Prehospital plasma in injured patients is associated with survival principally in blunt injury: Results from two randomized prehospital plasma trials

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INTRODUCTION: Recent evidence demonstrated that prehospital plasma in patients at risk of hemorrhagic shock was safe for ground transport and resulted in a 28-day survival benefit for air medical transport patients. Whether any beneficial effect of prehospital plasma varies across injury mechanism remains unknown.

METHODS: We performed a secondary analysis using a harmonized data set derived from two recent prehospital plasma randomized trials. Identical inclusion/exclusion criteria and primary/secondary outcomes were used for the trials. Prehospital time, arrival shock parameters, and 24-hour transfusion requirements were compared across plasma and control groups stratified by mechanism of injury. Stratified survival analysis and Cox hazard regression were performed to determine the independent survival benefits of plasma across blunt and penetrating injury.

RESULTS: Blunt patients had higher injury severity, were older, and had a lower Glasgow Coma Scale. Arrival indices of shock and coagulation parameters were similar across blunt and penetrating injury. The percentage of patients with a prehospital time less than 20 minutes was significantly higher for penetrating patients relative to blunt injured patients (28.0% vs. 11.6%, $p < 0.01$). Stratified Kaplan-Meier curves demonstrated a significant separation for blunt injured patients (n = 465, $p = 0.01$) with no separation demonstrated for penetrating injured patients (n = 161, $p = 0.60$) Stratified Cox hazard regression verified, after controlling for all important confounders, that prehospital plasma was associated with a 32% lower independent hazard for 28-day mortality in blunt injured patients (hazard ratio, 0.68; 95% confidence interval, 0.47–0.96; $p = 0.03$) with no independent survival benefit found in penetrating patients (hazard ratio, 1.16; 95% confidence interval, 0.4–3.1; $p = 0.78$).

CONCLUSION: A survival benefit associated with prehospital plasma at 24 hours and 28 days exists primarily in blunt injured patients with no benefit shown in penetrating trauma patients. No detrimental effects attributable to plasma are demonstrated in penetrating injury. These results have important relevance to military and civilian trauma systems. (*J Trauma Acute Care Surg.* 2020;88: 33–41. Copyright © 2019 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic, I.

KEY WORDS: Prehospital; plasma; blunt mechanism of injury.

The management of severe traumatic injury and hemorrhage has significantly evolved over the last decade with treatment priorities focusing on prevention of coagulopathy thru minimization of crystalloid infusion and early blood component-based resuscitation after arrival at definitive care.[1–4] Despite these beneficial changes, the majority of deaths due to hemorrhage continue to occur in the first hours after arrival, highlighting the importance of potentially beneficial resuscitation strategies during the early phase of care, as close to the time of injury as feasible.[5,6]

Early blood transfusion during the prehospital phase of care has previously been demonstrated to be associated with a survival benefit in both military and civilian settings.[7–9] Most recently, results from two recent prehospital clinical trials demonstrated the safety of early prehospital plasma for ground transport and a significant survival benefit of those transported via air medical transport.[10,11] Understanding those injured cohorts who benefit most from such prehospital interventions is of utmost importance allowing these early blood product resources to be provided to the most appropriate population. Patients significantly injured via blunt or penetrating mechanisms are both at risk of hemorrhage and poor outcome but their demographics, injury characteristics, management strategies, and response to injury vary.[12–16]

Whether the beneficial effect of prehospital plasma varies across blunt and penetrating injury mechanisms remains unknown. Our overall objective was to characterize prehospital plasma outcomes across mechanism of injury using harmonized data obtained from these two recently completed prehospital plasma clinical trials. We hypothesized that the safety and beneficial effects of prehospital plasma would be consistent across blunt and penetrating mechanism of injury.

METHODS

The current analysis is a predefined secondary analysis using data derived from two recently published studies, the Control of Major Bleeding After Trauma (COMBAT) trial[10] and the Prehospital Air Medical Plasma (PAMPer) trial.[11] These trials were purposefully harmonized prior to commencement of enrollment to address questions that could not be answered by either trial individually. Harmonization was performed allowing experimental treatment groups, inclusion/exclusion criteria, adverse events, and methods to account for patient transport time to be equivalent across the two trials. Inclusion criteria were hypotension (systolic blood pressure, < 90 mm Hg) and tachycardia (hazard ratio [HR], >108) or severe hypotension (systolic blood pressure, < 70 mm Hg) without the tachycardia requirement at any period in the prehospital environment. Common exclusion criteria included prisoner status, known pregnancy, isolated penetrating injury to the head, asystole or cardiopulmonary resuscitation (>5 minutes), known objection to blood products or wearing opt-out bracelets. For both trials, plasma was administered prior to other resuscitative fluids once the patient met all inclusion and no exclusion criteria. The FDA, Office of Research Protections of US Army Medical Research and Materiel Command

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and institutional review board at all participating institutions approved exception from informed consent requirements, after consultation with community members, and after public notification regarding the trial took place.

There were differences in the two prehospital plasma trials. The COMBAT was a single-center clinical trial. Enrolled patients were transported by ground ambulance directly from the scene to a Level I trauma center. Patients enrolled were administered either two units of thawed AB plasma or received ground transport standard care. Standard care was goal-directed crystalloid resuscitation using 0.9% saline. Randomization and enrollment were performed at the level of the ambulance. The PAMPer trial was a multicenter, cluster-randomized trial involving injured patients who were transported by air medical transport to a Level I trauma center, either directly from the scene or from a referring hospital. Patients enrolled in PAMPer received two units of either group AB or group A with a low anti-B antibody titer (<1:100) thawed plasma or received standard air medical care. Standard care consisted of goal-directed, crystalloid-based resuscitation on the basis of hemodynamic status for air transport teams at 14 of the 27 participating air medical bases. Air transport teams at the other 13 participating air medical bases also carried two units of universal donor red blood cell (RBC) on all flights. If a patient remained hypotensive after the plasma infusion or had obvious bleeding, transfusion of RBCs then proceeded according to the local protocol. Randomization was at the level of the air medical base for 1-month periods.

The primary outcome for the current secondary analysis was 28-day mortality. Secondary outcomes of interest included 24-hour mortality; prehospital transport time; presenting indices of shock and coagulopathy, units of in-hospital blood components administered within 24 hours. All analyses were carried out in the intention-to-treat randomized patients used in both published studies.

We first evaluated the treatment effect of prehospital plasma on 28-day mortality across blunt and penetrating mechanism of injury using a generalized estimating equations model.[17] The plasma and injury mechanism interaction was assessed for statistical significance, accounting for intratrial cluster effects and multiple cofounders.

We then performed Kaplan-Meier survival analysis comparing prehospital plasma patients versus standard care patients overall and across blunt and penetrating mechanisms of injury for both 24-hour and 28-day mortality using log rank comparison.

To verify these unadjusted findings, we then performed a multivariate analysis of survival with the use of a Cox proportional-hazard model to evaluate the treatment effect (plasma vs. standard care) with adjustment for stratification factors and other possible confounding factors on 24-hour and 28-day survival. The model was generated for the primary outcome in patients with blunt injury. All covariates statistically significant on univariate analysis (demographics, Abbreviated Injury Scale (AIS) score, and presenting initial vital signs) were assessed. In the final model, only covariates with a p-value <0.1 and/or that altered the HR for the treatment of interested by >5% were utilized to prevent over fitting of the model. All regression models passed the proportional-hazards assumption on the basis of Schoenfeld residuals.[18] The identical model was utilized for all Cox-regression analyses.

For the blood component transfusion comparisons, in order to account for the Poisson distribution of units of blood product transfusions within the first 24-hours following arrival, groups were compared with a univariate, negative binomial regression which is more appropriate than standard non-parametric comparison. These comparisons were performed for the harmonized cohort stratified by mechanism of injury as well as by randomized (plasma vs. standard care) group when stratified by injury type.

Descriptive statistics characterized the demographics and injuries of the patients and outcomes of interest. Categorical variables were presented as frequencies and percentages and tested using the Chi-square test. Prehospital transport time was defined as time in minutes from arrival on scene to arrival at the emergency department of the trauma center (ED). Continuous variables were expressed as means and standard deviations (SDs) or medians and interquartile ranges (IQRs) and were tested using the t-test or Mann-Whitney test as appropriate. Statistical significance was determined at the $p < 0.05$ level (two-sided). All data were analyzed using STATA version 10.0 and SAS, version 9.4 (SAS Institute Inc.).

RESULTS

In this harmonized prehospital plasma study cohort (PAMPer-501 patients, COMBAT-125 patients; total N = 626), patients were severely injured with a median injury severity of 22 (IQR, 12–34), a mean prehospital systolic blood pressure of 80 mm Hg (80 ± 31 mm Hg), a median Glasgow Coma Scale (GCS) score of 6 (IQR, 3–15), and an overall mortality of 24.8%. From the primary published studies, there was excellent randomization across plasma and standard care arms for both studies. Importantly, in the PAMPer study, patients in the standard care arm were more likely to receive prehospital packed RBCs and higher volumes of crystalloid prior to arrival, due to the absence of plasma resuscitation capabilities in the standard care arm.

Just under 75% of injuries for the study cohort were due to a blunt mechanism of injury (n = 465) with the remaining resulting from penetrating injury (n = 161). Importantly, there were 10 patients who suffered both blunt and penetrating injuries, and these were including in the penetrating subgroup. The majority of blunt injuries were secondary to motor vehicle collisions while penetrating injuries were almost equally divided across firearm injury and stabbings (Table 1). There were important differences in the study cohort across those who suffered blunt versus penetrating mechanisms of injury. Blunt injured patients were more commonly from the PAMPer study while penetrating injury represented the most common mechanism for the COMBAT study. Blunt injured patients were older; had higher injury severity overall; and greater head, chest, and extremity AIS scores. Blunt injured patients had a lower arrival systolic blood pressure and lower GCS score. Penetrating patients were more racially diverse and had significantly shorter prehospital times.

Upon arrival at the definitive trauma center, patients demonstrated no clinically significant differences in presenting hemoglobin or standard coagulation assays (Table 2). Blood gas comparison demonstrated that blunt injured patients were more likely acidotic and thromboelastography (TEG) differences were limited to non-clinically significant lysis at 30 minutes (LY30)

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TABLE 1. Injury Characteristics for Harmonize Study Cohort Patients Stratified by Blunt and Penetrating Mechanism of Injury

	Blunt (n = 465)	Penetrating (n = 161)	*p*
Classification of mechanism of injury			
Motor vehicle	247 (53.1%)		
Motorcycle	85 (18.3%)		
Pedestrian/cyclist	44 (9.5%)		
Fall	38 (8.2%)		
Other	51 (11.0%)		
Firearm		77 (47.8%)	
Stabbing		69 (41.0%)	
Other		15 (9.3%)	
Full cohort, n (%)	465 (74.3%)	161 (25.7%)	
COMBAT	59 (47.2%)	66 (52.8%)	
PAMPer	406 (81.0%)	95 (19.0%)	
Age, median (IQR)	45 (28, 61)	35 (26, 49)	<0.001
Male, n (%)	326 (70.1%)	141 (87.6%)	<0.001
Race, n (%)			
White	418 (89.9%)	108 (68.4%)	<0.001
Black	28 (6.0%)	45 (28.5%)	
Other/Unknown	19 (4.1%)	5 (3.1%)	
Hispanic, n (%)	33 (7.5%)	31 (20.5%)	<0.001
BMI, mean (SD)	30.2 (11.9)	27.7 (6.8)	0.040
ISS, median (IQR)	24 (17, 34)	14 (6, 25)	<0.001
AIS ≥3, n (%)			
Head	203 (43.7%)	15 (9.3%)	<0.001
Face	16 (3.4%)	6 (3.7%)	0.870
Chest	271 (58.3%)	54 (33.5%)	<0.001
Abdomen	133 (28.6%)	38 (23.6%)	0.220
Extremities	168 (36.1%)	25 (15.5%)	<0.001
Skin	8 (1.7%)	9 (5.6%)	0.009
Prehospital interval			
Minutes, median (IQR)	39.3 (28.4, 50.2)	30.6 (19.7, 43.7)	<0.001
≤20 minutes, n (%)	54 (11.6%)	45 (28.0%)	<0.001
Arrival vital signs, median (IQR)			
Heart rate	107 (89, 124)	105 (91 121)	0.500
Systolic blood pressure	98 (78, 119)	106 (80, 128)	0.034
GCS score	3 (3, 15)	14 (3, 15)	0.004
Mortality 24 h (%)	18.7%	11.8%	<0.001
Mortality 28 d (%)	29.2%	12.4%	<0.001

BMI, body mass index, BMI; ISS, Injury Severity Score; GCS, Glasgow Coma Scale.

measurements. There were missing laboratory values for a proportion of patients; however, the missingness did not vary across mechanism of injury.

For the full harmonized study cohort, patients who were randomized to the plasma arm of both studies had significantly lower 24-hour (13.5% vs. 20.1%; $p = 0.028$) and 28-day mortality rates (20.9% vs. 28.6%; $p = 0.026$) as compared with those patients randomized to standard care prehospital resuscitation. When we compared plasma versus standard care arms stratified by mechanism of injury, we found statistically significant differences in the blunt injury subgroup, without significant differences found in the penetrating group (Table 3). Based on this, we then tested to determine if the survival benefit of prehospital plasma was affected or altered by mechanism of injury. After accounting for intratrial clustering and differences across blunt and penetrating injury, we tested for and found a significant interaction between randomization group and mechanism of injury ($p < 0.001$).

We then performed survival analysis with Kaplan-Meier survival analysis for 24-hour and 28-day mortality to determine when survival differences occurred for each mechanism of injury subgroup (Fig. 1). This analysis revealed a significant and early separation starting around 3 hours from randomization that persisted out to 28 days for blunt injured patients (log rank $p = 0.01$). There was no significant separation apparent for those patients with penetrating injury (log rank, $p = 0.59$).

Multivariate analysis of survival with the use of a Cox proportional-hazard model verified that after adjusting for all clinically and statistically significant covariates that prehospital plasma was independently associated with a survival benefit at 24 hours (HR, 0.59; 95% confidence interval [CI], 0.370–0.947; $p = 0.029$) and at 28 days (HR, 0.68; 95% CI, 0.472–0.965; $p = 0.031$) in the blunt injured subgroup (Table 4). When the penetrating subgroup was similarly analyzed, no significant association with survival or mortality was found for the plasma variable at 24 hours (HR, 1.16; 95% CI, 0.430–3.103; $p = 0.775$) or at 28 days (HR, 1.16; 95% CI, 0.430–3.103; $p = 0.775$).

Finally, we compared 24-hour blood and blood component across randomization groups when stratified by mechanism of injury using univariate, negative binomial regression (Table 5). After taking into account the Poisson distribution of blood transfusion, prehospital plasma was associated with a 24% reduction in the risk of total blood transfusion (incident risk ratio [IRR], 0.76) as compared with standard care patients in those who suffered blunt injury. Similarly, prehospital plasma was associated with significant risk reductions for RBC and platelet transfusion in blunt injury (IRR, 0.77, 0.52, respectively). Importantly, no significant association

TABLE 2. Arrival Laboratory Measurements of Resuscitation, Shock Parameters and Coagulopathy Across Mechanism of Injury

Median (IQR)	Blunt	Penetrating	*p*
	465	161	
CBC and coagulation			
HGB	11.6 (9.7, 13.3)	11.5 (10.0, 13.5)	0.350
INR	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	0.580
PT	14.8 (13.25, 17.5)	14.4 (13.3, 16.5)	0.440
Arterial blood gas			
pH	7.28 (7.20, 7.34)	7.31 (7.25, 7.37)	0.028
Base Excess	−8.2 (−11.3, −6.0)	−10 (−15.9, −6.0)	0.129
Thromboelastogram			
R time	0.8 (0.6, 0.8)	0.8 (0.7, 0.8)	0.720
Kappa	1.7 (1.2, 2.7)	1.8 (1.2, 2.6)	0.840
αAngle	70.4 (62.0, 74.9)	70.2 (63.5, 74.7)	0.880
MA	58.3 (49.7, 64.5)	59.1 (49.6, 63.0)	0.500
LY30	0.3 (0.0, 2.0)	1.2 (0.0, 3.5)	0.006
ACT	113 (105, 136)	121 (105, 128)	0.310

CBC, complete blood count; HGB, hemoglobin; INR, International Normalized Ratio; PT, prothrombin time; P_{CO_2}, partial pressure of carbon dioxide; MA, maximum amplitude; LY30, Lysis at 30 minutes; ACT, activated clotting time.

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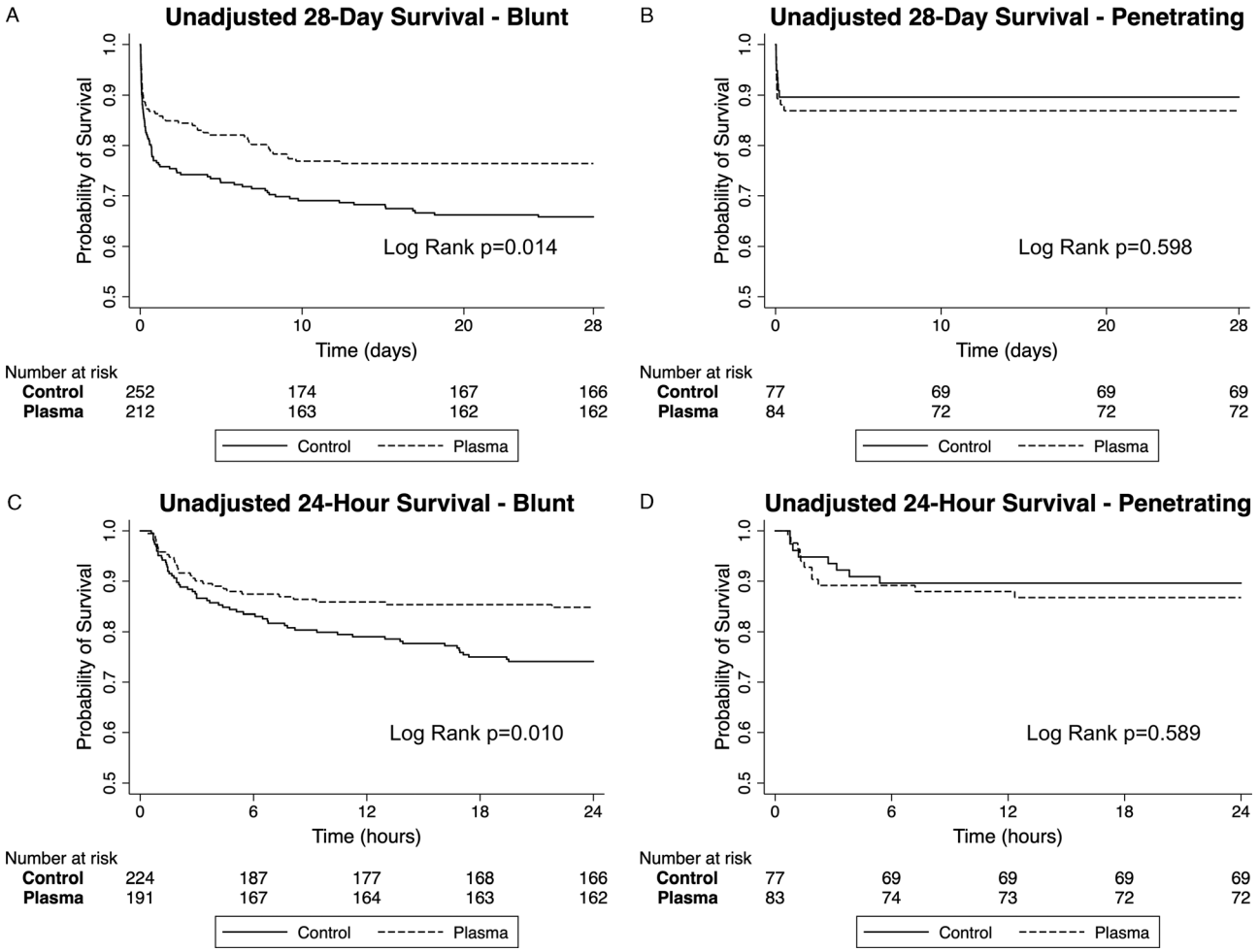

Figure 1. Kaplan-Meier Survival Analysis comparing plasma and standard care arms across blunt and penetrating mechanism of injury; caption (Unadjusted Kaplan Meier curves for 28-day (*A*, *B*) and 24-hour (*C*, *D*) survival for those with blunt (*A*, *C*) and penetrating injury (*B*, *D*) comparing prehospital standard of care (control) to plasma with associated log rank testing).

between prehospital plasma and blood or component transfusion was found in those patients with penetrating injury.

DISCUSSION

Initiating the principles of damage-control resuscitation during the prehospital phase of care, as close to the time of injury as feasible, has great potential to improve outcomes in those patients at high risk of hemorrhage and mortality. Plasma initiated in the prehospital environment has been demonstrated to be safe and result in a survival benefit in patients with longer prehospital transport times.[10,11] The current results derived from two a priori harmonized clinical trials demonstrate that the survival benefit resulting from prehospital plasma is most apparent in those with blunt mechanism of injury. These disparities in response to plasma across blunt and penetrating injury are independent of apparent differences in injury severity and study cohort characteristics and are disparate from the benefits demonstrated for in-hospital plasma.[4] Importantly, plasma was not associated with any harm in those with penetrating injury, and the penetrating cohort is large due to the harmonization of the two studies.

The original trials were not randomized or powered to compare mechanism of injury and the response to prehospital

TABLE 3. Twenty-Four Hour and 28-Day Mortality in Plasma Versus Standard Care Stratified by Injury Mechanism

	Blunt (n = 465)			Penetrating (n = 161)		
	Standard Care	Plasma	*p*	Standard Care	Plasma	*p*
24 h	58 (25.8%)	29 (15.2%)	0.010	8 (10.4%)	11 (13.23%)	0.595
28 d	86 (34.1%)	50 (23.5%)	0.012	8 (10.4%)	12 (14.3%)	0.454

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TABLE 4. Multivariate Cox-Hazard Regression Model in Blunt Injured Patients for 24-Hour and 28-Day Mortality

	HR	95% CI	*p*
Blunt 24 h			
Plasma (vs. standard care)	0.59	0.370–0.947	0.029
Age	1.01	0.999–1.023	0.074
ISS	1.00	0.987–1.019	0.751
Initial GCS	0.77	0.700–0.837	<0.001
PAMPer (vs. COMBAT)	1.29	0.627–5.137	0.276
Blunt 28 d			
Plasma (vs. standard care)	0.68	0.472–0.965	0.031
Age	1.02	1.007–1.029	0.001
ISS	1.02	1.001–1.029	0.031
Initial GCS	0.84	0.801–0.883	<0.001
PAMPer (vs. COMBAT)	2.35	0.980–5.628	0.055

plasma. With the given sample of penetrating injury, an effect size HR of 0.28 would be required to find a statistically significant difference between treatment groups in penetrating trauma. Therefore, although the harmonized data set provides a larger number of penetrating injuries to characterize the relationship, the sample size is too small to find a statistically significant difference and is underpowered to rule out an effect of prehospital plasma in penetrating injury. Assuming a similar range for the hazard ratio for 28-day survival (0.5–0.7), a sample size of 527 to 1,988 would be required to be appropriately powered.

There were differences in presenting shock severity and early measurements of coagulopathy across the blunt and penetrating injury cohorts that are clinically insignificant and unlikely to explain these disparate findings. Overall, mortality across blunt and penetrating injury was significantly lower for penetrating patients and occurred within the first hours of admission. The current analysis also demonstrated that transfusion requirements were significantly lower in those patients who received prehospital plasma as compared with standard care in those with blunt injury, without such findings in penetrating patients. These results suggest that the risks of death and poor outcome may be different across mechanism of injury and the benefits of plasma may vary accordingly. The plasma outcome benefits may in part be due to reduced transfusion requirements in those at highest risk of mortality.

The current results demonstrate that prehospital plasma was not associated with a beneficial survival effect in penetrating as compared with blunt injured patients. However, these results are limited to the injured cohorts analyzed in these two randomized trials. The benefits of prehospital plasma in penetrating injury may be more apparent in those penetrating patients with longer prehospital times and in those with combined injuries, such as the military setting.

The current findings are robust, yet blunt injured patients were significantly different relative to those with penetrating mechanism. They were older, had more significant injuries, including traumatic brain injury, had longer prehospital transit times and higher overall mortality. However, even when controlling for these factors in the statistical models, the survival benefit of plasma in blunt injury alone persisted. The benefits of damage-control resuscitation during the in-hospital phase of care have not previously been shown to vary across mechanism of injury. The benefits of plasma, such as the prevention of coagulopathy during the in-hospital phase of care, may play less of a role when given in smaller volumes and in the prehospital environment. The inflammatory benefits of plasma including endothelial cell protection may be most pertinent to multisystem blunt injury rather than penetrating mechanism.[19–21] The higher percentage of penetrating trauma in urban environments and the attributable shorter transport times may limit the benefit of plasma relative to current prehospital resuscitation. The early time course of mortality for patients who suffer penetrating injury may not allow the benefits of plasma to be appreciated. There may be a survival bias when enrolling penetrating injured patients as those who may benefit the most from prehospital plasma may be unable to be enrolled. Alternatively, those with penetrating injury have been previously shown to benefit from "permissive hypotension" or "controlled resuscitation."[22,23] Any benefit of prehospital plasma resuscitation in patients who suffer penetrating injury may oppose the benefits of hypotensive or controlled prehospital resuscitation and mitigate any overall outcome benefit. These disparate findings of prehospital plasma across blunt and penetrating have significant relevance to both military and civilian practice and provides the impetus to determine the underlying mechanisms responsible and promote further research to verify those injured cohorts who are most likely to benefit from prehospital resuscitation interventions.

LIMITATIONS

There are limitations to this secondary analysis. Although the two studies were harmonized a priori and derived from two prospective randomized clinical trials, there were important differences in the study cohorts and the protocols followed. Most

TABLE 5. Comparison of Blood and Blood Component Transfusion Across Plasma and Standard Care Patients Stratified by Mechanism of Injury

	Blunt			Penetrating		
24 Hour Transfusions	**IRR**	**95% CI**	***p***	**IRR**	**95% CI**	***p***
Total	0.76	0.59–0.98	0.035	0.79	0.44–1.38	0.400
RBC	0.77	0.61–0.98	0.033	0.87	0.46–1.65	0.671
Plasma	0.88	0.64–1.21	0.443	0.74	0.43–1.27	0.270
Platelets	0.52	0.30–0.91	0.020	0.58	0.24–1.34	0.198

Unadjusted negative binomial regression evaluating the IRR of transfusion requirements within the first 24 h.

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important was the differences in prehospital transport time and mortality risk between the two studies. Although we controlled for relevant differences via a robust statistical approach, the potential of residual confounding exists. The enrolled number of patients in the two clinical trials was different, and the results from the current secondary analysis may be primarily driven by the clinical trial with the larger enrolled population.[10,11]

There may be important differences across blunt and penetrating injuries that cannot be accounted for that may alter the current findings presented. Although the penetrating cohort was derived from combining both studies, the overall cohort may still be to small too provide a complete understanding of the relationship of prehospital plasma in penetrating patients. Further dividing penetrating injury into stab wounds and missile injuries limited the sample size even further. We attempted to determine if there was any interaction with the type of penetrating injury (stab vs. firearm) but mortality was too rare of an event for adequate modeling. It may be that subgroups of penetrating injury derive benefit from prehospital plasma, but the current study was unable to demonstrate any association. Although all data were collected prospectively, the acuity of these patients upon presentation limited the collection of time sensitive data, including but not limited to laboratory tests resulting in missingness. Although the missingness did not vary across any of the groups that were compared, missing data represent a significant limitation in interpreting the laboratory data and TEG data.

CONCLUSION

In conclusion, the survival benefit associated with prehospital plasma exists primarily in blunt injured patients with no appreciable benefit demonstrated in penetrating trauma patients for the current harmonized cohort of injured patients. An associated reduced transfusion requirement for plasma patients relative to standard care was also found in blunt injury alone. No detrimental effects attributable to plasma are demonstrated in penetrating injury. These results have important relevance to military and civilian trauma systems. It remains unknown if prehospital plasma is beneficial in penetrating patients in different prehospital environments, such as prolonged field care situations, with specific types of penetrating injuries or in those with particular injury severity. Using data derived from two civilian randomized prehospital plasma trials, 24 hour and 28-day survival benefit of prehospital plasma is principally demonstrated in blunt injured patients only.

AUTHORSHIP

All authors meet authorship criteria for this article as described below. All authors have seen and approved the final article as submitted. The first author (K.M.R.) had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. K.M.R., J.L.S., H.B.M., F.X.G., E.E.M., A.S., A.E.P. participated in the conception and design. J.L.S., H.B.M., F.X.G., E.E.M., A.S., A.E.P. participated in the acquisition of data. K.M.R., J.L.S., H.B.M., F.X.G., E.E.M., A.S., A.E.P. participated in the Analysis and interpretation of data. All authors participated in the article preparation and editing.

DISCLOSURE

The authors declare no conflicts of interest.

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DISCUSSION

DONALD H. JENKINS, M.D. presented by BRIAN EASTRIDGE, M.D. (San Antonio, Texas): Dr. Croce, Dr. Reilly, AAST members and guests, first I'd like to express my sincere appreciation for the ability to discuss this paper.

Dr. Jenkins, who was originally slated to be the discussant for this paper, is under the weather and sends his regrets but asked me to stand in for him.

Though we both extensively reviewed the manuscript, we came to similar conclusions, had similar issues, and questions. I will rely more heavily on Don's comments as they are much more entertaining.

Congratulations to Drs. Reitz, Moore, Sperry and colleagues from Pittsburgh and Denver who have, once again, provided yet another intriguing and practice-changing study.

The manuscript upon which the presentation was made and this response generated is thoughtfully conceived, the paper was thoughtfully conceived, well-written, and very detailed.

The work combines the data from two different but similar studies, which is the future of trauma-related research, where secondary analyses combining multiple research data sets are used for secondary analysis. This is both potentially very powerful and very problematic.

The COMBAT and PAMPER trial data sets were combined looking at severely-injured patients with hypotension requiring resuscitation. The populations were different in several ways and the study designs were different in that some received red blood cells in the PAMPER study but not in the other.

The striking finding from this analysis was that there was a significant difference in the 24- and 28-day survival in the blunt injured patients receiving plasma in the prehospital setting but no difference in survival in those with penetrating mechanism.

The ISS was notably lower in the penetrating population. Prehospital times were shorter. Systolic blood pressure was higher. And survival was better compared to the blunt group.

First, an overall observation. Even after reading the manuscript several times the data analysis is very complex. It is so convoluted as to be at times incomprehensible as to how much data manipulation was done to try to identify differences between the groups.

The data massaging was so confusing to me – us – that we had to ask two different biostats Ph.Ds. for their input to determine if the data was massaged to death or if this was some new version of Wagyu beef preparation or a sidewalk shell game. Each answered completely differently so our conundrum remains.

For the authors I would ask if you analyzed additional data points to include shock index and/or pulse pressure in either the prehospital or in your arrival vital sign data sets.

I would, likewise, be interested to learn if you analyzed or if there was a difference in the predicted probability of survival using TRISS methodology in the penetrating injury groups.

Do the authors have any plans to recreate this study in their evolving work with patients receiving platelets or whole blood?

How do the authors practically interpret this new knowledge in the context of contemporary resuscitation practice?

And, finally, this effort seems to highlight the potential value of common research data sets such as the National Trauma Research Repository. Do the authors have any advice for the rest of us as we start to perform more secondary analysis on combined big data sets on trauma and injury research?

Thank you, once again.

RONALD V. MAIER, M.D. (Seattle, Washington): Ron Maier from Seattle. Very nice study. I congratulate you. And, as usual, creates more questions than answers.

It appears if you take the data overall they seem to show that if you are more severely injured then plasma helped; if you are less severely injured the plasma didn't help.

And, as you postulate, the net effect may be a combination of benefit in some and a negative effect in others, leading to a net zero outcome. This hypothesis supports other data, which you didn't mention, that demonstrates giving plasma routinely to trauma patients who may not need aggressive resuscitation may actually have a detrimental effect on their outcome, which would fit with your data and the hypothesis that I just put forward.

My question is do you have any other insights into this potential conclusion? Your early data showed no ability to categorize your patients using coagulation status which appears to be unrelated to the outcome in the patients you studied in these two populations?

We assumed for many years a liberal transfusion trigger in the ICU would be beneficial. We have shown in critically-ill ICU patients, giving red cells to those who do not need them leads to a detrimental worse outcome. Does giving plasma to those who do not require it also lead to a detrimental outcome?

And the final question is, how do we identify those who are going to benefit from utilization of plasma transfusions?

WALTER L. BIFFL, M.D. (San Diego, California): Walt Biffl, San Diego. I found both of these papers interesting and it seemed that there was a big difference not only in the mechanism of injury but the transport times. So can you tell us how much of a confounder the transport times were?

And, also, the blunt injured patients had a much lower GCS so what was the attributable mortality? How many had severe TBI? Thanks.

JOHN B. HOLCOMB, M.D. (Birmingham, Alabama): Holcomb from Birmingham, Alabama. I have two questions. One, a follow-on from Walt's, the patients in Denver enrolled in a single-center study got to the hospital much quicker. How much plasma did they get in that shorter time frame? And did that modify the results?

And then maybe more philosophically, the balanced resuscitation paradigm that you discuss in your first couple of slides largely sprang from our experience with predominately

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penetrating injuries on the battlefield. Why did it work there and not in civilian penetrating injuries?

Thanks.

EILEEN M. BULGER, M.D. (Seattle, Washington): Thank you for this wonderful paper. I have just one question for you.

John Holcomb has taught us that the peak time of hemorrhagic death is three hours after injury. Your curves for the blunt trauma group start to separate at three hours. Do you have any data on the cause of death for these patients? Is it that they are dying less from brain injury or less from multiple organ failure because they require less blood products overall?

I think it's really important to understand whether this therapy in the prehospital environment is influencing our hemorrhagic deaths or is it some other mechanism of death that is more common in blunt injured patients?

KATHERINE REITZ, M.D. (Pittsburgh, Pennsylvania): Thank you for the questions. I'll try to address all of them.

So to start with the discussant questions, I appreciate the comments and the thoughts on the statistical analysis. While I don't have a Ph.D. I was able to complete the statistical analysis through what I've learned while getting my masters in clinical research within the University of Pittsburgh, and in consultation with the many really knowledgeable people within our department.

We completed our analysis with a standard Cox model. We did choose our covariates carefully and only selected those which changed the prehospital plasma hazard ratio by more than 10 percent of interest. Also, we were careful to limit the potential for covariates that were collinear which can result in an overfit model and destabilize our model.

Now, I will try to address the questions specific to pulse pressure, shock index, and TRISS. We didn't specifically look at pulse pressure or the shock index, but the variables for hospital admission in the emergency department vital signs were evaluated and included in the model only if they were significant in the ways that I previously described for our standard model building.

We didn't explore TRISS but, as I mentioned with the vital signs, many of the variables within TRISS were included within our data base.

Another interesting question was about, whether or not plasma is the key to improving survival or is either whole blood or platelet administration with or without plasma the future of resuscitation.

We have shown in an additional secondary analysis, that was recently published in *Annals* by Dr. Brown and Dr. Guyette, that in those patients who received prehospital plasma as well as packed red blood cells had the highest rate of survival despite the fact that patients who get packed red blood cells are the likely the sickest patients in prehospital transport.

We believe that prehospital plasma is a significant and useful tool for resuscitation. However, that really shows that whole blood may have an even more significant mortality benefit for traumatically injured patients.

In regards to future plans for additional secondary analysis, we were lucky and grateful for the fact that part of the planning of this trial included the DoD selecting two sites. The two groups were able to create the two trials together synchronizing the protocol which allowed for datasets that were easy to harmonize. So creating data and trials like that is one of the best ways to produce data that will allow us to make causal inferences and actually change practice.

In regards to the three-hour death window and how did they die, yes, we did see that the curve really separated around three hours for those with blunt injury. We did not specifically, in this study, look at the breakdown of mechanism of injury within the blunt groups nor how they died. However, Dr. Sperry is currently working on a separate secondary analysis further exploring where the signal is the strongest for those with blunt injury so you can stay tuned for that answer.

In regards to the transport time, in the urban center where patients were brought in much more quickly than they were for the multi-institution study or PAMPER. We have another secondary analysis of the harmonize data which is evaluating the prehospital transit time and it is currently under review. However, I do not specifically know the plasma volume differences between the two groups. Anyone who didn't receive all their prehospital plasma on transit did continue to receive the continued volume when they arrived to the hospital. The punchline is that patients that had a longer than 20-minute transit time had the most significant survival benefit, independent of mechanism.

I will just wrap it up and just say thank you for all the questions and the interest in the paper.

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