Published in final edited form as:

J Trauma Acute Care Surg. 2017 September ; 83(3): 398–405. doi:10.1097/TA.0000000000001581.

PREHOSPITAL PLASMA RESUSCITATION ASSOCIATED WITH IMPROVED NEUROLOGIC OUTCOMES AFTER TRAUMATIC BRAIN INJURY

Matthew C. Hernandez, MD¹, Cornelius A. Thiels, DO², Johnathon M. Aho, MD¹, Elizabeth B. Habermann, PhD², Martin D. Zielinski, MD¹, James A. Stubbs, MD³, Donald H. Jenkins, MD¹, and Scott P. Zietlow, MD¹

¹Department of Surgery, Division of Trauma Critical Care and General Surgery, Mayo Clinic, Rochester MN

²Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester MN

³Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester MN

Abstract

Introduction—Trauma related hypotension and coagulopathy worsen secondary brain injury in patients with traumatic brain injuries (TBI). Early damage control resuscitation with blood products may mitigate hypotension and coagulopathy. Preliminary data suggest resuscitation with plasma in large animals improve neurologic function after TBI; however, data in humans are lacking.

Methods—We retrospectively identified all poly-trauma patients age >15 years with head injuries undergoing prehospital resuscitation with blood products at a single level I trauma center from 01/2002 to 12/2013. Inclusion criteria were prehospital resuscitation with either packed red blood cells (pRBC) or thawed plasma as sole colloid resuscitation. Patients who died in hospital and those using anticoagulants were excluded. Primary outcomes were Glasgow Outcomes Score Extended (GOSE) and Disability Rating Score (DRS) at dismissal and during follow up.

Results—Of 76 patients meeting inclusion criteria 53% (n=40) received pre-hospital pRBC and 47% (n=36) received thawed plasma. Age, gender, injury severity (ISS) or TBI severity, arrival laboratory values, and number of prehospital units were similar (all p>0.05). Patients that received

Corresponding Author: Matthew Hernandez, Division of Trauma Critical Care and General Surgery, Department of Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Phone: 507-284-7467, hernandez.matthew@mayo.edu.

Conflicts of Interest

The authors have no relevant financial disclosures.

This work has not previously or concurrently been submitted for publication. The work was presented as an oral presentation at the AAST 75th Annual Meeting.

Author Contribution

MCH: data retrieval, analysis, interpretation, graphic creation, study design, manuscript writing and editing. CAH: data retrieval, manuscript writing and critical revisions. JMA: manuscript writing and critical revisions. EBH: manuscript writing and critical revisions. DHJ: Manuscript writing, critical revisions, study design and concept of prehospital blood product resuscitation. JAS: Manuscript writing and critical revisions. MDZ: manuscript writing and critical revisions. SPZ: Manuscript writing and critical revisions.

thawed plasma had an improved neurologic outcome compared to those receiving pRBC (median GOSE 7 [7–8] vs 5.5 [3–7], $p<0.001$). Additionally, patients that received thawed plasma had improved functionality compared to pRBC (median DRS 2 [1–3.5] vs 9 [3–13], $p<0.001$). Calculated GOSE and DRS scores during follow up, median 6 [5–7] months, demonstrated increased function in those resuscitated with thawed plasma compared to pRBC by both median GOSE (8 [7–8] vs 6 [6–7] $p<0.001$) and DRS (0 [0–1] vs 4 [2–8] $p<0.001$).

Conclusion—In critically injured trauma patients with TBI, early resuscitation with thawed plasma is associated with improved neurologic and functional outcomes at discharge and during follow up compared to pRBC alone. These preliminary data support the further investigation and use of plasma in the resuscitation of critically injured TBI patients.

Level of evidence—Level V – Retrospective Study

Study type—Retrospective single institution study

Keywords

Traumatic brain injury; GOSE; prehospital; resuscitation; blood product

Background

Traumatic brain injuries (TBI) represent approximately one third of all injury-related deaths in civilian settings (1). Although mortality after TBI has improved (1,2), poor neurologic outcomes continue to result in a significant burden for patients, their families, health systems, and society (3–5). Resuscitation of patients with TBIs is primarily focused on maintenance of hemodynamics to prevent secondary brain injury as hypoxemia and hypotension are independent predictors of worse outcomes(6). Large animal data suggest that the early resuscitation with plasma in combined TBI and hemorrhagic shock models may improve neurologic outcomes(7–10). In order to address these gaps in our TBI resuscitation approach, studies are underway evaluating crystalloid versus blood products in patients with hemorrhagic shock and TBI (11,12). More study is needed regarding the effects of coagulopathy and TBI in patients with multisystem trauma (13).

The goal of prehospital resuscitation in hypotensive TBI patients is to support oxygen delivery and restore cerebral perfusion(6). Previous work demonstrated that early use of packed red blood cells (pRBC) using remote damage control resuscitation techniques were associated with improved outcomes in severely injured trauma patients (14–20). Recent literature in favor of balanced massive transfusion protocols (equal parts pRBCs, plasma, and platelets) led to the use of thawed plasma in prehospital damage control resuscitation at limited centers (14,19,21). However, due to limited data on hypotensive poly-trauma patients with TBI, the current Brain Trauma Foundation guidelines continue to recommend resuscitation with crystalloid or colloid in the prehospital setting (6). These guidelines still recommend maintaining a systolic blood pressure of > 90 mmHg but do not comment on the ideal fluid.

Previous research has suggested that thirty-day survival was significantly improved in poly-trauma TBI patients undergoing massive transfusion with a high fresh frozen plasma (FFP)

to pRBC ratios (22). With improvements in mortality the focus of resuscitation must also consider improving neurologic outcomes given that the debility from long-term neurologic damage can be significant (23). To investigate neurologic outcomes, Halaweish and Alam et al. evaluated differing resuscitation protocols and determined a plasma based resuscitation approach was associated with improved cognitive function and reduced neurologic severity in swine (10).

In an effort to determine whether this benefit in swine translates to humans, we analyzed our experience with prehospital damage control resuscitation practices in hypotensive poly-trauma patients with TBI. Since patients with multisystem trauma and TBI incur significant debility, it was our aim was to determine whether a difference existed in neurologic and functional outcomes in patients receiving either thawed plasma or pRBC in the pre-hospital setting. We hypothesized that in hypotensive poly-trauma patients with TBI not on anticoagulation, remote damage control resuscitation with exclusively thawed plasma would have improved neurologic outcomes at dismissal and during short term follow-up when compared resuscitation with exclusively pRBCs.

Methods

Patient Cohort

After obtaining institutional review board approval, a prospectively maintained database of all trauma patients undergoing prehospital transfusion at a single rural Level I Trauma Center from January 2002 to December 2013 was retrospectively reviewed. All patients aged 15 years or older who presented with a diagnosis of hypotension, TBI, and received either exclusively thawed plasma or exclusively packed red blood cells (pRBC) alone in the prehospital setting were identified and screened against inclusion and exclusion criteria (Figure 1). All patients were transported by critical care rotor wing transport teams.

Institutional Protocol

The remote damage control blood transfusion protocol is initiated when patients meet criteria based on an institutional critical care transport guidelines (Figure 1) and is given to patients with evidence of hemorrhagic shock and hemodynamic instability or when reversal of INR is necessary (14). Our institution began transfusing pRBC in the prehospital setting in 1988 and thawed plasma in February of 2009 (16). Currently, thawed plasma is transfused first and then the units are alternated between pRBC and thawed plasma in patients with hemodynamic instability. Patients were transfused based on our adult prehospital transfusion guideline (14) (Figure 4).

Inclusion Criteria

The presence of multisystem trauma was defined as an Injury Severity Score (ISS) > 9. Patients were identified as having a TBI if they had head AIS ≥ 2. Patients transferred from another hospital were included if transported by rotor wing.

Exclusion Criteria

Patients with a history of anticoagulation or antiplatelet medications were excluded. Patients who died prior to dismissal were also excluded as our study was designed to focus on long-term neurologic outcomes. Patients transported via ground were also excluded given that the ground crews generally do not carry blood products. Lastly, patients who received mixed prehospital transfusions in the prehospital setting (both thawed plasma and pRBC) were excluded in order to evaluate the effect of thawed plasma and pRBC alone. We also excluded patients with a head AIS of 1 and 6 so that TBI was reflected in the degree of head injury.

Primary and Secondary Outcomes

The primary outcomes of Glasgow Outcome Score Extended (GOSE) and Disability Rating Scale (DRS) were calculated at dismissal and during follow up visits. The GOSE categorizes a patient's disability (24) and is measured on a scale from 1–8, with 1 meaning death and 8 describing a high functioning individual. DRS measures generalized functional changes during recovery (25). The DRS is measured on a scale from 1–29 with various intervals correlating with the degree of dysfunction at a given time, therefore a higher score reflects increased dysfunction. Outcomes utilizing GOSE and DRS scores were assessed as follows: categorical values (unfavorable) were assigned for GOSE less than 6 and DRS greater than 7 in order for patients to be considered for decreased functional outcome (26). Favorable outcomes were assigned as a GOSE ≥ 6 and DRS ≤ 7. Scores were retrospectively calculated based on physical medicine and rehabilitation, neurology, and physical/occupational therapist providers and throughout the patients' follow up rehabilitation period. Follow-up analysis included patients with GOSE and DRS assessments between 4 and 8 months following dismissal.

Secondary predictors included duration of stay, type and number of transfused units given in prehospital and in hospital setting, massive transfusion administration, critical administration threshold (CAT) status (27), hospital duration of stay, prehospital transportation duration, scene versus inter-facility transfer, emergency room vital signs, laboratories obtained at admission, trauma center arrival Glasgow Coma Scale (GCS), Injury Severity Score (ISS), radiologic diagnosis of intracranial pathology (multifocal intracranial hemorrhage (MIH), epidural hemorrhage (EDH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), intraparenchymal hemorrhage (IPH), and diffuse axonal injury (DAI)), and head Abbreviated Injury Score (AIS).

Statistical Analyses

Patients who received exclusively thawed plasma were compared to those that received exclusively pRBC in the prehospital environment via our institution's remote damage control resuscitation protocol (14). Summary univariate comparisons were performed. Independent variables were analyzed to determine their associations with improved neurocognitive function with Disability Rating Scale and Glasgow Outcome Score Extended. These variables included patient age, gender, severity of TBI, head AIS, GCS, head injury diagnosis, ISS, laboratory values on arrival to the ED including hemoglobin, INR, lactate, admission blood alcohol level, thromboelastography, emergency room vital signs, the number of units of prehospital blood product given, total volume of prehospital

crystalloid administered. Univariate analysis evaluated the aforementioned variables associations with GOSE and DRS.

Continuous variables were described using means with standard deviations (SD) if normally distributed and medians with inter-quartile ranges (IQR) for non-normally distributed data, and two tailed t-tests or Wilcoxon rank sum tests were performed to compare patient and injury factors between plasma and pRBC groups. Categorical variables were summarized as proportions, and differences were evaluated using chi-square tests or Fisher's exact tests when appropriate.

To confirm that observed differences in outcomes between plasma and pRBC groups were not due to confounding factors that affected the likelihood of a patient to receive one treatment or the other, a propensity score for receiving plasma was developed using age, ISS, and GCS, which were deemed to be most clinically relevant to assigning treatment type. Multivariable logistic regression models assessed the relationship between treatment type and neurologic outcomes after adjusting for the logit transformation of the propensity score. Model results are reported as Odds Ratios (OR) and 95% Confidence Intervals (CI), and model fit was assessed with Area Under the Curve (AUC). All p-values were considered significant at $p < 0.05$. Data were analyzed with JMP (SAS Institute, Inc. Cary NC) and SAS version 9.4 (SAS Institute, Inc. Cary NC). We utilized GraphPad Prism (GraphPad Software, Inc. La Jolla CA) for all visual graphics.

Results

After applying inclusion and exclusion criteria (Figure 2), we identified a total of 76 subjects. Sensitivity analysis was performed comparing in-hospital mortality in the plasma group to those in the pRBC group and no significant difference in mortality rate between transfusion groups plasma (16%) and pRBC (23%, $p = 0.32$). Mean age was 53.6 ± 25 years and 61.8% were male. Overall, the median ISS [IQR] was 24 [17–29], and median head AIS score was 3 [2–5]. No patients experienced transfusion related adverse reactions as identified by transfusion related lung injury, febrile transfusion reactions, hemolytic reactions, anaphylaxis, or transfusion associated circulatory overload.

There was no significant difference in patient age, gender, severity of TBI, head AIS, GCS, head injury diagnosis, ISS, laboratory values on arrival to the ED including hemoglobin, INR, lactate, the number of units of prehospital blood product given, total volume of prehospital crystalloid administered or length of stay (all $p > 0.05$, Table 1). The indications for transfusion were: hypotension ($n = 76$, 100%), and tachycardia ($n = 76$, 100%) as noted in prehospital medical records.

There were no significant difference between the transportation time of each patient between thawed plasma (median 26.5 [18–40]) minutes and pRBC (median 26 [21–40]) minutes. Twenty-five patients (33%) received massive transfusion protocol and 13 (17%) met Critical Administration Threshold for pRBC administration. With regard to inpatient blood product administration, there was no significant difference between the prehospital thawed plasma and pRBC groups, ($p > 0.05$), Figure 3. Among prehospital transfusion groups, there were no

significant differences between inter-facility transfers between (thawed plasma n=12 vs pRBC n=14, p=0.53) as well as scene transfer (n=24 vs n=26, p=0.8).

Neurologic Outcomes

Improved functional neurologic outcomes at dismissal (Figure 4), demonstrated by a higher median [IQR] GOSE, was seen in patients receiving plasma (7 [7–8]) compared to those receiving pRBC (5.5 [3–7], p<0.001). Utilizing median [IQR] DRS scores at dismissal also demonstrated improved outcomes in patients that received thawed plasma (2 [1–3.5]) compared to pRBC (9 [3–13], p<0.001). These improvements in neurologic outcomes as assessed by the GOSE and DRS scores reflect that a prehospital resuscitation with thawed plasma as opposed to pRBCs. Among the 54 patients with neurologic assessments during the follow up period (median 6 [5–7] months, Figure 4), the improvements seen at dismissal persisted in patients resuscitated with thawed plasma compared to pRBCs. The median [IQR] GOSE during follow up demonstrated improved neurocognitive function in those resuscitated with thawed plasma (8 [7–8]) compared to those with pRBC (6 [6–7] p<0.001). Similarly, decreased median [IQR] DRS score (improved function) was demonstrated in the thawed plasma resuscitation group (0 [0–1]) compared the pRBC resuscitation (4 [2–8] p<0.001).

Table 2 highlights the differences of unfavorable and favorable classification of GOSE and DRS scores between prehospital transfusion strategies (thawed plasma versus pRBC). Table 2 also demonstrates these categorical differences by increasing head AIS. Patients with increased unfavorable neurologic and functional outcomes (GOSE <6 or DRS >7) were associated with prehospital pRBC transfusion. After adjusting for propensity score, patients in the plasma resuscitation group were more likely to have a favorable GOSE score (OR 18.0 [95% CI: 3.1–103.8], p=0.001, AUC 0.89 [95% CI: 0.82–0.96]) and favorable DRS score (OR 11.3 [95% CI: 2.6–48.7], p=0.001, AUC 0.86 [95% CI: 0.77–0.96]) at dismissal compared to patients in the pRBC resuscitation group. The very low number of events (n=5 for unfavorable GOSE and n=8 for unfavorable DRS) at follow-up precluded performing similar multivariable analysis on the follow-up neurologic outcome measures.

Review of CT head imaging demonstrated the following findings: multifocal hemorrhage (n=20, 26%), intraparenchymal hemorrhage (n=16, 21%), subarachnoid hemorrhage (n=16, 21%), subdural hemorrhage (n=20, 26%), epidural hemorrhage (n=1, 2%), and diffuse axonal injury (n=3, 4%). Nearly half of all patients had progressive hemorrhagic injury as diagnosed by a board certified radiologist using head CT (n=37, 49%). Six patients required craniectomy and n=18, 24% required intracranial pressure monitoring.

Discussion

Analysis of this highly selected group of trauma patients demonstrated that pre-hospital damage control resuscitation with plasma is associated with improved neurologic outcomes compared to resuscitation with pRBC alone in hypotensive poly-trauma patients with TBI. This is the first retrospective analysis comparing the neurologic functional outcome of patients with multisystem trauma and TBI with either plasma or pRBC alone. Specifically, greater GOSE and lower DRS scores were seen in patients receiving plasma. This suggests

that both neurologic and functional outcomes may be improved with the early use of plasma. These findings support recent large animal studies, (8,10), and highlight the need for further prospective research to ensure optimized neurologic outcomes in trauma patients with TBI.

The current guidelines recommend using isotonic fluids to maintain perfusion; however, supporting data are conflicting (6). Retrospective studies have demonstrated improved survival for poly-trauma TBI patients receiving a high FFP:pRBC resuscitation (18,22). The mechanism behind this survival benefit is likely related to acute traumatic coagulopathy (ATC), which may affect poly-trauma patients with TBI (28,29). For patients with TBI and ATC, the activation of protein C systematically via the endothelia may be a mediator driving hypotension in affected patients (29). ATC is multifactorial state of activated, dynamic, leaky endothelia worsened by hypotension and, potentially, crystalloid resuscitation (30). It is believed that this coagulopathy occurs early after trauma and thus early resuscitation aimed at correcting the coagulopathy may improve outcomes (31,32). In the setting of TBI and hemodynamic instability, high volume crystalloid resuscitation may increase cerebral edema and secondary brain injury (30). Resuscitation with a colloid fluid comprised of coagulation factors and fibrinogen, like plasma, may mitigate the early effects of ATC, and thus potentially prevent secondary neurologic dysfunction in polytrauma patients with a TBI (33).

The preliminary finding that improved neurologic outcomes at patient dismissal are associated with the use of prehospital plasma transfusion is crucial first step towards the identification of an ideal resuscitative fluid in hypotensive poly-trauma patients with TBI. The potential benefit is twofold. First plasma may be used as the initial fluid in damage control resuscitation for hemodynamic instability to provide necessary volume. Replenishing this volume with plasma may be a better adjunct than pRBC and the ideal first step to a balanced and neurocognitive protective resuscitation. Second, the association of improved functional and neurocognitive outcomes via early use of plasma may be an additional indication given the disparate outcomes of severe TBI in poly-trauma patients. While it is unknown what the exact mechanism is due to the complex nature of the fluid, it is increasingly an important adjunct in trauma resuscitation and its incorporation into TBI research may have increased therapeutic potential. Additionally, our data support the theory that the replacement of coagulation factors promotes increased neuroprotective genetic transcription to reduce brain lesion size and swelling, and this mechanism may be associated with the improved neurologic function of this patient cohort (34).

As the prehospital and inpatient care of patients with TBI continue to improve, further research should be given to the study of prehospital blood product administration and type. Evaluation of the ongoing studies will provide an important foundation for transfusion strategies (11–12). These studies may identify or posit additional questions for the determination of the optimal plasma: blood transfusion ratio in patients with hemorrhagic shock and TBI. Future translational directions could also potentially incorporate various drugs with properties to potentially remove neurotoxins or promote stabilization of the blood brain barrier with plasma administration for the optimal prevention of secondary brain injury and improve neurocognitive function. Moreover, the feasibility and the efficacy of lyophilized plasma will need to be addressed as well.

Limitations

The present study has a number of limitations related to the retrospective nature of the study design and highly selected cohort. The highly selective study inclusion and exclusion criteria were used to remove diminishes generalizability but it is necessary for answering our hypothesis. In addition, the exclusion of patients who died prior to dismissal, despite being similar in both groups, may result in survival bias; however, functional outcomes are not applicable to these patients. Our institution has administered blood product in transport beginning in 1988; therefore we were unable to include a control cohort of patients that did not receive any blood products. We elected to exclude patients transfused with a mixed ratio (pRBC:plasma) in the prehospital setting in order to attempt to analyze which fluid, if any, demonstrated an effect on neurocognitive function at dismissal. Additionally, analysis of newer mixes of fluids, like platelet enriched plasma, may have additional benefits in TBI; however, we lack prospective data comparing each type with outcome.

While DRS is a validated scoring system, it can become insensitive at measuring differences of function at the low (more functional) end of the TBI spectrum. Lastly, our limited sample size prevented us from conducting sub-group analyses or utilizing propensity scores. However, these findings suggest that a prospective multi-institutional study to determine the ideal resuscitation fluid in poly-trauma patients with TBI is warranted.

Conclusion

In poly-trauma TBI patients with hemodynamic instability, prehospital fluid resuscitation with plasma was associated with improved neurologic outcomes compared to resuscitation with pRBC alone. Any improvement in neurologic outcomes in TBI is important and warrants further research.

Acknowledgments

Source of Funding: Support provided by the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery (Thiels and Habermann), CTSA grant KL2 TR000136 (Zielinski), and by the National Heart, Lung, and Blood Institute T32 HL105355(Aho).

Support provided by the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery (Thiels and Habermann), CTSA grant KL2 TR000136 (Zielinski), and by the National Heart, Lung, and Blood Institute T32 HL105355 (Aho).

References

1. Coronado VG, Xu L, Basavaraju SV, McGuire LC, Wald MM, Faul MD, Guzman BR, Hemphill JD. Surveillance for traumatic brain injury-related deaths--United States, 1997–2007. *MMWR Surveill Summ.* 2011; 60(5):1–32.
2. Coronado VG, McGuire LC, Sarmiento K, Bell J, Lionbarger MR, Jones CD, Geller AI, Khoury N, Xu L. Trends in Traumatic Brain Injury in the U.S. and the public health response: 1995–2009. *J Safety Res.* 2012; 43(4):299–307. [PubMed: 23127680]
3. Cuthbert JP, Harrison-Felix C, Corrigan JD, Bell JM, Haarbauer-Krupa JK, Miller AC. Unemployment in the United States after traumatic brain injury for working-age individuals: prevalence and associated factors 2 years postinjury. *J Head Trauma Rehabil.* 2015; 30(3):160–74. [PubMed: 25955703]
4. Connor KD, Cuthbert JP, Whyte J, Corrigan JD, Faul M, Harrison-Felix C. Traumatic Brain Injury among Older Adults. *J Neurotrauma.* 2013:2001–13. [PubMed: 23962046]

5. Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. *J Head Trauma Rehabil.* 2003; 21(6):544–8.
6. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. *J Neurotrauma.* 2007; 24(Suppl 1):S7–13. [PubMed: 17511549]
7. Sillesen M, Jin G, Johansson PI, Alam HB. Resuscitation speed affects brain injury in a large animal model of traumatic brain injury and shock. *Scand J Trauma Resus Emerg Med.* 2014; 22(1):1–10.
8. Imam AM, Jin G, Sillesen M, Duggan M, Jepsen CH, Hwabejire JO, Lu J, Liu B, DeMoya MA, Velmahos GC, Alam HB. Early treatment with lyophilized plasma protects the brain in a large animal model of combined traumatic brain injury and hemorrhagic shock. *J Trauma Acute Care Surg.* 2013; 75(6):976–83. [PubMed: 24256669]
9. Moore HB, Moore EE, Gonzalez E, Wiener G, Chapman MP, Dzieciatkowska M, Sauaia A, Banjeree A, Hansen KC, Silliman C. Plasma Is the Physiologic Buffer of Tissue Plasminogen Activator-Mediated Fibrinolysis: Rationale for Plasma-First Resuscitation after Life-Threatening Hemorrhage. *J Am Coll Surg.* 2015; 220(5):872–9. [PubMed: 25840538]
10. Halaweish I, Bambakidis T, He W, Linzel D, Chang Z. Early Resuscitation with Fresh Frozen Plasma for Traumatic Brain Injury Combined with Hemorrhagic Shock Improves Neurologic Recovery. *J Am Coll Surg.* 2015; 220(5):809–19. [PubMed: 25907868]
11. Brown JB, Guyette FX, Neal MD, Claridge JA, Daley BJ, Harbrecht BG, Miller RS, Phelan HA, Adams PW, Early BJ. Taking the Blood Bank to the Field: The Design and Rationale of the Prehospital Air Medical Plasma (PAMPer) Trial. *Prehosp Emerg Care.* 2015; 19(3):343–50. [PubMed: 25658881]
12. Chapman MP, Moore EE, Chin TL, Ghasabian A, Chandler J, Stringham J, Gonzalez E, Moore HB, Banjeree A, Silliman CC. Combat. Shock. 2015; 44:63–70. [PubMed: 25784527]
13. Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D. Coagulopathy in severe traumatic brain injury: a prospective study. *J Trauma.* 2009; 66(1):55–61-2. [PubMed: 19131806]
14. Thiels CA, Aho JM, Fahy AS, Parker ME, Glasgow AE, Berns KS, et al. Prehospital Blood Transfusions in Non-Trauma Patients. *World J Surg.* 2016
15. Higgins GL, Baumann MR, Kendall KM, Watts MA, Strout TD. Red Blood Cell Transfusion: Experience in a Rural Aeromedical Transport Service. *Prehosp Disaster Med.* 2012; 27(3):231–4. [PubMed: 22687337]
16. Jenkins D, Stubbs J, Williams S, Berns K, Zielinski M, Stranden G, Zietlow SP. Implementation and Execution of Civilian Remote Damage Control Resuscitation Programs. *Shock.* 2014; 41:84–9. [PubMed: 24662783]
17. Riskin DJ, Tsai TC, Riskin L, Hernandez-Boussard T, Purtill M, Maggio PM, Spain DA, Brundage SI. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. *J Am Coll Surg.* 2009; 209(2):198–205. [PubMed: 19632596]
18. Mitra B, Mori A, Cameron PA, Fitzgerald M, Paul E, Street A. Fresh frozen plasma (FFP) use during massive blood transfusion in trauma resuscitation. *Injury.* 2010; 41(1):35–9. [PubMed: 19833331]
19. del Junco DJ, Holcomb JB, Fox EE, Brasel KJ, Phelan HA, Bulger EM, Schreiber MA, Muskat P, Alarcon LH, Cohen MJ. Resuscitate early with plasma and platelets or balance blood products gradually: findings from the PROMMTT study. *J Trauma Acute Care Surg.* 2013; 75(1 Suppl 1):S24–30. [PubMed: 23778507]
20. Novak DJ, Bai Y, Cooke RK, Marques MB, Fontaine MJ, Gottschall JL, Carey PM, Scanlan RM, Fiebig EW, Schulman I. Making thawed universal donor plasma available rapidly for massively bleeding trauma patients: experience from the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial. *Transfusion.* 2015; 55(6):1331–9. [PubMed: 25823522]
21. Bhangu A, Nepogodiev D, Doughty H, Bowley DM. Meta-analysis of plasma to red blood cell ratios and mortality in massive blood transfusions for trauma. *Injury.* 2013; 44(12):1693–9. [PubMed: 23021369]

22. Peiniger S, Nienaber U, Lefering R, Braun M, Wafaisade A, Wutzler S, Borgmann M, Spinella PC, Maegele M. Balanced massive transfusion ratios in multiple injury patients with traumatic brain injury. *Crit Care*. 2011; 15(1):R68. [PubMed: 21342499]
23. Cooper DJ, Myles PS, Mcdermott FT, Murray LJ, Laidlaw J, Tremayne AB, Bernard SS. Prehospital Hypertonic Saline Resuscitation of Patients With Hypotension and Severe Traumatic Brain Injury. *JAMA*. 2016; 291(11)
24. King JT, Carlier PM, Marion DW. Early Glasgow Outcome Scale scores predict long-term functional outcome in patients with severe traumatic brain injury. *J Neurotrauma*. 2005; 22(9): 947–54. [PubMed: 16156710]
25. Ditunno JF. Functional assessment measures in CNS trauma. *J Neurotrauma*. 1992; 9(Suppl 1):S301–5. [PubMed: 1588620]
26. Wilson JT, Pettigrew LE, Teasdale GM. Emotional and cognitive consequences of head injury in relation to the glasgow outcome scale. *J Neurol Neurosurg Psychiatry*. 2000; 69(2):204–9. [PubMed: 10896694]
27. Savage SA, Sumislawski JJ, Zarzaur BL, Dutton WP, Croce MA, Fabian TC. The new metric to define large-volume hemorrhage: results of a prospective study of the critical administration threshold. *J Trauma Acute Care Surg*. 2015; 78(2):224–30. [PubMed: 25757105]
28. Cohen MJ, Brohi K, Ganter MT, Manley GT, Mackersie RC, Pittet JF. Early coagulopathy after traumatic brain injury: the role of hypoperfusion and the protein C pathway. *J Trauma*. 2007; 63(6):1254–61-2. [PubMed: 18212647]
29. Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC, Pittet JF. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma*. 2008; 64(5):1211–7. [PubMed: 18469643]
30. Maegele M. Acute traumatic coagulopathy: Incidence, risk stratification and therapeutic options. *World J Emerg Med*. 2010; 1(1):12–21. [PubMed: 25214935]
31. Epstein DS, Mitra B, O'Reilly G, Rosenfeld JV, Cameron PA. Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: a systematic review and meta-analysis. *Injury*. 2014; 45(5):819–24. [PubMed: 24529718]
32. Epstein DS, Mitra B, Cameron PA, Fitzgerald M, Rosenfeld JV. Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: Definition, incidence and outcomes. *Br J Neurosurg*. 2014; 25:1–5.
33. Epstein DS, Mitra B, Cameron PA, Fitzgerald M, Rosenfeld JV. Normalization of coagulopathy is associated with improved outcome after isolated traumatic brain injury. *J Clin Neurosci*. 2016; 29:64–9. [PubMed: 26947341]
34. Sillesen M, Bambakidis T, Dekker S, Li Y, Alam HB. Fresh Frozen Plasma Modulates Brain Gene Expression in a Swine model of Traumatic Brain Injury and Shock: A Network Analysis. *J Am Coll Surg*. 2017; 224(1):49–58. [PubMed: 27725221]

Figure 1.
Prehospital Transfusion Guidelines in Adults

Figure 2.
Inclusion and exclusion criteria flowchart

Figure 3.
Inpatient hospital transfusion data by prehospital group, thawed plasma versus pRBC

Figure 4.
Comparison of GOSE and DRS scores at dismissal and during follow up

Table 1

Patient factors by prehospital product type

		Thawed Plasma vs pRBC		
	All (n=76)	pRBC (n=40)	Plasma (n=36)	P-value
Sex				0.41
Female n (%)	29 (38.2)	17 (42.5)	12 (33.3)	
Male n (%)	47 (61.8)	23 (57.5)	24 (66.7)	
Age *	54 (29.5,77.5)	47.5 (23.5,71)	65 (38,81.5)	0.09
Injury Severity Score *	24.5 (17,29.5)	25.5 (20.5,34)	22 (17,28)	0.10
Head AIS *	3 (2,4.5)	3 (2,5)	3 (2,4)	0.11
Head AIS, n (%)				0.38
2	26 (34.2)	11 (27.5)	15 (41.7)	
3	23 (30.3)	12 (30.0)	11 (30.6)	
4	8 (10.5)	4 (10.0)	4 (11.1)	
5	19 (25.0)	13 (32.5)	6 (16.7)	
Total number of units given *	1.5 (1,2)	1.5 (1,2)	1.5 (1,2)	0.53
Duration of Stay *	11.5 (6,18.5)	12.5 (7.5,22)	11 (5.5,14.5)	0.15
ED GCS *	5.5 (3,15)	4 (3,14)	8 (3,15)	0.14
Hgb *	12 (10.4,12.9)	11.65 (10.15,12.55)	12.1 (10.6,13.1)	0.32
INR *	1.2 (1.1,1.5)	1.15 (1.1,1.5)	1.2 (1.05,1.45)	0.91
Lactate *	2.515 (1.875,4.15)	2.515 (1.99,4.265)	2.62 (1.435,3.765)	0.73
Systolic Blood Pressure *	121 (110,134.5)	117 (110,130)	128.5 (110,137.5)	0.30
Plt *	186.5 (150.5,217)	191 (151.5,212.5)	182.5 (148.5,220.5)	0.83
Ptt *	29 (26,33)	29 (27.5,33)	29 (26,31)	0.43
MA *	57 (0,66.05)	55.25 (0,63.9)	61.9 (0,67.25)	0.13
Angle *	63.6 (0,69.35)	59.55 (0,68.1)	65.25 (0,70.8)	0.35
K *	1.3 (0,1.7)	1.4 (0,1.85)	1.25 (0,1.65)	0.46
R *	4.2 (0,5.6)	3.75 (0,5.6)	4.45 (0,5.65)	0.66
Ly 30 *	0 (0,0.3)	0 (0,0)	0 (0,1.2)	0.072

* Median [IQR]

Table 2

Categorical neurocognitive outcomes based on prehospital transfusion type

		Thawed Plasma vs pRBC		
Overall	All (n=76)	pRBC (n=40)	Plasma (n=36)	P-value
GOSE <6 vs ≥6, no. (col %)				<0.001
<6	22 (28.9)	20 (50.0)	2 (5.6)	
≥6	54 (71.1)	20 (50.0)	34 (94.4)	
DRS 7 vs >7, no. (col %)				<0.001
7	52 (68.4)	19 (47.5)	33 (91.7)	
>7	24 (31.6)	21 (52.5)	3 (8.3)	
Head AIS 2				
GOSE <6 vs ≥6, no. (col %)				0.42
<6	1 (3.8)	1 (9.1)	0 (0.0)	
≥6	25 (96.2)	10 (90.9)	15 (100.0)	
DRS 7 vs >7, no. (col %)				0.42
7	25 (96.2)	10 (90.9)	15 (100.0)	
>7	1 (3.8)	1 (9.1)	0 (0.0)	
Head AIS 3				
GOSE <6 vs ≥6, no. (col %)				0.014
<6	6 (26.1)	6 (50.0)	0 (0.0)	
≥6	17 (73.9)	6 (50.0)	11 (100.0)	
DRS 7 vs >7, no. (col %)				0.014
7	17 (73.9)	6 (50.0)	11 (100.0)	
>7	6 (26.1)	6 (50.0)	0 (0.0)	
Head AIS 4				
GOSE <6 vs ≥6, no. (col %)				1.00
<6	3 (37.5)	2 (50.0)	1 (25.0)	
≥6	5 (62.5)	2 (50.0)	3 (75.0)	
DRS 7 vs >7, no. (col %)				1.00
7	5 (62.5)	2 (50.0)	3 (75.0)	
>7	3 (37.5)	2 (50.0)	1 (25.0)	
Head AIS 5				
GOSE <6 vs ≥6, no. (col %)				0.010
<6	12 (63.2)	11 (84.6)	1 (16.7)	
≥6	7 (36.8)	2 (15.4)	5 (83.3)	
DRS 7 vs >7, no. (col %)				0.017
7	5 (26.3)	1 (7.7)	4 (66.7)	
>7	14 (73.7)	12 (92.3)	2 (33.3)	