EE Moore
Denver Health / University of Colorado Denver

Disclosure: Haemonetics, Instrumentation Laboratory, Stago, Prytime & Humacyte
Research Support / Haemonetics Shared IP
Co-founder ThromboTherapeutics Inc
NIH P50 / RM1 / T32 / UMI & DOD Grants

National Heart, Lung, and Blood Institute
Bleeding is Most Common Preventable Cause of Death: Is Early Plasma the Solution?

**US Military: Potentially Survivable**

*Iraq Oct 2001 - Nov 2004*

- Hemorrhage: 79%
- MOF: 6%
- CNS: 4%
- Airway: 12%

**FFP: RBC Ratio / 24 Hr – Military Experience**

- High: 1:1.4 (19% mortality)
- Medium: 1:2.5 (34% mortality)
- Low: 1:8 (65% mortality)

**Plasma: RBC Ratio Groups**

* Borgman, Holcomb et al, J Trauma 2007*
Plasma is an Effective Multifunctional Colloid

- Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock.
  Kozar et al. Anesth Analg 2011

- Fresh frozen plasma lessens pulmonary endothelial inflammation and hyperpermeability after hemorrhagic shock and is associated with loss of syndecan 1.
  Peng et al. 2013

- Plasma is the physiologic buffer of tissue plasminogen activator-mediated fibrinolysis: rationale for plasma-first resuscitation after life-threatening hemorrhage.
  Moore et al. JACS 2015

- Plasma-Mediated Gut Protection After Hemorrhagic Shock is Lessened in Syndecan-1/-/- MICE.
  Ban et al. Shock 2015

- Plasma First Resuscitation Reduces Lactate Acidosis, Enhances Redox Homeostasis, Amino Acid and Purine Catabolism in a Rat Model of Profound Hemorrhagic Shock.
  D'Alessandro et al. Shock 2016
Harmonized Data Collection

»The US DoD and the National Heart Lung and Blood Institute (NHLBI) worked collaboratively on these DoD-funded studies under an interagency strategic plan.

» (Pusateri et al)

»The agreed collaboration included the requirement for the studies to be harmonized in terms of design and data collection, and for samples and data from the studies to be shared.
## COMBAT Research Study

<table>
<thead>
<tr>
<th>Control Arm</th>
<th>Experimental Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normal Saline</td>
<td>1. Plasma Transfusion</td>
</tr>
<tr>
<td>2. RBC Transfusion</td>
<td>2. RBC Transfusion</td>
</tr>
</tbody>
</table>

**X** & **&**
Trial Design: Prehospital

Severely injured trauma patients with life-threatening bleeding
SBP < 70 mmHg or SBP < 90 with HR > 108 / min (ROC Study Group)
Estimated 31% mortality in control group

50% Standard Group
50% Experimental Group: Receive Plasma first
Study Objectives

Determine if “plasma first”:

- **Attenuates trauma-induced coagulopathy**
- Decreases blood product use
- **Improves metabolic recover**
- Decreases ARDS, MOF, death

FDA ... 30 day Mortality
PAMPPer Trial

P: Prehospital
A: Air
M: Medical
P: Plasma

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812
JULY 26, 2018
VOL. 379 NO. 4
Study Population

- **Male** (73%)
- **Blunt mechanism** (82%)
- Median **Injury Severity Score** of 22

- **Prehospital intubation** (51%)
- **Prehospital red blood cell transfusion** (35%)

- Surgeons performed urgent operative procedures on 58%
Results

At 30-days ... 89 (34.1%) deaths in the standard care group and 53 (24.0%) deaths in the plasma group.

Accounting for intra-cluster variation.

23.2% vs. 33.0%

95%CI -18.6, -1.0; p=0.029
30-Day Mortality

Log-rank chi-square 5.70, p=0.02

Survival

Number at risk
Standard Care 271 194 181 179 173 172 172
Plasma 230 183 172 170 169 168 168

Hours
Prospective randomized study of fresh frozen plasma versus crystalloid as initial prehospital fluid resuscitation

Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial

Hunter B Moore MD, Ernest E Moore Prof, Michael P Chapman MD, Kevin McVaney MD, Gary Bryskiewicz, Robert Blechar, Theresa Chin MD, Clay Cothren Burlow MD, Fredric Pieracci MD, F Bernadette West MD, Courtney D Fleming, Arsen Ghasabayan MPH, James Chandler, Christopher C Silliman Prof, Anirban Banerjee Prof and Angela Sauaia Prof

COMBAT Study Design

Type AB

No Antibodies

( No Pregnancy / Transfusions )

4%  →  1% of Population

Limited Resource
COMBAT : FP24 Thawing

Plasma Storage

Paramedic Division Freezers - 30° C
Ambulance Coolers - 18° C

Water Bath (Plasmatherm)
Thaw < 3.5 minutes
Mobile Ambulance Plasma Delivery System

A: Shore power connection, 110 VAC, 20 A, ignition ejector safety and cord reel to GFCI wall receptacle ($1500)
B: Combination 2000 W, 110 VAC power inverter and 100 A, 14.6 VDC battery charger ($1200)
C: 300 Amp-Hour, 12 VDC lithium ion battery with onboard controller ($3000)
D: Plasmatherm Dry Water Bath – can run in continuous mode at 37 °C for 36 hours on battery power ($7000)
E: Charging/power inversion system control panel ($300)
F: FFP storage cooler, vacuum insulated and passively cooled with -23 °C phase change material; rated for ≥72 hours at ≤-18 °C ($600)
Denver EMS Skills / Enthusiasm
COMBAT Team

Arsen Ghasabyan  
Jim Chandler  
Raymond Shepherd-Singh  
Courtney Fleming  

In hospital 24/7

Megan Swope  
Josh Ryon  
Stephanie Jarvis  
Sam McGuffin
COMBAT Study

144 patients potentially eligible randomized by paramedic

11 exclusions/withdrawals:
- 2 age < 18 years
- 1 transferred to another facility
- 7 no consent
- 0 ineligible vitals
- 1 no trauma

69 patients randomized to Control (saline)

60 included patients received Control (saline)

2 patients mistakenly received Saline

As-treated analysis

175 patients randomized to Plasma

65 included patients received Plasma

8 exclusions/withdrawals:
- 2 age < 18 years
- 0 transferred to another facility
- 2 no consent
- 3 ineligible vitals
- 1 no trauma

Intent-to-treat analysis

April 1, 2014 – Mar 31, 2017
## Effectiveness of Randomization

<table>
<thead>
<tr>
<th>Injury related variables</th>
<th>Control</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>% or Median (IQR)</td>
<td>% or Median (IQR)</td>
<td></td>
</tr>
<tr>
<td><strong>PHYSIOLOGY/SHOCK</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst HR</td>
<td>112 (100-120)</td>
<td>110 (98-120)</td>
</tr>
<tr>
<td><strong>Worst SBP</strong></td>
<td>70 (55-80)</td>
<td>64 (50-80)</td>
</tr>
<tr>
<td><strong>Severe shock (SBP&lt;=70mmHg)</strong></td>
<td>55%</td>
<td>68%</td>
</tr>
<tr>
<td>Worst Temp</td>
<td>36 (35.1-37)</td>
<td>36 (34.8-36.6)</td>
</tr>
<tr>
<td>Worst GCS</td>
<td>14 (8-15)</td>
<td>14 (7-15)</td>
</tr>
<tr>
<td>Hgb</td>
<td>14.2 (13.1-16)</td>
<td>15.1 (13.5-15.7)</td>
</tr>
<tr>
<td>Platelet Count (1000)</td>
<td>273.5 (218-336)</td>
<td>300.5 (250-357)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>278 (250-331)</td>
<td>253 (224-310)</td>
</tr>
</tbody>
</table>
Time from injury to 1\textsuperscript{st} Plasma

**Conclusion:** by design, Plasma group patients received plasma earlier (~ 30 minutes before) than Controls.
# Primary Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>Control</th>
<th>Plasma</th>
<th>P-value</th>
<th>Expected %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=60</strong></td>
<td>N=65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>28-day Mortality</strong></td>
<td>3 (5%)</td>
<td>4 (6%)</td>
<td>0.37</td>
<td>ROC trial (2006-08): 25%</td>
</tr>
<tr>
<td></td>
<td>potentially</td>
<td>potentially</td>
<td></td>
<td>MTP trial (2011-14): 20%</td>
</tr>
<tr>
<td></td>
<td>non-preventable</td>
<td>non-preventable</td>
<td></td>
<td>PROPHET (2010-11): 18%</td>
</tr>
<tr>
<td></td>
<td>3 (5%)</td>
<td>6 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>28-day MOF</strong></td>
<td>1 (2%)</td>
<td>4 (6%)</td>
<td>0.37</td>
<td>Glue Grant: 10%</td>
</tr>
<tr>
<td><strong>Death or MOF (composite)</strong></td>
<td>7 (12%)</td>
<td>14 (21%)</td>
<td>0.14</td>
<td>Glue grant: 16%</td>
</tr>
</tbody>
</table>

**Product-Limit Survival Estimates**

With Number of Subjects at Risk

![Survival Probability vs Survival (hours)](image-url)
## Secondary Endpoints

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control N=60</th>
<th>Plasma N=65</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival INR</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>p-value</td>
</tr>
<tr>
<td>INR &gt; 1.3</td>
<td>1.15 (1.08-1.29)</td>
<td>1.27 (1.11-1.40)</td>
<td>0.10</td>
</tr>
<tr>
<td>BD &gt; 8 mEq/L</td>
<td>52%</td>
<td>55%</td>
<td>0.77</td>
</tr>
<tr>
<td>Lactate &gt; 5 mmol/L</td>
<td>48%</td>
<td>51%</td>
<td>0.77</td>
</tr>
<tr>
<td>Hyperfibrinolysis (&gt;3%)</td>
<td>25%</td>
<td>24%</td>
<td>0.93</td>
</tr>
<tr>
<td>Physiologic (0.9-3%)</td>
<td>45%</td>
<td>44%</td>
<td>0.93</td>
</tr>
<tr>
<td>Shutdown (&lt;0.9%)</td>
<td>29%</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>
COMBAT Conclusions

In a mature urban trauma system with rapid transport to a level I trauma center ....

pre-hospital plasma does not improve outcome
PREHOSPITAL PLASMA IMPROVES SURVIVAL IN TRAUMA PATIENTS WITH HEMORRHAGIC SHOCK WHEN TRANSPORT TIMES ARE LONGER THAN 20 MINUTES

Anthony E. Pusateri, PhD; Ernest E. Moore, MD; Hunter B. Moore, MD, PhD; Tuan D. Le, MD, DrPH; Francis X. Guyette, MD, MPH; Michael P. Chapman, MD; Angela Sauaia, MD, PhD; Arsen Ghasabyan, MPH; James Chandler; Kevin McVaney, MD; Joshua B. Brown, MD; Brian J. Daley, MD; Richard S. Miller, MD; Brian G. Harbrecht, MD; Jeffrey A. Claridge, MD; Herb A. Phelan, MD, MSc; William R. Witham, MD; A. Tyler Putnam, MD; Jason L. Sperry, MD, MPH

**PAMPPer & COMBAT**

- **COMBAT** (N=144)
  - Standard of Care (N=69)
  - Plasma (N=75)

- **PAMPPer** (N=561)
  - Standard of Care (N=309)
  - Plasma (N=352)

Harmonization (N=705)

49 Excluded
- 28 Withdrawal
- 7 Age <18/missing
- 14 Incomplete data

378 Patients received Standard of Care (SOC)
327 Patients received Plasma

329 Patients met inclusion criteria
297 Patients met inclusion criteria

30 Excluded
- 14 Withdrawal
- 6 Age <18/missing
- 10 Incomplete data

Same populations (n=626) included in original two published studies
# Demographics (1/2)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>SC</th>
<th>Plasma</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants, No. (%)</strong></td>
<td>626 (100)</td>
<td>329 (52.6)</td>
<td>297 (47.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Cohort, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMBAT</td>
<td>125 (20.0)</td>
<td>58 (17.6)</td>
<td>67 (22.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>PAMPer</td>
<td>501 (80.0)</td>
<td>271 (82.4)</td>
<td>230 (77.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Male sex, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>467 (74.6)</td>
<td>251 (76.3)</td>
<td>216 (72.7)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td><strong>Median age (IQR), y</strong></td>
<td>42 (27-57)</td>
<td>42 (26-57)</td>
<td>43 (29-56)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Race/Ethnicity, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>White</td>
<td>453 (72.4)</td>
<td>239 (72.6)</td>
<td>214 (72.1)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>69 (11.0)</td>
<td>40 (12.2)</td>
<td>29 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>64 (10.2)</td>
<td>27 (8.2)</td>
<td>37 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Other/ Unknown</td>
<td>40 (6.4)</td>
<td>23 (7.0)</td>
<td>17 (5.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Mechanism of injury, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>Fall</td>
<td>38 (6.1)</td>
<td>23 (7.0)</td>
<td>15 (5.1)</td>
<td></td>
</tr>
<tr>
<td>MVC (Motorcyclist/cyclist and occupant)</td>
<td>338 (54.0)</td>
<td>185 (56.2)</td>
<td>153 (51.2)</td>
<td></td>
</tr>
<tr>
<td>MVC (Pedestrian or struck by or against)</td>
<td>57 (9.1)</td>
<td>29 (8.8)</td>
<td>28 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Firearm</td>
<td>77 (12.3)</td>
<td>35 (10.6)</td>
<td>42 (14.1)</td>
<td></td>
</tr>
<tr>
<td>Stab wound</td>
<td>69 (11.0)</td>
<td>32 (9.7)</td>
<td>37 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>47 (7.5)</td>
<td>25 (7.6)</td>
<td>22 (7.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of injury, No. (%) (10 pts count for both)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Blunt</td>
<td>475 (74.7)</td>
<td>257 (78.1)</td>
<td>218 (73.4)</td>
<td></td>
</tr>
<tr>
<td>Penetrating</td>
<td>161 (25.3)</td>
<td>77 (23.4)</td>
<td>84 (28.3)</td>
<td></td>
</tr>
</tbody>
</table>
Median prehospital transport time was longer in the PAMPPer study compared to COMBAT, 41 minutes vs. 18 minutes; $P<.001$, but there was overlap between the two studies.
Prehospital Plasma Reduced Mortality

Plasma vs Saline Control

**Mortality**

<table>
<thead>
<tr>
<th></th>
<th>SC</th>
<th>Plasma</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 d</td>
<td>94 (28.6)</td>
<td>61 (20.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>24 h</td>
<td>67 (20.4)</td>
<td>40 (13.5)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Log-rank $P=0.02$
HR (95% CI): 0.65 (0.47-0.90); $P=0.01$
Conclusion:

- Prehospital Plasma Improves Survival with Transport Time > 20 min

- Impact of Prehospital Blood Products Depends on the Environment
Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock


Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial


Prof and Angela Saura, Prof