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Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes

A Post Hoc Analysis of the PAMPer and COMBAT Clinical Trials

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IMPORTANCE Both military and civilian clinical practice guidelines include early plasma transfusion to achieve a plasma to red cell ratio approaching 1:1 to 1:2. However, it was not known how early plasma should be given for optimal benefit. Two recent randomized clinical trials were published, with apparently contradictory results. The Prehospital Air Medical Plasma (PAMPer) clinical trial showed a nearly 30% reduction in mortality with plasma transfusion in the prehospital environment, while the Control of Major Bleeding After Trauma (COMBAT) clinical trial showed no survival improvement.

OBJECTIVE To facilitate a post hoc combined analysis of the COMBAT and PAMPer trials to examine questions that could not be answered by either clinical trial alone. We hypothesized that prehospital transport time influenced the effects of prehospital plasma on 28-day mortality.

DESIGN, SETTING, AND PARTICIPANTS A total of 626 patients in the 2 clinical trials were included. Patients with trauma and hemorrhagic shock were randomly assigned to receive either standard care or 2 U of thawed plasma followed by standard care in the prehospital environment. Data analysis was performed between September 2018 and January 2019.

INTERVENTIONS Prehospital transfusion of 2 U of plasma compared with crystalloid-based resuscitation.

MAIN OUTCOMES AND MEASURES The main outcome was 28-day mortality.

RESULTS In this post hoc analysis of 626 patients (467 men [74.6%] and 159 women [25.4%]; median [interquartile range] age, 42 [27-57] years) who had trauma with hemorrhagic shock, a Cox regression analysis showed a significant overall survival benefit for plasma (hazard ratio [HR], 0.65; 95% CI, 0.47-0.90; $P = .01$) after adjustment for injury severity, age, and clinical trial cohort (COMBAT or PAMPer). A significant association with prehospital transport time was detected (from arrival on scene to arrival at the trauma center). Increased mortality was observed in patients in the standard care group when prehospital transport was longer than 20 minutes (HR, 2.12; 95% CI, 1.05-4.30; $P = .04$), while increased mortality was not observed in patients in the prehospital plasma group (HR, 0.78; 95% CI, 0.40-1.51; $P = .46$). No serious adverse events were associated with prehospital plasma transfusion.

CONCLUSIONS AND RELEVANCE These data suggest that prehospital plasma is associated with a survival benefit when transport times are longer than 20 minutes and that the benefit-risk ratio is favorable for use of prehospital plasma.

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Invited Commentary
Author Audio Interview
Supplemental content

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Over the past 10 years, the critical role of initial blood component transfusion for resuscitation following severe trauma and hemorrhagic shock has been demonstrated, and early transfusion has been incorporated into military and civilian clinical practice guidelines.[1-3] In contrast to earlier approaches, which relied heavily on crystalloids and red blood cells (RBCs), the emphasis is to include plasma early to achieve a 1:1 to 1:2 plasma to RBC ratio.[4] The survival benefit of early plasma is most evident among patients likely to die within the first 6 hours as a result of bleeding.[5-7] Studies conducted between 2015 and 2018 have demonstrated a survival benefit associated with initiating transfusions earlier, at the scene of injury or en route to a trauma center.[8-10] Consequently, a number of trauma systems have begun to incorporate RBCs, plasma, or whole blood in the prehospital setting.[8,9,11-19]

Two prospective randomized studies of the prehospital administration of plasma were recently completed.[10,20] The US Department of Defense and the National Heart, Lung, and Blood Institute worked collaboratively by harmonizing the studies in terms of design and data collection and by sharing the samples and data.[21,22] Sperry et al[10] conducted a multicenter study of more than 500 trauma patients with hemorrhagic shock who were transported by helicopter. Patients received standard care en route with or without the addition of 2 U of thawed plasma prior to other resuscitation measures. Prehospital administration of plasma resulted in a significantly lower 30-day mortality (23.2% vs 33.0%; $P = .03$) compared with the standard care group. In contrast, Moore et al[20] reported that 2 U of thawed plasma prior to other fluids during ground ambulance transport in a single-center clinical trial (with short transport times and immediate in-hospital access to blood components) did not improve survival. Recent commentaries have addressed the potential implications of these studies.[23-25]

The reasons for these apparently contradictory results are not clear. One hypothesis is that the very short prehospital transport times in the ground ambulance study may have eliminated the potential for prehospital plasma to improve survival because in-hospital transfusion was not delayed significantly by transport. It was not possible to determine a time effect within either study independently, but analysis of the combined data from both studies offers the opportunity to examine this question. Therefore, we examined the combined data set to address the post hoc hypothesis that the benefits of prehospital administration of plasma are influenced by prehospital transport time.

Key Points

Question Is prehospital plasma administration more beneficial when patient transport times are longer?

Findings This post hoc analysis was performed using harmonized data from 2 randomized clinical trials, Control of Major Bleeding After Trauma and Prehospital Air Medical Plasma, which included 626 patients with trauma and hemorrhagic shock. Patients who received prehospital plasma transfusion had significantly reduced 28-day mortality compared with standard care when prehospital transport times were longer than 20 minutes.

Meaning Prehospital plasma administration is associated with reduced mortality in patients with trauma and significant hemorrhage when transport times are prolonged.

Methods

This analysis brings together data from 2 previously published studies, the Control of Major Bleeding After Trauma (COMBAT) and the Prehospital Air Medical Plasma (PAMPer) clinical trials.[10,20,26,27] These clinical trials were harmonized in advance to enable a combined per-patient analysis to address questions that could not be answered by either trial individually. During protocol development, harmonization was performed to standardize as much as possible the 2 studies in the following key areas: (1) experimental treatment groups, (2) inclusion and exclusion criteria, (3) timing of blood samples, (4) monitoring of adverse events, (5) methods to account for patient transport time, and (6) data collection.

Data sets were developed for each study independently and provided to the data coordinating center of the closely aligned Trans-Agency Consortium for Trauma-Induced Coagulopathy (TACTIC).[22] The TACTIC data coordinating center established the combined data set, ensured agreement of all data elements, and provided the combined data set for the present post hoc analysis, which was performed between September 2018 and January 2019.

Because of the pragmatic character of the clinical trials and requirements for rapid enrollment and randomization, the studies were exempted from the requirement for advanced written informed consent. Each individual clinical study protocol (COMBAT and PAMPer) was approved by its respective local institutional review board and by the Human Research Protections Office of the US Army Medical Research and Materiel Command. The protocols are available in Supplement 1. The requirement to obtain informed consent for emergency research was waived in accordance with Code of Federal Regulations Title 21, Part 50—Protection of Human Subjects, Subpart B—Informed Consent in Human Subjects and SEC 50.24—Exception from Informed Consent Requirement for Emergency Research.

COMBAT Clinical Trial

COMBAT was a pragmatic randomized placebo-controlled single-center clinical trial. Eligible patients were assessed and enrolled at the scene according to the harmonized inclusion and exclusion criteria (eTables 1 and 2 in Supplement 2). Patients were transported by ground ambulance directly from the scene to an urban level 1 trauma center with blood components immediately available in the emergency department (ED).

Patients enrolled in the COMBAT clinical trial were administered either 2 U of thawed AB plasma (universal donor plasma of approximately 250 mL each) followed by standard care or standard care with crystalloid en route. Plasma was administered intravenously by paramedics in the ambulance before other resuscitative fluids were initiated. Plasma transfusion was

continued into the hospital setting if necessary to complete the 2 U. Standard care was goal-directed crystalloid resuscitation using 0.9% saline. Time of arrival on scene (AOS) and time of arrival at the trauma center were recorded by ambulance staff. Randomization and enrollment were performed at the level of the ambulance.[20,26]

PAMPer Clinical Trial

The PAMPer clinical trial was a pragmatic multicenter cluster-randomized clinical trial involving injured patients who were transported by air medical transport to a level 1 trauma center, either directly from the scene or from a referring hospital. Eligible patients were assessed and enrolled at the scene according to the harmonized inclusion and exclusion criteria (eTables 1 and 2 in Supplement 2).

Patients enrolled in PAMPer received 2 U of either group AB or group A with a low anti-B antibody titer (<1:100) thawed plasma followed by standard care, or standard care. Plasma was administered by paramedics prior to other resuscitation fluids. Both units of the prehospital-initiated plasma were infused to completion even if the infusion was still ongoing at the time of arrival at the trauma center. In cases in which completion of the infusion of the 2 U of plasma occurred during flight, standard trauma resuscitation (as defined by the local protocol) resumed until arrival at the trauma center. 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 13 other participating air medical bases also carried 2 U of universal donor RBC on all flights. If a patient remained hypotensive after the plasma infusion or had obvious bleeding, transfusion of RBC then proceeded according to the local protocol. Following RBC transfusion, these teams reverted to crystalloid-based resuscitation. Time of AOS and time of arrival at the trauma center were recorded by helicopter staff. Randomization was at the level of the air medical base.[10,27] Interventions for each of the studies are summarized (eTable 3 in Supplement 2).

Outcomes

The primary outcome measure was 28-day mortality. Secondary outcomes included 24-hour mortality, volumes of in-hospital blood components administered within 6 and 24 hours, ventilator-free days among patients alive at 28 days, intensive care unit–free days among patients alive at 28 days, and international normalized ratio.

Statistical Analysis

Follow-up times were prespecified in this study as 28 days or 24 hours from randomization (or AOS) until death or censoring on the 28th day or 24th hour after AOS. Prehospital transport time was defined as time in minutes from ambulance AOS to arrival at the ED of the trauma center. The prehospital transport time was a priori defined as shorter or longer transport time if prehospital transport time was within 20 minutes or longer than 20 minutes, respectively. All efficacy analyses were carried out in the intention-to-treat randomized patients. A multivariate analysis of survival was performed with the use of a Cox proportional hazards model (for computing hazard ratios [HRs]) to evaluate the treatment effect (plasma vs standard care) and time effect (longer vs shorter), with adjustment for stratification factors and other possible confounding factors (age, injury severity score [ISS], and clinical trial cohort in overall models). The Kolmogorov-type supremum test was used for the Cox proportional hazards assumption. Cohort was included as a random effect because of the heterogeneity inherent in the 2 cohorts. Logistic regression models (for computing the odds ratios [ORs]) were used for likelihood of mortality.

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 a χ^2 test. Continuous variables were expressed as means and 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 $P < .05$ level (2-sided). All data were analyzed using SAS, version 9.4, and JMP 13 software (SAS Institute Inc).

Results

We reviewed 705 patients who were randomly assigned to either the standard care group or the plasma group (**Figure 1**). A total of 626 patients (467 men [74.6%] and 159 women [25.4%]; median [IQR] age, 42 [27-57] years) met inclusion criteria for the primary outcome (Figure 1). Of those, 125 patients were reported for the COMBAT clinical trial and 501 were reported for the PAMPer clinical trial.[10,20] Among the 2 study cohorts, median (IQR) prehospital transport time was longer in the PAMPer study compared with the COMBAT study (41 [33-52] vs 18 [15-22] minutes, respectively; $P < .001$), but there was overlap between the 2 studies (eFigures 1, 2, and 3 in Supplement 2).

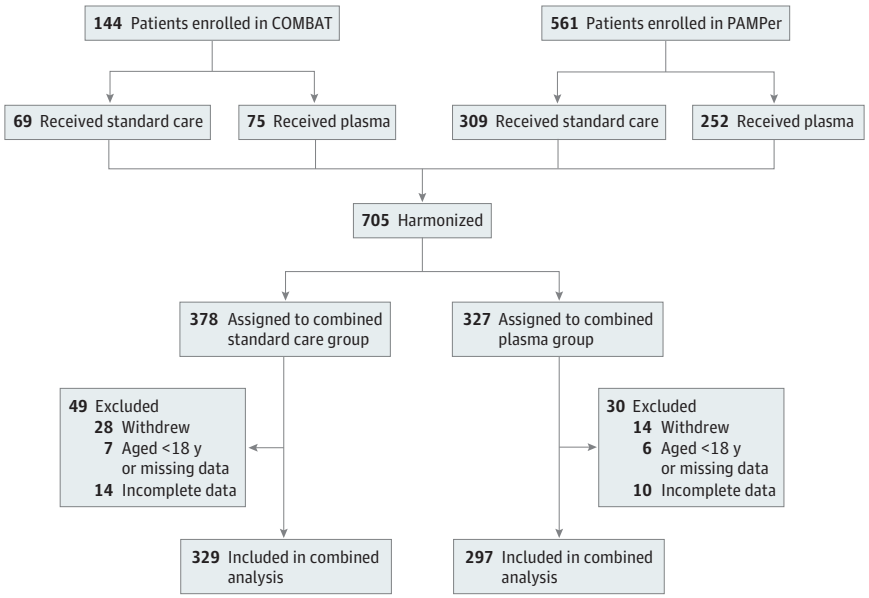
Randomization and harmonization procedures resulted in similar patients being enrolled in the plasma or standard care groups. Patient characteristics are described in **Table 1**. There were no significant differences observed in any demographic or injury characteristic, and there were no differences observed in baseline physiological status (heart rate and systolic blood pressure). Median transport times were also similar between study groups.

Prehospital Plasma and Survival

The 28-day mortality was lower in the plasma group (61 of 297 patients [20.5%]) than in the standard care group (94 of 329 patients [28.6%]) ($P = .02$) (**Table 2** and **Figure 2**). The HR generated by a Cox regression model adjusted for age, injury severity, and trial cohort (COMBAT or PAMPer) indicated lower mortality in the plasma group (HR, 0.65; 95% CI, 0.47-0.90; $P = .01$) (**Table 3**). A similar pattern was observed for 24-hour mortality (HR, 0.62; 95% CI, 0.42-0.93; $P = .02$) (Table 3). Most deaths in both groups occurred within the first 6 hours after injury (Figure 2).

A Cox regression model showed that, in addition to treatment group, survival was influenced by ISS, age, and prehospital transport time. Sensitivity analysis revealed that a change

Figure 1. Study Population Flowchart



COMBAT indicates Control of Major Bleeding After Trauma clinical trial; PAMPer, Prehospital Air Medical Plasma clinical trial.

in response was evident for prehospital times longer than 20 minutes (P = .003 vs P = .007 for 17 minutes, P = .006 for 22 minutes, P = .01 for 25 minutes, and P = .02 for 30 minutes). Transport time (≤20 minutes vs >20 minutes) was not associated with survival when examined across treatment groups (HR, 1.37; 95% CI, 0.85-2.21; P = .20) (Figure 2). However, stratified analysis revealed that in patients who received standard care, rate and likelihood of mortality were significantly increased by 2-fold with transport times greater than 20 minutes (HR, 2.12; 95% CI, 1.05-4.30; P = .04) (Table 3 and Figure 2). Among patients who received prehospital plasma, this association with transport time was eliminated (HR, 0.78; 95% CI, 0.40-1.51; P = .46) (Table 3 and Figure 2). Among patients with short transport times (≤20 minutes), survival in the plasma group and the standard care group did not differ (HR, 1.71; 95% CI, 0.70-4.16; P = .24) (Table 3 and Figure 2). Among patients with longer transport times (>20 minutes), survival was improved in the plasma group (HR, 0.56; 95% CI, 0.40-0.80; P = .001) (Table 3 and Figure 2).

Prehospital Plasma and Secondary Outcomes

Patients who received prehospital plasma were 47% less likely to present to the ED with coagulopathy (international normalized ratio >1.3) compared with those who received standard care (OR, 0.53; 95% CI, 0.35-0.80; P = .002) (eFigure 4 in Supplement 2), and this association was isolated to the group with transport times longer than 20 minutes. Among patients with transport times of 20 minutes or less, in-hospital transfusion requirements did not differ for RBC, fresh frozen plasma, and platelets in the first 6 hours after ED admission, while patients who received plasma during longer transports required less in-hospital transfusion, with median (IQR) in-hospital transfusion requirements of 5 (2-10) vs 2 (2-4) U of plasma (P < .001), 5 (3-10) vs 4 (2-8) U of RBC (P = .05), and 2 (1-3) vs 1 (1-2) U of platelets (P = .04) at 6 hours (Table 2). Similar results were found in the first 24 hours after ED admission (Table 2). Total plasma requirements (including prehospital plasma) did not differ between groups (data not shown). Intensive care unit-free days among patients alive at 28 days did not differ between groups, while ventilator-free days were slightly lower in the plasma group (Table 2). Secondary outcomes based on transport time are shown in eTable 4 in Supplement 2.

Discussion

Prehospital administration of plasma was associated with significantly reduced 24-hour and 28-day mortality compared with standard care in this harmonized data set (Figure 2). This finding is consistent with that reported for the PAMPer clinical trial but not for the COMBAT clinical trial.[10,20] The ability to observe this overall association in the harmonized data set may have been owing to the larger overall number of patients included. This association appears to be robust since, even after adjustment for clinical trial cohort, age, and injury severity, the HR was 0.65 (Table 3). This finding is consistent with previous observations that the survival benefit of early in-hospital plasma transfusion is most substantial among patients likely to die as a result of bleeding within the first 6 hours of injury.[5-7] We also found that transport times longer than 20 minutes were associated with increased mortality in the standard care group and that this increase in mortality was mitigated when prehospital plasma was administered. The present findings suggest that prehospital plasma administration provides a benefit beyond that of a balanced in-hospital transfusion regimen, as was practiced at all involved centers in the COMBAT and PAMPer clinical trials.[10,20]

Table 1. Patient Characteristics and Prehospital Transport Times by Treatment

Characteristic	No. (%)			*P* Value[a]
	Total Patients	SC Group	Plasma Group	
Participants	626 (100)	329 (52.6)	297 (47.4)	NA
Cohort				.12
COMBAT	125 (20.0)	58 (17.6)	67 (22.6)	
PAMPer	501 (80.0)	271 (82.4)	230 (77.4)	
Men	467 (74.6)	251 (76.3)	216 (72.7)	.31
Age, median (IQR), y	42 (27-57)	42 (26-57)	43 (29-56)	.67
Race/ethnicity				
White	453 (72.4)	239 (72.6)	214 (72.1)	.26
Black	69 (11.0)	40 (12.2)	29 (9.8)	
Hispanic	64 (10.2)	27 (8.2)	37 (12.5)	
Other/unknown	40 (6.4)	23 (7.0)	17 (5.7)	
Mechanism of injury				
Fall	38 (6.1)	23 (7.0)	15 (5.1)	.51
Motor vehicle crash				
Motorcyclist/cyclist and occupant	338 (54.0)	185 (56.2)	153 (51.2)	
Pedestrian or struck by or against	57 (9.1)	29 (8.8)	28 (9.4)	
Firearm	77 (12.3)	35 (1.6)	42 (14.1)	
Stab wound	69 (11.0)	32 (9.7)	37 (12.5)	
Other	47 (7.5)	25 (7.6)	22 (7.4)	
Type of injury[b]				
Blunt	465 (+10)	257 (78.1)	218 (73.4)	.37
Penetrating	148 (+10)	77 (23.4)	84 (28.3)	
Injured body region				
Head/neck	306 (48.9)	155 (47.1)	151 (50.8)	.35
Face	157 (25.1)	92 (28.0)	65 (21.9)	.08
Thorax	416 (66.5)	214 (65.1)	202 (68.0)	.43
Abdomen	322 (51.4)	170 (51.7)	152 (51.2)	.90
Extremities	362 (57.8)	189 (57.5)	173 (58.3)	.84
External	372 (59.4)	202 (61.4)	170 (57.2)	.29
AIS score for head, median (IQR)	0 (0-3)	0 (0-3)	1 (0-3)	.73
Severity traumatic brain injury (AIS score ≥3)	213 (34.0)	111 (33.7)	102 (34.3)	.87
ISS, median (IQR)	22 (12-34)	22 (12-33)	22 (12-34)	.35
Prehospital time, median (IQR), min				
From POI to ED[c]	59 (27-97)	61 (26-99)	54 (29-92)	.83
From POI to AOS[d]	20 (7-45)	22 (6-49)	17 (8-45)	.88
From AOS to ED[e]	38 (26-49)	37 (26-48)	39 (27-49)	.51
Vital signs at baseline, median (IQR)				
Lowest or qualifying systolic blood pressure[f]	82 (66-100)	80 (64-97)	82 (70-101)	.07
Highest or qualifying heart rate[g]	117 (98-133)	117 (98-136)	118 (100-130)	.64

Abbreviations: AIS, Abbreviated Injury Scale (score range, 1-6, with 1 indicating minor injury and 6 indicating severe injury incompatible with life); AOS, arrival on scene; COMBAT, Control of Major Bleeding After Trauma clinical trial; ED, emergency department; IQR, interquartile range; ISS, injury severity score (range, 1-75, with 1 indicating minimum severity and 75 indicating maximum severity); NA, not applicable; PAMPer, Prehospital Air Medical Plasma clinical trial; POI, point of injury; SC, standard care.

[a] *P* values were calculated using a χ^2 test, *t* test, or Wilcoxon Mann-Whitney test as appropriate.

[b] A total of 10 patients had both blunt and penetrating injuries, including 5 patients in the SC group and 5 patients in the plasma group. These patients were counted in both blunt and penetrating groups, resulting in a total of 636 instead of 626 patients and a total percentage of more than 100%.

[c] Of 626 patients, 270 had time recorded from POI to ED, including 138 patients in the SC group and 132 patients in the plasma group.

[d] Of 626 patients, 270 had time recorded from POI to AOS, including 138 patients in the SC group and 132 patients in the plasma group.

[e] All 626 patients had time recorded from AOS to ED, which ranged from 7 to 166 minutes in the SC group and from 8 to 176 minutes in the plasma group.

[f] A total of 610 patients had lowest systolic blood pressure measures, including 323 patients in the SC group and 287 patients in the plasma group.

[g] A total of 609 patients had highest heart rate measures, including 323 patients in the SC group and 286 patients in the plasma group.

In a recently published meta-analysis, it was suggested that the case for prehospital plasma could not yet be made in light of the differing results of the COMBAT and PAMPer studies.[24] We were able to adjust for confounding factors and to specifically address the potential effects of prehospital transport time. In the present analysis, the median prehospital transport time was 38 minutes and represented a broad range (Table 1; eFigure 1, eFigure 2, and eFigure 3 in Supplement 2). A survival advantage associated with prehospital plasma was observed in the PAMPer trial but not in the COMBAT trial.[10,20] The reason for these apparently contradictory results are not clear. One difference between the 2 primary studies was that the median prehospital transport times were substantially different (18 minutes in the COMBAT study vs 41 minutes in the PAMPer study). Considering the detrimental effects of transfusion delays on survival,[9,28] we hypothesized that the very short prehospital transport time in the COMBAT trial may have eliminated the potential for prehospital plasma to improve survival because in-hospital transfusion was not delayed to a degree sufficient to influence mortality. We found that prehospital transport time influenced the response to prehospital plasma. Prehospital transport times longer than 20 minutes were associated with increased mortality in patients who received standard care (Figure 2). In contrast, the increased mortality associated with

Table 2. Mortality and Secondary Outcomes

Outcome	Median (IQR)			*P* Value[a]
	Total Patients	SC Group	Plasma Group	
Participants, No. (%)	626 (100)	329 (52.6)	297 (47.4)	NA
Mortality, No. (%)				
28 d	155 (24.8)	94 (28.6)	61 (20.5)	.02
24 h	106 (16.9)	66 (20.1)	40 (13.5)	.03
Transfusion units received[b]				
First 6 h after ED admission				
RBC	5 (2-10)	6 (2-10)	5 (2-8)	.19
≤20 min	6 (2-13)	6 (2-12)	8 (2-17)	.36
>20 min	5 (2-9)	5 (3-10)	4 (2-8)	.05
FFP	3 (2-6)	4 (2-9)	2 (2-5)	<.001
≤20 min	4 (2-8)	4 (2-8)	4 (2-8)	.94
>20 min	2 (2-6)	5 (2-10)	2 (2-4)	<.001
Platelet	2 (1-3)	2 (1-3)	1 (1-2)	.07
≤20 min	1 (1-2)	1 (1-2)	2 (1-2)	.68
>20 min	2 (1-3)	2 (1-3)	1 (1-2)	.04
First 24 h after ED admission				
RBC	5 (2-10)	6 (3-10)	5 (2-10)	.19
≤20 min	7 (2-13)	7 (2-13)	7 (2-17)	.53
>20 min	5 (2-10)	6 (3-10)	4 (2-8)	.07
FFP	3 (2-7)	4 (2-10)	2 (2-6)	<.001
≤20 min	4 (2-9)	4 (2-9)	5 (2-10)	.40
>20 min	3 (2-6)	5 (2-10)	2 (2-4)	<.001
Platelets	2 (1-3)	2 (1-3)	1 (1-2)	.09
≤20 min	2 (1-2)	1 (1-3)	2 (1-2)	.94
>20 min	2 (1-3)	2 (1-3)	1 (1-2)	.07
INR at ED arrival				
Overall units	NA	1.3 (1.1-1.6)	1.2 (1.1-1.3)	.004
≤20 min	NA	1.1 (1.1-1.5)	1.3 (1.2-1.4)	.06
>20 min	NA	1.3 (1.1-1.6)	1.2 (1.1-1.3)	<.001
Ventilator-free days, 28-d follow-up				
Survivors (n = 471)	27 (22-28)	27 (24-28)	26 (20-28)	.03
ICU-free days, 28-d follow-up				
Survivors (n = 471)	23 (15-26)	23 (16-26)	23 (14-26)	.72

Abbreviations: ED, emergency department; FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; NA, not applicable; RBC, red blood cell; SC, standard care.

[a] *P* values were calculated using a χ^2 test, *t* test, or Wilcoxon Mann-Whitney test as appropriate.

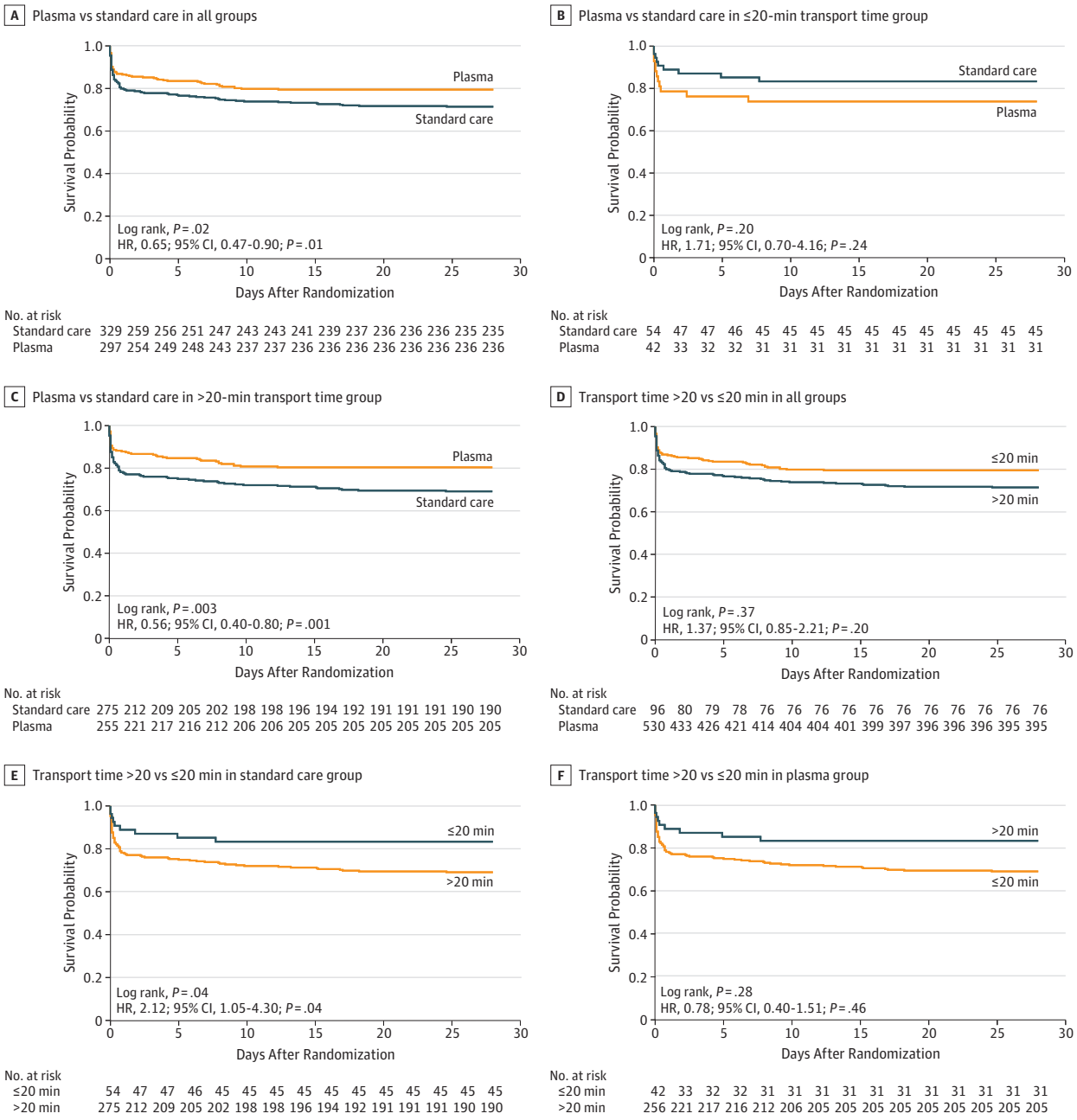
[b] One unit was equivalent to 250 mL.

longer transport times was eliminated in patients who received prehospital plasma (Figure 2).

In a study of 502 casualties evacuated by US military MEDEVAC in Afghanistan from 2012 to 2015, the initiation of transfusion within 15 minutes of MEDEVAC rescue (median time of MEDEVAC rescue, 29 minutes after injury) was associated with improved survival (mortality HR, 0.17), while delays beyond that eliminated the association.[9] Another report found that early in-hospital delays in the initiation of transfusion were associated with progressively increasing mortality rates.[28] While prehospital transport time is a more available measure, the more pathophysiologically relevant measure is the time from injury to transfusion. In the present study, the time of injury was available only in a subset of patients. The median time from injury to AOS was 20 minutes. Extrapolating this to the observed dichotomy between transport times longer or shorter than 20 minutes, it may be estimated that the benefit associated with prehospital plasma was most evident in patients who could not be delivered for in-hospital transfusion within approximately 40 (20 plus 20) minutes of injury. This is similar to the total time to transfusion of 36 minutes reported by Shackelford et al,[9] when time from injury to MEDEVAC rescue is included. All centers involved in COMBAT and PAMPer had blood products readily available in the ED, likely minimizing possible in-hospital delays. However, time from ED arrival to initiation of transfusion must be considered in estimating transfusion delays and may differ based on local availability.

The finding that transport times longer than 20 minutes were associated with increased mortality in the standard care group emphasizes the importance of minimizing time to definitive care, as recently demonstrated in a national database analysis.[29] The importance of rapid hemostasis must also be recognized, and potential delays in getting to an operating room for surgical hemostasis could be a more significant factor than the time to transfusion.

Figure 2. 28-Day Survival Rate by Treatment and Transport Time



Transport time was measured from arrival on scene to arrival at emergency department. HR indicates hazard ratio.

Other factors may explain the observed differences in survival. Most patients with prolonged prehospital transport times were transported by helicopter. It has been reported that helicopter transport is associated with a survival advantage that may be a result of the higher level of training among helicopter medical crews.[30-32] In the present study, participating ground ambulance crews included paramedics. In addition, overall survival was better with ground transport, although this occurred with shorter transport times. Therefore, a difference in personnel training is not likely to account for the time-related differences observed. The association with transport time may also be explained by injury severity. The ISS in the COMBAT trial, which included most patients with short transport times, was lower than that in the PAMPer trial. However, the differential association of prehospital transport time in patients who did or did not receive prehospital plasma remained significant even after adjusting for ISS in the regression model (Table 3).

Among patients with longer transport times, those who received prehospital plasma had lower early transfusion

Table 3. Rate and Likelihood of 28-Day and 24-Hour Mortality

	Mortality							
	28 d				24 h			
Model	HR (95% CI)	*P* Value	OR (95% CI)	*P* Value	HR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Unadjusted								
Treatment								
Plasma vs SC group[a]	0.69 (0.50-0.95)	.02	0.65 (0.45-0.94)	.02	0.66 (0.44-0.97)	.04	0.64 (0.42-0.99)	.04
Transport time from AOS to ED								
>20 vs ≤20 min								
Overall[b]	1.24 (0.77-1.98)	.38	1.30 (0.76-2.21)	.33	1.11 (0.64-1.91)	.72	1.12 (0.62-2.03)	.71
SC group[c]	2.00 (1.01-3.98)	.05	2.24 (1.05-4.78)	.04	2.08 (0.90-4.81)	.09	2.23 (0.91-5.47)	.08
Plasma group[d]	0.70 (0.37-1.35)	.29	0.69 (0.32-1.46)	.33	0.54 (0.26-1.14)	.11	0.51 (0.22-1.16)	.11
≤20 min								
Plasma vs SC group	1.68 (0.70-4.06)	.25	1.77 (0.66-4.79)	.26	2.04 (0.73-5.73)	.18	2.18 (0.71-6.71)	.17
>20 min								
Plasma vs SC group	0.60 (0.42-0.85)	.004	0.55 (0.37-0.81)	.003	0.54 (0.35-0.83)	.005	0.50 (0.31-0.80)	.004
Adjusted								
Model 1: overall[e]								
Plasma vs SC group	0.65 (0.47-0.90)	.01	0.60 (0.40-0.88)	.01	0.62 (0.42-0.93)	.02	0.58 (0.37-0.90)	.02
Model 2: overall[f]								
>20 vs ≤20 min	1.37 (0.85-2.21)	.20	1.54 (0.86-2.73)	.15	1.25 (0.71-2.22)	.45	1.33 (0.70-2.51)	.38
Model 3: SC treatment[g]								
>20 vs ≤20 min	2.12 (1.05-4.30)	.04	2.67 (1.16-6.16)	.02	2.14 (0.91-5.04)	.08	2.51 (0.97-6.48)	.06
Model 4: plasma treatment[g]								
>20 vs ≤20 min	0.78 (0.40-1.51)	.46	0.78 (0.35-1.75)	.55	0.68 (0.31-1.50)	.34	0.64 (0.27-1.56)	.33
Model 5: transport time ≤20 min[h]								
Plasma vs SC group	1.71 (0.70-4.16)	.24	1.94 (0.64-5.93)	.24	1.89 (0.65-5.40)	.25	2.44 (0.67-8.87)	.18
Model 6: transport time >20 min[h]								
Plasma vs SC group	0.56 (0.40-0.80)	.001	0.49 (0.33-0.75)	.001	0.53 (0.34-0.82)	.004	0.48 (0.29-0.77)	.003

Abbreviations: AOS, arrival on scene; ED, emergency department; HR, hazard ratio; OR, odds ratio; SC, standard care.

[a] Plasma group (n = 297) vs SC group (n = 329).

[b] More than 20 minutes (n = 530) vs 20 minutes or less (n = 96).

[c] More than 20 minutes (n = 275) vs 20 minutes or less (n = 54).

[d] More than 20 minutes (n = 255) vs 20 minutes or less (n = 42).

[e] Model 1 was adjusted for cohort, age, and injury severity score (ISS).

[f] Model 2 was adjusted for treatment, age, and ISS.

[g] Models 3 and 4 comprised analyses of treatment groups (SC or plasma) adjusted for age and ISS.

[h] Models 5 and 6 comprised stratification analyses of transport times (≤20 or >20 minutes) adjusted for age and ISS.

requirements (Table 2). Reduced transfusion requirements suggest improved hemodynamic stability among patients who received prehospital plasma. These patients also had improved international normalized ratios (Table 2; eTable 4 and eFigure 4 in Supplement 2). Plasma transfusion mitigates the coagulopathy that can complicate traumatic hemorrhage and has also been reported to improve inflammatory response after injury, reduce permeability of endothelial cells, reduce gut permeability, and mitigate metabolic derangements after trauma and hemorrhagic shock.[17,33-40] Therefore, reduced transfusion requirements may reflect improved hemostasis, improved endothelial integrity, or a more favorable inflammatory status.

It is important that no significant differences in safety outcomes and adverse events between the plasma and standard care groups were previously reported for the individual studies.[10,20] The lack of differences in intensive care unit-free days and the small difference in ventilator-free days in the present analysis are consistent with these observations. This suggests that the benefit-risk ratio is favorable for the prehospital administration of plasma in cases in which there is a doubt about how rapidly patients can be delivered for in-hospital transfusion. More logistically supportable products, such as dried plasma, are needed to enable the broader use of plasma in the prehospital setting.[41]

Limitations

One limitation of the present analysis is the fact that the mode of transport differed in the 2 cohorts. Because other important aspects of the studies were harmonized and because there was some degree of overlap in transport times across the 2 studies, we believe that it is possible to draw generalizable conclusions regarding the influence of prehospital plasma and transport time on patient outcomes. Another limitation is that the pragmatic nature of the 2 studies precluded complete standardization of crystalloid type, specific plasma type, and the use of RBC. However, standardization did ensure that the common factor among all

patients who received plasma was that they received 2 U before other standard care fluids. In addition, randomization ensured that the plasma treatment group was represented across all local variations in standard care. A third limitation is that the exact time from patient injury to administration of plasma could not be determined. Time of injury was documented for only a small subset of patients and, therefore, this analysis was not possible. Time to surgical hemostasis was also not recorded and could not be analyzed. Nonetheless, we believe that prehospital transport time is an important component of total prehospital time and the most relevant in terms of providing interventions such as plasma.

Conclusions

The present findings have important implications for the treatment of patients with traumatic hemorrhage when surgical care and in-hospital transfusion may be delayed, such as in military settings, in rural and remote trauma, and in civilian disaster scenarios. The benefit-risk ratio favors prehospital plasma, but logistical and cost constraints may limit feasibility. Thawed plasma is a viable option for helicopter ambulance systems but is more challenging for ground ambulances with short transport times.

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