The Use of Lyophilized Plasma in a Severe Multi-

Martin A. Schreiber, MD FACS
Professor of Surgery
The Oregon Health & Science
Background

- Hemorrhage – leading cause of preventable death after trauma
- Acute coagulopathy of trauma – 25% of trauma patients
- High mortality in massively transfused

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

John B. Holcomb, MD,* Charles E. Wade, PhD,* Joel E. Michalek, PhD,† Gary B. Chisholm, PhD,† Lee Ann Zarzabal, MS,† Martin A. Schreiber, MD,‡ Ernest A. Gonzalez, MD,§ Gregory J. Pomper, MD,¶ Jeremy G. Perkins, MD,‖ Phillip C. Spinella, MD,** Kari L. Williams, RN,* and Myung S. Park, MD*

![Graph showing percent surviving and percent alive over days to death from admission with different patient groupings and significance levels.](image_url)
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., Chitra N. Sambasivan, M.D., John B. Holcomb, M.D.,
Gary Chisholm, Ph.D., Martin A. Schreiber, M.D.*

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

<table>
<thead>
<tr>
<th>Product ratio</th>
<th>Measure</th>
<th>Transfusion ratio in first 6 hours</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>&lt;1:4</td>
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<tr>
<td>FFP:PRBC</td>
<td>6 hour mortality %</td>
<td>37.3*</td>
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<td>In-hospital mortality %</td>
<td>54.9*</td>
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<td></td>
<td>Ventilator free days†</td>
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<td>PLT:PRBC</td>
<td>6 hour mortality %</td>
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<td>43.7</td>
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<td>Ventilator-free days†</td>
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*Significant difference from other two ratios.
**P = non-significant (0.79).
†Massive transfusion patients who survived ≥30 days (n = 277). Fisher exact test.
“The goal in transfusion of the patient with need for massive transfusion is to deliver a ratio of PRBCs to plasma to platelets of 1:1:1”
High ratios problematic

- Plasma must be frozen
- Not immediately available
- Not available in far forward settings
- FFP must be typed
- Risk of infection and TRALI
Objectives

• Evaluate the effect of lyophilization on factor activity
• Compare LP to FFP in a severe multi-system model
• Compare different acids for reconstitution
• Assess the effects of RBC’s on coagulation
Methods

• Whole blood steriley removed from swine
• Plasma component separated
• Lyophilized by HemCon® Medical Technologies, Inc.
• Powdered plasma returned
• Reconstituted prior to transfusion

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Methods

• LP very alkalotic
• Requires addition of acid to reconstitution fluid
• Vitamin C utilized
• Reconstitute to original volume
Residual Activity

Spoerke et al, Arch Surg; 2009;144:829-34.
Residual Activity

Methods: Swine

• Multi – center trial
• OHSU, USAISR, Mass General
• Previously validated model
• 32 Yorkshire crossbred swine
• Anesthetized, mechanically ventilated
• Carotid and jugular catheters placed

• Syverud et al, Resuscitation 1988
• Wladis et al, Shock 2001
• Kiraly et al, J Trauma 2006
• Cho et al, Shock 2008
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Shuja, et al, J Trauma 2008

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Femur fracture

Baseline Resuscitation Phase
Injury Phase
Hemorrhage Phase
Operative Phase
Hemostatic Phase

Femur fracture

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• 60% of estimated blood volume removed

Baseline Resuscitation Phase 
Injury Phase 
Hemorrhage Phase 
Operative Phase 
Hemostatic Phase 

Femur fracture
onsdag 5. september 2012
• 60% of estimated blood volume removed
• Hypothermia, acidosis, coagulopathy induced

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Femur fracture
Controlled hemorrhage

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**60% of estimated blood volume removed**

**Hypothermia, acidosis, coagulopathy induced**

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Baseline Resuscitation Phase
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Hemorrhage Phase
Operative Phase
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Femur fracture
Controlled hemorrhage
Grade V liver injury

Shock
3:1 NS
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Femur fracture

Controlled hemorrhage

Grade V liver injury

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- Volume equal to controlled hemorrhage
- Volume equal to controlled hemorrhage
- Re-warmed to 37°C
- Baseline Resuscitation Phase
- Injury Phase
- Hemorrhage Phase
- Operative Phase

- 4 randomized groups
  - FFP
  - LP
  - FFP : PRBC
  - LP : PRBC

- Volume equal to controlled hemorrhage
- Re-warmed to 37°C
- Labs drawn hourly

- Femur fracture
- Controlled hemorrhage
- Grade V liver injury

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• 4 randomized groups
  – FFP
  – LP
  – FFP : PRBC
  – LP : PRBC

• Volume equal to controlled hemorrhage
• Re-warmed to 37°C
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Baseline Resuscitation Phase

Injury Phase

Hemorrhage Phase

Operative Phase

Hemostatic Phase

Femur fracture

Controlled hemorrhage

Grade V liver injury

1hr 2hr 3hr 4hr

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Blood loss after liver injury
IL-6

![Graph showing IL-6 levels at baseline, 2 hours, and 4 hours with different treatments: FFP, LP, FFP:PRBC, and LP:PRBC.](Image)
Hematocrit

*p<0.001 comparing 1:1 groups to pure plasma groups

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R time

a = FFP greater than FFP:PRBC
b = FFP greater than LP:PRBC
c = LP greater than FFP:PRBC
d = LP greater than LP:PRBC
Activated Clotting

a = FFP:PRBC less than FFP
b = FFP:PRBC less than LP
c = LP:PRBC less than FFP
d = LP:PRBC less than LP

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Mechanisms

• RBC crucial participant in clot – cell membrane, phospholipids
Serum Interleukin-6
8-OH-2'-deoxyguanosine
Discussion

• AA inhibits NFκB activation and ROS

• In vitro studies – decreased IL–6 and TNF–α expression when monocytes incubated with AA prior to LPS stimulation

  • Hartel et al, Cytokine, 2004
  • Bowie et al, J Immunol, 2000
Discussion

• Decreased oxidative DNA damage associated with increased AA levels
  – Rat model of periodontitis
    • AA group had decreased 8-OHdG and IL-1 increased glutathione

Hypertonic LP

- LP insoluble at 20% volume
- Swine did not tolerate 30% and 40% LP infusions
- 20 Swine survived using 50%LP and 100%LP
## Comparison of Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>50%LP (n=8)</th>
<th>100%LP (n=8)</th>
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<tr>
<td>Na (mmol/L)</td>
<td>297 ± 48</td>
<td>171 ± 22</td>
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<td>K (mmol/L)</td>
<td>9.2 ± 3.1</td>
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<td>Cl (mmol/L)</td>
<td>139 ± 30</td>
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*onsdag 5. september 2012*
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## In Vitro Coagulation Factor Analysis

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<th>Fresh Plasma</th>
<th>FFP</th>
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<th>50%LP</th>
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<td>Fibrinogen (mg/dL)</td>
<td>196 ± 46</td>
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<td>Factor II (IU/L)</td>
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Lactate (mmol/L)

Hct (%)

Study Fluid

Femur Fracture

Controlled hemorrhage

50% LP

100% LP

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Lactate (mmol/L)

Hct (%)

p > 0.05

Femur Fracture Controlled hemorrhage

Study Fluid

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Lactate (mmol/L) and Hct (%) changes over time with different study fluids in femur fracture with controlled hemorrhage. The graph shows a significant decrease in Hct (%) with time, indicating fluid resuscitation is necessary. The study was conducted on September 5, 2012.
MAP (mm Hg)

HR (bpm)

p > 0.05

p > 0.20

Baseline  Pre-Saline  Pre-Liver Injury  1 HR  2 HR  3 HR  4 HR

50% LP

100% LP

Femur Fracture Controlled hemorrhage

Study Fluid

onsdag 5. september 2012
MAP (mm Hg)

HR (bpm)

p > 0.05

p > 0.20

Study Fluid

Femur Fracture Controlled hemorrhage

Study Fluid

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Blood Loss

$p = 0.26$  
$(n = 10)$

$p = 0.71$  

$p = 0.82$  
$(n = 10)$

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Future Studies

• Optimize type of reconstitution fluid
  – LR
  – NS
  – Hextend

• Study optimal vitamin C concentration
  – Other anti-oxidants
Observational

- 87 combat casualties
- French Role 3 at Kabul
- 70% Afghani, 30% coalition
- 67% in shock
- 10% mortality

TABLE 1. Transfusion Data Before Administration of FDP

<table>
<thead>
<tr>
<th>Blood Products, Fluids, and Agents Given Before the Use of FDP</th>
<th>Median</th>
<th>Range</th>
<th>Percent of Patients</th>
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<tr>
<td>Red blood cells (units)</td>
<td>3</td>
<td>1–13</td>
<td>32</td>
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<td>Whole blood (units)</td>
<td>4</td>
<td>1–7</td>
<td>5</td>
</tr>
<tr>
<td>Crystalloid (L)</td>
<td>1</td>
<td>0.2–5</td>
<td>56</td>
</tr>
<tr>
<td>Colloid (mL)</td>
<td>500</td>
<td>100–8,000</td>
<td>15</td>
</tr>
<tr>
<td>rFVIIa (mg)</td>
<td>2</td>
<td>1–7</td>
<td>9</td>
</tr>
<tr>
<td>Fibrinogen (g)</td>
<td>1.5</td>
<td>1–3</td>
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Comparison of prothrombin time before and after FDP administration.
Ongoing Status

• LP also being used by Dutch and Germans (All citrated)
• LP approved for use by US Special Forces
• HemCon product
  – Completed phase I safety trials
  – Entering phase II in cirrhotics and coumadin reversal
Back to the Future
Acknowledgements

• HemCon Medical Technologies, Inc.
  – Lisa Buckley MPH

• USAISR
  – Jill Sondeen PhD
  – John Holcomb MD

• US Army Medical Research Acquisition Activity Award Number W81XWH-04-1-0104