Published in final edited form as:

Prehosp Emerg Care. 2015 ; 19(3): 343–350. doi:10.3109/10903127.2014.995851.

Taking the Blood Bank to the Field: The Design and Rationale of the Prehospital Air Medical Plasma (PAMPer) Trial

Joshua B. Brown, MD, Francis X. Guyette, MD, MPH, Matthew D. Neal, MD, Jeffrey A. Claridge, MD, Brian J. Daley, MD, Brian G. Harbrecht, MD, Richard S. Miller, MD, Herb A. Phelan, MD, Peter W. Adams, BS, Barbara J. Early, BSN, Andrew B. Peitzman, MD, Timothy R. Billiar, MD, and Jason L. Sperry, MD, MPH

Division of General Surgery and Trauma, Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania (JBB, MDN, PWA, BJE, ABP, TRB, JLS), Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (FXG), Department of Surgery, MetroHealth Medical Center Campus, University Hospitals Case Medical Center, Cleveland, Ohio (JAC), Department of Surgery, University of Tennessee Medical Center, Knoxville, Tennessee (BJD), Department of Surgery University of Louisville School of Medicine, Louisville, Kentucky (BGH), Department of Surgery, Vanderbilt Medical Center, Nashville, Tennessee (RSM), and Department of Surgery, UT Southwestern Medical Center, Dallas, Texas (HAP)

Abstract

Hemorrhage and trauma induced coagulopathy remain major drivers of early preventable mortality in military and civilian trauma. Interest in the use of prehospital plasma in hemorrhaging patients as a primary resuscitation agent has grown recently. Trauma center-based damage control resuscitation using early and aggressive plasma transfusion has consistently demonstrated improved outcomes in hemorrhaging patients. Additionally, plasma has been shown to have several favorable immunomodulatory effects. Preliminary evidence with prehospital plasma transfusion has demonstrated feasibility and improved short-term outcomes. Applying state-of-the-art resuscitation strategies to the civilian prehospital arena is compelling. We describe here the rationale, design, and challenges of the Prehospital Air Medical Plasma (PAMPer) trial. The primary objective is to determine the effect of prehospital plasma transfusion during air medical transport on 30-day mortality in patients at risk for traumatic hemorrhage. This study is a multicenter cluster randomized clinical trial. The trial will enroll trauma patients with profound hypotension (SBP < 70 mmHg) or hypotension (SBP 71–90 mmHg) and tachycardia (HR > 108 bpm) from six level I trauma center air medical transport programs. The trial will also explore the effects of prehospital plasma transfusion on the coagulation and inflammatory response following injury. The trial will be conducted under exception for informed consent for emergency research with an investigational new drug approval from the U.S. Food and Drug Administration utilizing a multipronged community consultation process. It is one of three ongoing Department of Defense-funded trials aimed at expanding our understanding of the optimal therapeutic approaches to coagulopathy in the hemorrhaging trauma patient.

Address correspondence to Jason L. Sperry, MD, MPH, Division of General Surgery and Trauma, Department of Surgery, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213, USA. sperryjl@upmc.edu.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Keywords

trauma; prehospital; plasma; randomized; clinical trial; helicopter

Introduction

Hemorrhage and coagulopathy remain major drivers of preventable early death following injury.¹⁻⁴ Recent studies focus on early resuscitation to reduce this burden.⁵⁻¹³ With the increasing recognition that trauma-induced coagulopathy (TIC) is an early phenomenon with a significant deleterious impact on outcomes, focus has shifted to directly addressing this entity.¹⁴ High ratio of plasma to red blood cell (RBC) transfusion is associated with improved outcomes in both military and civilian settings.^{5,7,12,15,16} Given the encouraging results from the military and trauma center resuscitation strategies, applying the lessons learned to the civilian prehospital setting is appealing.

To this end, the U.S. Department of Defense (DoD) issued the Prehospital Use of Plasma for Traumatic Hemorrhage program announcement, seeking to fund three awards to study the use of plasma for traumatic hemorrhage in the prehospital environment.¹⁷ While the use of early plasma has been incorporated into U.S. military damage control resuscitation guidelines as well as many civilian trauma centers, uncertainty remains about the effectiveness of plasma in the pre-hospital setting.¹⁸ The Prehospital Air Medical Plasma (PAMPer) trial seeks to address this question.

Trauma-induced Coagulopathy

As the subject of intense recent study, our understanding of TIC has evolved significantly.^{2,19-21} Evidence suggests that 25% of severely injured patients are coagulopathic at admission, independent of hemodilution.^{22,23} Further evidence demonstrates coagulopathy develops within minutes of injury. Patients that develop TIC consistently have worse outcomes, with documented increases in morbidity and mortality.^{2,19,24,25}

Hypoperfusion in trauma and hemorrhage results in excessive activation of protein C, which leads to rapid depletion of multiple hemostatic factors and hyperfibrinolysis.^{26,27} Hyperfibrinolysis is a strong predictor of massive transfusion of mortality.^{23,28} Hyperfibrinolysis also has emerged as a promising therapeutic target, based on decreased mortality in patients receiving anti-fibrinolytics in the CRASH-II trial.²⁹ Our group is also leading a trial to examine the effects of prehospital administration of tranexamic acid in trauma patients.³⁰ Finally, the identification of early platelet dysfunction is a key new area of investigation in TIC research. Platelets play a key role not only in the hemostatic response following injury but also as inflammatory sentinels, serving to activate other immune cell types at the site of injury.³¹⁻³³

Thus, TIC involves a complex cascade of events related to direct tissue injury, hypoperfusion, and inflammation that results in systemic activation of protein C,

hyperfibrinolysis, endothelial and platelet dysfunction, complement activation, and release of inflammatory mediators.^{34–39}

Rationale for Plasma in Traumatic Shock

Analysis of U.S. combat casualties reveals that non-compressible hemorrhage underlies the majority of potentially preventable mortality.⁴⁰ The military responded by devising a resuscitation strategy to replace blood components in a fashion that attempts to reconstitute whole blood. Beginning with the landmark paper by Borgman and colleagues, several retrospective studies in military and civilian populations demonstrate increasing ratios of plasma and platelets to RBCs are associated with improved outcomes.^{5,7,12,16} This has been confirmed in the prospective PROMMTT cohort study, where increased ratios of plasma to RBCs are associated with increased survival over the first 24 hours.⁴¹ Based on these studies, most trauma centers in the United States aim to provide plasma to RBC ratios between 1:1 and 1:2.

Plasma has garnered significant interest recently for use in prehospital resuscitation. Prehospital plasma transfusion replaces critical coagulation factors deficiencies at the point of injury, which can occur as early as 15 minutes from injury.^{40,42,43} Plasma also represents an ideal volume expander, which remains in the intravascular space. Plasma contains several immunologically active and potentially cytoprotective proteins.⁴⁴ Further, plasma prevents endothelial glycocalyx degradation and reduces endothelial permeability leading to an improved inflammatory response to injury compared to conventional isotonic crystalloids.^{40,42} Early experience with prehospital plasma resuscitation is favorable, demonstrating feasibility and improvement in short-term outcomes such as transfusion requirements and TIC parameters.^{45–47}

Design of the PAMPer Trial

In response to the DoD request for proposals for trials to study the effectiveness of prehospital plasma transfusion in traumatic shock, we designed the PAMPer trial as a multicenter randomized clinical trial.⁴⁸ The primary objective of this trial is to determine the effect of transfusion of 2 units of AB plasma during prehospital air medical transport on 30-day mortality in trauma patients with hemorrhagic shock as compared to standard air medical care. We hypothesize that prehospital plasma transfusion will reduce mortality as well as reduce in-hospital transfusion requirements and improve measures of coagulopathy. The specific aims for the PAMPer trial are included in Table 1.

PAMPer is designed as a multicenter prospective open-label cluster randomized trial. Participating sites include the University of Pittsburgh (coordinating site), Case Western University, University of Louisville, University of Texas Southwestern, University of Tennessee, and Vanderbilt University. All sites are large academic level I trauma centers with active air medical helicopter transport programs.

Eligible subjects include blunt or penetrating trauma patients undergoing air medical transport to one of the participating centers with 1) systolic blood pressure (SBP) < 70 mmHg, or 2) SBP 71–90 mmHg with heart rate (HR) > 108 bpm (SBP and HR criteria need

not be simultaneous). Vital sign inclusion criteria are met if documented at the scene, any time during transport, or at an outside referring facility while awaiting transport. We selected these inclusion criteria to identify patients at highest risk for hemorrhagic shock and thus the greatest chance of benefit from the intervention. Exclusion criteria include age <18 or >90 years old, inability to obtain intravenous or interosseous access, isolated fall from standing mechanisms, radiographically documented cervical spinal cord injury with motor deficit, prisoner, pregnancy, cardiac arrest >5 minutes without return of vital signs, penetrating cranial injury, traumatic brain injury with brain matter exposed, isolated drowning or hanging victims, isolated burn injury with >20% estimated total body surface area, referral from facility for an in-patient, or wearing an opt-out bracelet (see below).

The intervention arm of the trial includes provision of standard air medical care plus two units of AB thawed plasma between 0 and 5 days old. Plasma will be provided to air medical bases participating in the trial by each center's blood bank and will be stored at the air base and on the helicopter according to established standards. The respective blood banks will regularly exchange any unused plasma to allow use of plasma by the blood bank in-hospital while ensuring the air bases remain stocked with plasma for the study.

Given the challenges in providing and maintaining plasma in the prehospital environment, and the inability to blind blood product transfusion, a single-stage cluster randomization scheme was utilized. Between two and six air medical bases at each participating center will be block randomized to the intervention or control arm for 1-month periods. Block sizes will vary randomly over the entire trial enrollment period; the randomization scheme was generated by a computer random number generator. Thus, each participating air base will be the unit of randomization to either a plasma (intervention) month or control month over the study duration. Due to the nature of the intervention, blinding will not be performed for patients, prehospital providers, trauma center staff, or enrolling research staff as to the air base trial arm assignment or treatment received by individual subjects in the study. Separate outcome assessors will not be informed of the study intervention received and will be blinded where possible.

Subjects who meet inclusion and exclusion criteria and are transported by a helicopter assigned to a plasma intervention month will have the initiation of 2 units of AB thawed plasma transfused through an intravenous or interosseous line (Figure 1). In the event that the plasma transfusion is complete prior to arrival at the participating trauma center, a goal-directed resuscitation protocol will be followed in addition to standard air medical care.⁶ Subjects with persistent hypotension (SBP < 90 mmHg) after plasma transfusion will receive either a 500-mL crystalloid bolus or RBC transfusion if the capability exists under the air medical provider's existing protocols. When hypotension is resolved or absent, crystalloid infusion to maintain intravenous line patency or heparin-saline lock will be provided only. In the event the plasma transfusion is not completed prior to arrival at the participating center, the transfusion of a total 2 units of plasma will be completed in the trauma resuscitation area, with further resuscitation at the discretion of the attending trauma surgeon.

Subjects who meet inclusion and exclusion criteria and are transported by a helicopter assigned to a control month will undergo standard air medical care with goal-directed resuscitation described above. Standard air medical care will be that under each air medical providers' existing operating procedures. Three air medical providers included in the trial carry and administer up to 2 units of O-negative RBCs for patients with persistent hypotension following 1–2 L of crystalloid or clinical evidence of ongoing hemorrhage. A sham plasma bag will be placed with each control patient by the air medical providers to maintain focus on the study and minimize potential hospital provider bias. The goal was to generally reduce treatment bias by hospital-based treatment team with the appearance of an empty plasma bag to casual observation; however, if questions arise regarding complications potentially related to blood product administration that require immediate attention, careful inspection will allow determination by the treating providers whether the patients received the plasma intervention or not.

Upon arrival at the participating site, 24-hour available research staff will enroll subjects through a web-based secure program built for the trial. No further study intervention will be performed outside of completing transfusion of the 2 units of AB plasma if not completed en route. The participating sites will continue care of the subjects according to local protocols and standards of care. All sites have damage control resuscitation protocols, including aggressive blood product administration based on best practices established in the literature, which should reduce significant variation in early care.

To address the aims of the study, research staff will collect blood for laboratory analysis and outcome data at several time points. Upon arrival, blood will be drawn for laboratory analysis. Blood will also be collected at 24 and 72 hours. Laboratory analysis includes rapid thromboelastography (TEG), conventional coagulation parameters (prothrombin time, partial thromboplastin time, international normalized ratio), base deficit, lactate, complete blood count, and D-dimer. As part of the investigation into the inflammatory response, serum IL-6, thrombomodulin, and protein C-levels will be determined using standard immunoassay techniques. Mortality outcomes will be collected at 24 hours, 30 days, and in-hospital. Resuscitation requirements of packed RBCs, plasma, platelets, and crystalloid will be collected at 3, 6, 12, 18, and 24 hours. Specific adverse events to be collected in-hospital include multiple organ failure (MOF), nosocomial infection (NI), acute lung injury (ALI), and transfusion acute lung injury (TRALI).

Sample size was determined using the primary outcome of 30-day mortality. We estimated a 22% baseline mortality based on mortality for patients requiring 4 units of blood transfusion in the first 6 hours from injury in the Inflammation and the Host Response to Injury study conducted at eight large academic level I trauma centers in the United States, which included two participating sites for this trial.⁴⁹ We sought to detect a 14% absolute reduction in 30-day mortality again based on mortality in subjects receiving high plasma to RBC transfusion in the Inflammation and the Host Response to Injury study. Using a two-sided alpha of 0.05 and power of 88%, 144 subjects are required per arm. This sample size was corrected by a factor of 1.75 to account for the clustered randomization design and 5% missing outcome data for a final sample size of 265 subjects per arm with 530 subjects total. Based on the expected volume of eligible patients across the participating sites, recruitment

will occur over a 4-year period to achieve our sample size. All analyses will be conducted as intention to treat and site stratification will be accounted for in statistical tests. Generalized estimating equations regression will be used to adjust for clustering as well as prehospital transport time and prehospital RBC transfusion in outcome analysis. Several predefined exploratory subgroup analyses are planned in subjects based on mechanism of injury, requirement for massive transfusion, and preexisting coagulopathies.

This trial will enroll subjects under exception from informed consent for emergency research as outlined under U.S. Federal regulation 21 CFR 50.24.⁵⁰ Under this regulation, any study that will enroll under an exception from informed consent must meet the conditions in Table 2.⁵¹ For studies pursuing an exception from informed consent for emergency research, the institutional review board (IRB) must determine whether the proposed intervention and study falls under the regulation of the FDA. Since our intervention falls within the jurisdiction of the FDA, we are required to obtain an investigational new drug application (IND# 15117). This process is required due to the waiver of consent even though plasma is an FDA-regulated and American Association of Blood Bankers (AABB)-approved therapeutic.

The exception from informed consent for emergency research also requires a community consultation process at each participating site. This process consists of two parts: 1) public notification, and 2) community consultation. For this study, a multipronged approach was utilized and has been completed. The notification process included distribution of information regarding the trial in several mediums. A website was created within the existing acute care research website for the University of Pittsburgh (acutecarereseach.org). Each participating center also developed an informational website for the trial. Bumper ads on Pittsburgh Port Authority buses were designed to direct people to the website. Fliers were distributed throughout area hospital waiting rooms and local community center boards. In-person presentations were conducted for several local-area EMS, fire, and police agencies regarding the study. Additionally, an informational video is available on YouTube (www.youtube.com/watch?v=fWgC1nXwGwE).

The consultation process involves monitoring traffic and hits on the above websites. Additionally, the website allows email communication with the study coordinators either anonymously or with return contact information. A telephone survey was conducted by an independent company with random digit dialing for 500 households in each study region. The survey provides information regarding demographics, social economic status, willingness to be enrolled in the trial, and potential concerns. Periodic sampling of the experience of enrolled subjects and family were recorded.

Finally, opt-out bracelets are available to any community member by phone or by email. The bracelet is to be worn at all times by the individual who prospectively does not wish to be enrolled in the case of severe injury, and air medical providers have been trained to look for these prior to enrolling the patient. For patients who are enrolled, informed consent will be obtained to use the patient's data from the patient or legally authorized representative as soon as feasible after in the intervention, as required for exception from informed consent.

Although this process is demanding, it is necessary to assure ethically responsible and high-quality emergency research trials, while maintaining public trust and confidence.

Potential Pitfalls and Limitation

As with any trial conducted in the course of clinical care, particularly under emergency conditions, several potential pitfalls and limitations may be anticipated. Given the nature of the intervention, blinding of patients and providers is not feasible. This limitation exposes the trial to potential bias and may influence subsequent treatment decisions by providers. We have attempted to mitigate this by blinding outcome assessors as well as selecting primary and secondary outcomes that are objective and robust to bias.

Intervention nonadherence is a potential source of bias. We anticipate the most common nonadherence will be subjects not receiving the intervention when eligible (drop-out), and expect a 3–5% rate. We also expect a small proportion (1% or less) of noneligible subjects receiving the intervention (drop-in). Subjects in these circumstances will be analyzed as intention-to-treat in the assigned treatment group. Further, we anticipate a 3% missing data rate in the primary outcome based on the objective and easily collected nature of mortality. We have adjusted the sample size to account for up to 5% missing data, and have planned sensitivity analyses using multiple imputation. We have designated a 15% rate of missing primary outcome data as unacceptable for analysis and in this case would report the outcome as descriptive.

Finally, the use of a cluster design significantly inflates the necessary sample size, and feasibility of adequate enrollment requires careful consideration. In the event that 30-day mortality is not significantly reduced by the intervention, we strongly anticipate other significant and clinically relevant advantages will be seen in the plasma arm when analyzing secondary outcomes.

Summary and Future Directions

The aims of this trial have implications for the care of both civilian and military trauma patients, and allow evidence-based decisions regarding the incorporation of plasma into prehospital resuscitation protocols. Furthermore, this trial will lend insight into the inflammatory response after injury and resuscitation. This trial is one of three awards funded by the DoD to investigate prehospital plasma transfusion in traumatic shock. The Denver group (PI: Gene Moore, MD) has undertaken the Control of Major Bleeding after Trauma (COMBAT) trial with ground ambulance plasma administration, looking at the effect on TIC, transfusion requirements, metabolic recovery, organ failure, and mortality.⁵² The Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH) trial through Virginia Commonwealth University (PI: Bruce Spiess, MD) will also examine the impact of using thawed prehospital plasma on mortality and coagulopathy.⁵³

Under the auspices and collaboration of the Department of Defense and the National Heart Lung and Blood Institute (NHLBI), a Transagency Collaboration for Trauma Induced Coagulopathy (TACTIC) consortium was initiated and funded, which is now beginning the difficult task of deciphering the mechanisms and driving factors that promote TIC following

injury. Most of the inclusion criteria, safety events, laboratory analysis, and outcomes of the three DoD-funded pre-hospital plasma trials are harmonized to allow pooled analysis of enrolled subjects and promote generalizability and sharing of resources between trial infrastructures. This approach enhances the potential for reaching meaningful conclusion from the data, and should be considered for trials conducted in the future. These efforts will contribute tremendously to our understanding of the mechanism and optimal therapeutic approaches to coagulopathy in the hemorrhaging trauma patient.

Acknowledgments

This trial is supported by the following grant: Department of Defense W81XWH 12-2-0023.

References

1. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma*. 2006; 60:S3–S11. [PubMed: 16763478]
2. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. *J Trauma*. 2003; 55:39–44. [PubMed: 12855879]
3. Rahbar E, Fox EE, del Junco DJ, Harvin JA, Holcomb JB, Wade CE, Schreiber MA, Rahbar MH, Bulger EM, Phelan HA, Brasel KJ, Alarcon LH, Myers JG, Cohen MJ, Muskat P, Cotton BA. Early resuscitation intensity as a surrogate for bleeding severity and early mortality in the PROMMTT study. *J Trauma Acute Care Surg*. 2013; 75:S16–S23. [PubMed: 23778506]
4. Shackford SR, Mackersie RC, Holbrook TL, Davis JW, Hollingsworth-Fridlund P, Hoyt DB, Wolf PL. The epidemiology of traumatic death: a population-based analysis. *Arch Surg*. 1993; 128:571–5. [PubMed: 8489391]
5. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007; 63:805–13. [PubMed: 18090009]
6. Brown JB, Cohen MJ, Minei JP, Maier RV, West MA, Billiar TR, Peitzman AB, Moore EE, Cuschieri J, Sperry JL. Inflammation, the Host Response to Injury I. Goal-directed resuscitation in the prehospital setting: a propensity-adjusted analysis. *J Trauma Acute Care Surg*. 2013; 74:1207–12. discussion 1212–4. [PubMed: 23609269]
7. Brown JB, Cohen MJ, Minei JP, Maier RV, West MA, Billiar TR, Peitzman AB, Moore EE, Cuschieri J, Sperry JL. Inflammation, the Host Response to Injury I. Debunking the survival bias myth: characterization of mortality during the initial 24 hours for patients requiring massive transfusion. *J Trauma Acute Care Surg*. 2012; 73:358–64. discussion 364. [PubMed: 22846940]
8. Cotton BA, Gunter OL, Isbell J, Au BK, Robertson AM, Morris JA Jr, St Jacques P, Young PP. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma*. 2008; 64:1177–82. discussion 1182–3. [PubMed: 18469638]
9. Kasotakis G, Sideris A, Yang Y, de Moya M, Alam H, King DR, Tompkins R, Velmahos G. Inflammation, Host Response to Injury I. Aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients: an analysis of the Glue Grant database. *J Trauma Acute Care Surg*. 2013; 74:1215–21. discussion 1221–2. [PubMed: 23609270]
10. Moore FA. The use of lactated ringer's in shock resuscitation: the good, the bad and the ugly. *J Trauma*. 2011; 70:S15–S16. [PubMed: 21841560]
11. Schreiber MA. The use of normal saline for resuscitation in trauma. *J Trauma*. 2011; 70:S13–S14. [PubMed: 21841559]
12. Sperry JL, Ochoa JB, Gunn SR, Alarcon LH, Minei JP, Cuschieri J, Rosengart MR, Maier RV, Billiar TR, Peitzman AB, Moore EE. Inflammation the Host Response to Injury I. An FFP:PRBC transfusion ratio 1:1.5 is associated with a lower risk of mortality after massive transfusion. *J Trauma*. 2008; 65:986–93. [PubMed: 19001962]

13. Neal MD, Hoffman MK, Cuschieri J, Minei JP, Maier RV, Harbrecht BG, Billiar TR, Peitzman AB, Moore EE, Cohen MJ, Sperry JL. Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes a long way. *J Trauma Acute Care Surg.* 2012; 72:892–8. [PubMed: 22491601]
14. Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, Cox ED, Gehrke MJ, Beilman GJ, Schreiber M, Flaherty SF, Grathwohl KW, Spinella PC, Perkins JG, Beekley AC, McMullin NR, Park MS, Gonzalez EA, Wade CE, Dubick MA, Schwab CW, Moore FA, Champion HR, Hoyt DB, Hess JR. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma.* 2007; 62:307–10. [PubMed: 17297317]
15. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, Cotton BA, Matijevic N, Muskat P, Myers JG, Phelan HA, White CE, Zhang J, Rahbar MH, Group PS. The prospective, observational, multicenter, major trauma transfusion (PROMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg.* 2013; 148:127–36. [PubMed: 23560283]
16. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, Gonzalez EA, Pomper GJ, Perkins JG, Spinella PC, Williams KL, Park MS. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg.* 2008; 248:447–58. 410.1097/SLA.1090b1013e318185a318189ad. [PubMed: 18791365]
17. Department of Defense Telemedicine and Advanced Technology Research Center. [Accessed: Aug 8, 2014] Prehospital Use of Plasma for Traumatic Hemorrhage Program Announcement W81XWH-11-PUPTH-IIa. Available at: apply07.grants.gov/apply/opportunities/instructions/oppW81XWH-11-PUPTH-IIA-cfda12.420-instructions.pdf
18. Joint Theater Trauma System Clinical Practice Guideline. [Accessed: March 13, 2014] Damage control resuscitation at level IIb/III treatment facilities. Available at: www.usaisr.amedd.army.mil/assets/cpgs/Damage%20Control%20Resuscitation%20-%201%20Feb%202013.pdf
19. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma.* 2003; 54:1127–30. [PubMed: 12813333]
20. Floccard B, Rugeri L, Faure A, Saint Denis M, Boyle EM, Peguet O, Levrat A, Guillaume C, Marcotte G, Vulliez A, Hautin E, David JS, Negrier C, Allaouchiche B. Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury.* 2012; 43:26–32. [PubMed: 21112053]
21. Trentzsch H, Huber-Wagner S, Hildebrand F, Kanz KG, Faist E, Piltz S, Lefering R. TraumaRegistry DGU. Hypothermia for prediction of death in severely injured blunt trauma patients. *Shock.* 2012; 37:131–9. [PubMed: 22249218]
22. Maegele M, Schochl H, Cohen MJ. An update on the coagulopathy of trauma. *Shock.* 2014; 41(Suppl 1):21–5. [PubMed: 24192549]
23. McDaniel LM, Etchill EW, Raval JS, Neal MD. State of the art: massive transfusion. *Transfus Med.* 2014; 24:138–44. [PubMed: 24889805]
24. Brown JB, Cohen MJ, Minei JP, Maier RV, West MA, Billiar TR, Peitzman AB, Moore EE, Cuschieri J, Sperry JL. Inflammation, the Host Response to Injury I. Characterization of acute coagulopathy and sexual dimorphism after injury: females and coagulopathy just do not mix. *J Trauma Acute Care Surg.* 2012; 73:1395–400. [PubMed: 23064602]
25. Niles SE, McLaughlin DF, Perkins JG, Wade CE, Li Y, Spinella PC, Holcomb JB. Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma.* 2008; 64:1459–1463. discussion 1463–55. [PubMed: 18545109]
26. Cardenas JC, Matijevic N, Baer LA, Holcomb JB, Cotton BA, Wade CE. Elevated tissue plasminogen activator and reduced plasminogen activator inhibitor promote hyperfibrinolysis in trauma patients. *Shock.* 2014; 41:514–21. [PubMed: 24667610]
27. Chin TL, Moore EE, Moore HB, Gonzalez E, Chapman MP, Stringham JR, Ramos CR, Banerjee A, Sauaia A. A principal component analysis of postinjury viscoelastic assays: clotting factor depletion versus fibrinolysis. *Surgery.* 2014; 156:570–7. [PubMed: 24962188]
28. Chapman MP, Moore EE, Ramos CR, Ghasabyan A, Harr JN, Chin TL, Stringham JR, Sauaia A, Silliman CC, Banerjee A. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. *J Trauma Acute Care Surg.* 2013; 75:961–7. discussion 967. [PubMed: 24256667]

29. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejia-Mantilla J, Miranda J, Morales C, Olaomi O, Oildashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010; 376:23–32. [PubMed: 20554319]
30. Brown JB, Neal MD, Guyette FX, Peitzman AB, Billiar TR, Zuckerbraun BS, Sperry JL. Design of the Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial: Addressing the knowledge gaps. *Prehosp Emerg Care*. 2015 Jan-Mar;19(1):79–86. [PubMed: 25076119]
31. Kornblith LZ, Kutcher ME, Redick BJ, Calfee CS, Vilardi RF, Cohen MJ. Fibrinogen and platelet contributions to clot formation: implications for trauma resuscitation and thromboprophylaxis. *J Trauma Acute Care Surg*. 2014; 76:255–6. discussion 262–3. [PubMed: 24458031]
32. Kutcher ME, Redick BJ, McCreery RC, Crane IM, Greenberg MD, Cachola LM, Nelson MF, Cohen MJ. Characterization of platelet dysfunction after trauma. *J Trauma Acute Care Surg*. 2012; 73:13–9. [PubMed: 22743367]
33. Twardy DJ, Khoshnevis MR, Yu B, Mastrangelo MA, Hardison EG, Lopez JA. Essential role for platelets in organ injury and inflammation in resuscitated hemorrhagic shock. *Shock*. 2006; 26:386–90. [PubMed: 16980886]
34. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg*. 2007; 245:812–8. [PubMed: 17457176]
35. Burk AM, Martin M, Flierl MA, Rittirsch D, Helm M, Lampl L, Bruckner U, Stahl GL, Blom AM, Perl M, Gebhard F, Huber-Lang M. Early complementopathy after multiple injuries in humans. *Shock*. 2012; 37:348–54. [PubMed: 22258234]
36. Cohen MJ, West M. Acute traumatic coagulopathy: from endogenous acute coagulopathy to systemic acquired coagulopathy and back. *J Trauma*. 2011; 70:S47–S49. [PubMed: 21841573]
37. Ganter MT, Brohi K, Cohen MJ, Shaffer LA, Walsh MC, Stahl GL, Pittet JF. Role of the alternative pathway in the early complement activation following major trauma. *Shock*. 2007; 28:29–34. [PubMed: 17510601]
38. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, Mackway-Jones K, Parr MJ, Rizoli SB, Yukioka T, Hoyt DB, Bouillon B. The coagulopathy of trauma: a review of mechanisms. *J Trauma*. 2008; 65:748–54. [PubMed: 18849786]
39. Maegele M, Schochl H, Cohen MJ. An update on the coagulopathy of trauma. *Shock*. 2014 May; 41(Suppl 1):21–5. [PubMed: 24192549]
40. Moore EE, Chin TL, Chapman MC, Gonzalez E, Moore HB, Silliman CC, Hansen KC, Sauaia A, Banerjee A. Plasma first in the field for postinjury hemorrhagic shock. *Shock*. 2014 May; 41(Suppl 1):35–8. [PubMed: 24317352]
41. Holcomb JB. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study: comparative effectiveness of a time-varying treatment with competing risks. *Arch Surg*. 2012; 148:127–36.
42. Holcomb JB, Pati S. Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective. *Hematol Am Soc Hematol Educ Program*. 2013; 2013:656–9.
43. Lee L, Moore EE, Hansen KC, Silliman CC, Chandler JG, Banerjee A. It's not your grandfather's field plasma. *Surgery*. 2013; 153:857–60. [PubMed: 23122899]
44. Silliman CC, Dzieciatkowska M, Moore EE, Kelher MR, Banerjee A, Liang X, Land KJ, Hansen KC. Proteomic analyses of human plasma: Venus versus Mars. *Transfusion*. 2012; 52:417–24. [PubMed: 21880043]
45. Holcomb JB, Donathan DP, Cotton BA, Del Junco DJ, Brown G, Wenckstern TV, Podbielski JM, Camp EA, Hobbs R, Bai Y, Brito M, Hartwell E, Duke JR, Wade CE. Prehospital transfusion of plasma and red blood cells in trauma patients. *Prehosp Emerg Care*. 2015 Jan-Mar;19(1):1–9. [PubMed: 24932734]

46. Kim BD, Zielinski MD, Jenkins DH, Schiller HJ, Berns KS, Zietlow SP. The effects of prehospital plasma on patients with injury: a prehospital plasma resuscitation. *J Trauma Acute Care Surg*. 2012; 73:S49–S53. [PubMed: 22847094]
47. Zielinski MD, Smoot DL, Stubbs JR, Jenkins DH, Park MS, Zietlow SP. The development and feasibility of a remote damage control resuscitation prehospital plasma transfusion protocol for warfarin reversal for patients with traumatic brain injury. *Transfusion*. 2013; 53(Suppl 1):59S–64S. [PubMed: 23301974]
48. [Accessed: July 13, 2014] Prehospital Air Medical Plasma Trial (PAMPer). Available at: clinicaltrials.gov/show/NCT01818427
49. Maier RV, Bankey P, McKinley B, Freeman B, Harbrecht BG, Johnson JL, Minei JP, Moore EE, Moore F, Nathens AB, Shapiro M, Tompkins RG, West M. Inflammation t, Investigators tHRtI. Inflammation and the Host Response to Injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care: foreward. *J Trauma Acute Care Surg*. 2005; 59:762–3.
50. United States Food and Drug Administration. [Accessed: March 13, 2014] Code of Federal Regulations Title 21: Section 50.24 Eception from informed consent requirements for emergency research. Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24
51. Food and Drug Administration. [Accessed: April 9, 2014] Guidance fo Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research. Available at: www.fda.gov/downloads/regulatoryinformation/guidances/ucm249673.pdf
52. [Accessed: July 21, 2014] Control of Major Bleeding after Trauma Study (COMBAT). Available at: clinicaltrials.gov/show/NCT01838863
53. Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH) Study. [Accessed: July 14, 2014] Available at: www.cctr.vcu.edu/news/feature/plasma.html
54. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. *Shock*. 2009; 31:438–47. [PubMed: 18838942]
55. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American–European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994; 149:818–24. [PubMed: 7509706]
56. Toy P, Popovsky MA, Abraham E, Ambruso DR, Holness LG, Kopko PM, McFarland JG, Nathens AB, Silliman CC, Stroncek D. Transfusion-related acute lung injury: definition and review. *Crit Care Med*. 2005; 33:721–6. [PubMed: 15818095]

Figure 1.
Prehospital Air Medical Plasma (PAMPer) trial intervention schematic.

Table 1
Specific aims of the PAMPer trial

Primary aim	Determine whether prehospital transfusion of 2 units of AB plasma compared to standard air medical care reduces 30-day mortality in trauma patients at risk for hemorrhagic shock
Secondary aim 1	Determine whether prehospital transfusion of 2 units of AB plasma compared to standard air medical care results in lower 24-hour RBC transfusion requirement, incidence of MOF, NI, ALI, and TRALI ^a
Secondary aim 2	Determine whether transfusion of 2 units of AB plasma compared to standard air medical care results in a lower 24-hour plasma, platelet, crystalloid, colloid, and vasopressor requirement
Secondary aim 3	Determine whether transfusion of 2 units of AB plasma compared to standard air medical care results in improved INR, PT/PTT, and TEG measures of coagulopathy ^b
Secondary aim 4	Determine whether transfusion of 2 units of AB plasma compared to standard air medical care modulates the early immune response ^c

^aMOF defined as Denver MOF score >3 ⁵⁴; NI defined by quantitative culture data for pneumonia ($>10^4$ CFU/mL BAL), catheter associated blood stream infections (>15 CFU/segment), and urinary tract infections ($>10^5$ organisms/mL urine); ALI defined as 1992 American-European Consensus Conference definition⁵⁵; TRALI defined as ALI with onset of symptoms within 6 hours of plasma-containing blood products.⁵⁶

^bINR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; TEG, thromboelastography.

^cEarly immune response as represented by IL-6 serum levels, thrombomodulin levels, and protein C levels.

Table 2
Conditions for exception from informed consent for emergency research

<ul style="list-style-type: none">• Life-threatening medical condition present that requires immediate intervention• Existing therapies are unproven or have unsatisfactory outcomes• Scientific study is necessary to determine the proposed intervention's effectiveness and/or safety• Consent cannot be given due to the medical condition• Narrow therapeutic window for intervention that precludes obtaining consent from patient or representative prior to administration• Potential direct benefits to subjects• Cannot prospectively identify potential participants prior to eligibility for enrollment• Study cannot be practicably performed without waiver of consent