospital plasma and POC testing
- Early Diagnosis in ED
- 1:1 ratio (thawed plasma to RBC)
  - Plasma-first transfusion sequence
  - ED use of rFVIIa or PCC?
- Frequent TEG and early platelet use
- Minimal crystalloid
- Repeated doses of PCC in OR and ICU as required by TEG
Unpublished Communication

- Holcomb, Cotton et al in Houston have pre-hospital plasma program:
  - Verbal communication last month regarding first 100 patients transfused plasma in pre-hospital setting versus control group
  - Lower 6-hour and hospital mortality
  - Much earlier transfusion of first plasma unit
Why Freeze Dried Plasma?
Why Freeze Dried Plasma?

Remote Damage Control Resuscitation!
Advocates for Prehospital Plasma

- Mayo Clinic
- Memorial Hermann – Houston
- U. S. Special Operations Command
- US Army Special Operations Command
- Army Surgeon General’s DCBI Task Force
- Army Special Missions Unit
- Navy Special Missions Unit
- U.S. Army Institute of Surgical Research
- Committee on TCCC
- DHB Trauma and Injury Subcommittee
- French, German, British militaries
Earlier Thawed Plasma

Placement of thawed plasma in the Emergency Department vs having to request it from the Blood Bank has been done at Memorial Hermann in Houston and has resulted in shorter time to first transfusion (42 min vs 83 min), reduction in subsequent transfusion requirements, and increased 30-day survival (86% vs 75%).

Cotton

ATACCC 2011
Remote Damage Control Resusc

• Austere/rural environment patients
  • Modified transfusion strategy
  • Different than those with scene/pre-hospital time < 30 minutes
  • Limited resources available
  • Lack of plasma availability
  • 40% of the population, 60% of the trauma mortality
• Current treatment options for uncontrolled hemorrhage in this environment are very limited
• >75% of combat fatalities occur in the field
History

• WWII
  • Plasma was resusc fluid of choice
  • 10 million units of freeze dried plasma made in US
  • British used whole blood in North Africa 1943

• Korean War
  • Viral hepatitis transmission
  • Freeze dried plasma program abandoned
Prehospital Plasma for Ground Medics, Corpsmen, PJs

- Liquid plasma not an option for ground troops (or civilian rural hospitals/EMS)
- Dried plasma (freeze-dried or spray-dried) is currently the best option for units not able to utilize liquid plasma
- Dried plasma contain approximately the same levels of clotting proteins as liquid plasma
- French, German, British militaries are using freeze-dried plasma at present
FDA-Approved Dried Plasma Product

- None at present
- HemCon freeze-dried product in Phase I trials
- Entegrion - pooled spray-dried product in development
- Velico – single donor spray-dried plasma system in development
- Arrival of an FDA-approved dried plasma product is not imminent – ETA 2015 or beyond
Lyophilized Plasma Animal Study

• Schreiber, et al studied efficacy of 100% lyophilized plasma in a multi-injury severe hemorrhage model comparing to FFP
  • Less blood loss with LP than FFP
  • No difference in mortality = just as efficacious

• Schreiber, et al studied efficacy of 50% reconstituted volume lyophilized plasma in a multi-injury severe hemorrhage model comparing to 100% LP
  • No difference in vital signs, blood loss or TEG
  • Higher coagulation factor activity/unit volume
<table>
<thead>
<tr>
<th>Factor</th>
<th>Fresh plasma (n = 12)</th>
<th>FFP (n = 16)</th>
<th>100%LP (n = 9)</th>
<th>50%LP (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>196 ± 46</td>
<td>180 ± 48</td>
<td>170 ± 51</td>
<td>248 ± 41*†</td>
</tr>
<tr>
<td>Factor II (IU/L)</td>
<td>46 ± 5</td>
<td>41 ± 7</td>
<td>34 ± 6</td>
<td>51 ± 13*</td>
</tr>
<tr>
<td>Factor V (IU/L)</td>
<td>601 ± 91</td>
<td>594 ± 133</td>
<td>550 ± 121</td>
<td>782 ± 223*†</td>
</tr>
<tr>
<td>Factor VII (IU/L)</td>
<td>164 ± 22</td>
<td>158 ± 43</td>
<td>136 ± 40</td>
<td>232 ± 77*†</td>
</tr>
<tr>
<td>Factor VIII (IU/L)</td>
<td>742 ± 221</td>
<td>607 ± 130</td>
<td>554 ± 149</td>
<td>1024 ± 290*†</td>
</tr>
<tr>
<td>Factor IX (IU/L)</td>
<td>284 ± 47</td>
<td>204 ± 35</td>
<td>181 ± 32</td>
<td>330 ± 79*</td>
</tr>
<tr>
<td>Factor X (IU/L)</td>
<td>134 ± 19</td>
<td>82 ± 82</td>
<td>73 ± 23</td>
<td>138 ± 50*</td>
</tr>
<tr>
<td>Factor XI (IU/L)</td>
<td>117 ± 25</td>
<td>63 ± 16</td>
<td>54 ± 15</td>
<td>136 ± 45*</td>
</tr>
<tr>
<td>Factor XII (IU/L)</td>
<td>1304 ± 326</td>
<td>1271 ± 215</td>
<td>1347 ± 213</td>
<td>2223 ± 385*†</td>
</tr>
</tbody>
</table>

Values presented as mean (SD).
* p < 0.05 compared with FFP.
† p < 0.05 compared with fresh plasma.
FFP = fresh frozen plasma; LP = lyophilized plasma; SD = standard deviation.
• Long history dating to 1949
• Produced in its present form since 1994
• Used only by its military; shelf life 2 years room temperature
• Universal donor and pH buffered; no adverse events in 8 yrs
• Produced from pools of 5 – 10 donors, leukoreduced
• ABO Universal and takes 6 minutes to reconstitute
• Now confident of their Cerus pathogen intercept technology
• $800 per unit; over 1100 uses, no reactions and no infections
• Decrease in FV (25%) and FVIII (20%); no reduction in hemostatic effectiveness (fibrinogen is unchanged and stable)
• Afghanistan use: 93 patients (2/3 in shock), PT decreased by 3.3 sec
• Recommend use in war, civilian rural and mass casualty events
German FDP - LyoPlas

- Each unit of LyoPlas is drawn from only one donor
- Tested for all pertinent bloodborne pathogens; quarantined for 4 months until the donor is re-tested.
- Type specific; shelf life 1.5 years
- Must be reconstituted with buffering solution, since it is alkaline as supplied
- $100 per unit
Spray Dried Plasma (Entegrion)

- Hemostasis and circulating volume may not be the only advantages of plasma
- Vascular endothelial permeability is stabilized
- Spray dried solvent-detergent treated plasma study:
  - FFP and SDP equivalent permeability and WBC binding
  - SDP process does not affect the ability to modulate endothelial function
  - SDP has a stabilizing effect similar to FFP
I am requesting a waiver to the Health Care policy regarding non-Food and Drug Administration approved blood products. The specific product is freeze-dried plasma, currently being fielded and used by German medical units in the existing theaters of operation. I am seeking this waiver as our Special Operations medics are often the sole medical providers in remote and austere locations where SOF frequently operate—many of which are beyond the range of immediate medical evacuation and access to surgical care. Within these environments, German certified freeze-dried plasma would serve as a critical enabler in reconstituting blood in cases of traumatic loss, specifically at the point of injury. Although we are monitoring an American company’s development of freeze-dried plasma, the German product offers an immediately-available, modality-proven, clinically tested, and very low-risk interim capability.
The Honorable Charles Rice
Assistant Secretary of Defense, Health Affairs
1200 Defense Pentagon
Washington, DC 20301-1200

Thank you for your full consideration. This is a real life saver with very low risk.

Sincerely,

Eric T. Olson
Admiral, U.S. Navy
Commander
Army Surgeon General Perspective

“I have reviewed your request to use non-FDA licensed freeze dried plasma in support of special forces operations which occur in austere environments. I fully support your request from a clinical perspective. However, legal and regulatory concerns prevent the acquisition and use of these non-licensed products for the foreseeable future. General Counsel has stated that the only legal option to use these products is under an Investigational New Drug. Unfortunately, neither of the European manufacturers plan to bring their product to the U.S. and seek FDA licensure.” (Schoomaker 2010)
“The consensus of discussants at the USAISR-sponsored symposium on prehospital fluid resuscitation overwhelmingly favored the development of a dried plasma product that could expand and maintain blood volume while providing lost coagulation factors resulting from the traumatic injury.“

Dr. Michael Dubick
USAISR
AMEDD Journal 2011
RECOMMENDATIONS

37. The Board advises the Department to consider taking all necessary steps to expedite the fielding of dried plasma to ground medics, corpsmen, and pararescuemen, as well as to aeromedical evacuation platforms that do not have liquid plasma and PRBCs. These steps include:

f. Discussing other options for the use of FDP that may include an exception to policy (ETP) or waiver to DoDI 6200.02 and 21CFR312 "Investigational New Drug Application" in order to permit the acquisition and OCONUS use of well-proven European-manufactured dried plasma.

38. The above recommendations were unanimously approved.
Lorne - Thanks for sharing this great news! It's remarkable to reflect on how much work went into achieving this milestone - this is a story that needs to be told somewhere down the road. Frank

From: "Blackbourne, Lorne H COL MIL USA MEDCOM AISR
To: "'Frank Butler'
Sent: Wednesday, July 18, 2012 7:42 PM
Subject: Fw: FDP: Historic day!

-----Original Message-----
From: F Bowling
Sent: Wednesday, July 18, 2012 3:20 PM
To: Blackbourne, Lorne H COL MIL USA MEDCOM AISR
Subject: FDP
The FDP made its first trip outside the wire. We’ll let all of you know ASAP if it is used.
Thanks for all of the help. F. Bowling
“Awake, arise or be forever fall’n”

John Milton: *Paradise Lost*, Book I, Line 330

Richard Weiskopf (Transfusion Jan 2013):

“John Milton recognized that important action requires enthusiasm and invigoration to replace complacency. Trauma care specialists and industry are spearheading active research; it is time for the blood banking community to consider that currently provided products and our civilian-based hospital procedures do not suit the needs of all patients and to join the quest.”
Summary

• Trauma patients die from shock
• Our job is to limit preventable trauma death
• Pre-hospital resuscitation with plasma can prevent the trauma induced coagulopathy and limit the risk of death due to hemorrhage
• Making dried plasma available in the rural and pre-hospital/austere environment will save lives
John P. Pryor, KIA Mosul Iraq 25 December 2008


Burns C: TCCC from the Role III. CoTCCC meeting minutes; February 2011

Butler FK: A brief history and current status of fluid resuscitation in Tactical Combat Casualty Care. Accepted for publication in Journal of Trauma.


Butler FK, Hagmann J, and Butler EG. Tactical Combat Casualty Care in Special Operations. Milit Med 161; Supplement; August 1996
Butler FK; Tactical Combat Casualty Care: Update 2009; J Trauma 2010;69:S10-S13

Caravalho J: Army Surgeon General’s Task Force on Complex Dismounted Blast Injuries; Executive Summary; May, 2011

Committee on Tactical Combat Casualty Care (CoTCCC) meeting minutes; November 2010


Deal V: US SOCOM TCCC Issues; CoTCCC meeting minutes; November 2010


Joint Theater Trauma System Clinical Practice Guideline for Damage Control Resuscitation; March 2011


Laint J: ISR Prehospital Trauma Interventions study; CoTCCC meeting minutes; November 2010

Ley EJ, Clond MA, Sprour MK, et al: Emergency department crystalloid resuscitation of 1.5 L or more is associated with increased mortality in elderly and non-elderly trauma patients. J Trauma 2011;70:398-400

Mabry R: OEF MEDEVAC and Enroute Care Director After-Action Report dtd 7 February 2011

McSwain N, Champion HR, Fabian T: State of the Art of Fluid Resuscitation 2010: Prehospital and Immediate Transition to the Emergency Department (ED); accepted for Journal of Trauma

Mitra B, Cameron P, Mori A, Fitzgerald M: Acute coagulopathy and early deaths post major trauma. Injury 2010


Salehpour F, Bazzazi AM, Porhomayon J, Nader NF: Correlation between coagulopathy and outcome in severe head trauma in neurointensive care and trauma units. J Crit Care 2011; In press

Schoomaker EB: OTSG Memorandum for COL Peter Benson, USASOC Surgeon, on Non-FDA Licensed Freeze Dried Plasma. 17 November 2010

U.S. Army Medical Research and Materiel Command Information Paper on Dried Plasma. 6 July 2010


