Time to early resuscitative intervention association with mortality in trauma patients at risk for hemorrhage

Andrew-Paul Deeb, MD, MSc, Francis X. Guyette, MD, MPH, Brian J. Daley, MD, Richard S. Miller, MD, Brian G. Harbrecht, MD, Jeffrey A. Claridge, MD, Herb A. Phelan, MD, MSCS, Brian J. Eastridge, MD, Bellal Joseph, MD, Raminder Nirula, MD, MPH, Gary A. Vercruysse, MD, Jason L. Sperry, MD, MPH, *and* **Joshua B. Brown, MD, MSc**, *Pittsburgh, Pennsylvania*

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Andrew-Paul Deeb, Francis X. Guyette, Brian J. Daley, Richard S. Miller, Brian G. Harbrecht, Jeffrey A. Claridge, Herb A. Phelan, Brian J. Eastridge, Bellal Joseph, Raminder Nirula, Gary A. Vercruysse, Jason L. Sperry, and Joshua B. Brown have nothing to disclose.

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BACKGROUND: Hemorrhage is the leading cause of preventable death after injury. Others have shown that delays in massive transfusion cooler arrival increase mortality, while prehospital blood product resuscitation can reduce mortality. Our objective was to evaluate if time to resuscitation initiation impacts mortality.

METHODS: We combined data from the Prehospital Air Medical Plasma (PAMPer) trial in which patients received prehospital plasma or standard care and the Study of Tranexamic Acid during Air and ground Medical Prehospital transport (STAAMP) trial in which patients received prehospital tranexamic acid or placebo. We evaluated the time to early resuscitative intervention (TERI) as time from emergency medical services arrival to packed red blood cells, plasma, or tranexamic acid initiation in the field or within 90 minutes of trauma center arrival. For patients not receiving an early resuscitative intervention, the TERI was calculated based on trauma center arrival as earliest opportunity to receive a resuscitative intervention and were propensity matched to those that did to account for selection bias. Mixed-effects logistic regression assessed the association of 30-day and 24-hour mortality with TERI adjusting for confounders. We also evaluated a subgroup of only patients receiving an early resuscitative intervention as defined above.

RESULTS: Among the 1,504 propensity-matched patients, every 1-minute delay in TERI was associated with 2% increase in the odds of 30-day mortality (adjusted odds ratio [aOR], 1.020; 95% confidence interval [CI], 1.006–1.033; $p < 0.01$) and 1.5% increase in odds of 24-hour mortality (aOR, 1.015; 95% CI, 1.001–1.029; $p = 0.03$). Among the 799 patients receiving an early resuscitative intervention, every 1-minute increase in TERI was associated with a 2% increase in the odds of 30-day mortality (aOR, 1.021; 95% CI, 1.005–1.038; $p = 0.01$) and 24-hour mortality (aOR, 1.023; 95% CI, 1.005–1.042; $p = 0.01$).

CONCLUSION: Time to early resuscitative intervention is associated with morality in trauma patients with hemorrhagic shock. Bleeding patients need resuscitation initiated early, whether at the trauma center in systems with short prehospital times or in the field when prehospital time is prolonged. (*J Trauma Acute Care Surg.* 2023;94: 504–512. Copyright © 2023 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level III.

KEY WORDS: Emergency medical services; transfusion; outcome; blood; tranexamic acid.

Hemorrhage is the leading cause of preventable death in civilian and military trauma.[1,2] The science of resuscitation has made great strides with the advent of damage-control resuscitation with emphasis on balanced early blood product resuscitation, minimizing crystalloid, treatment of trauma induced coagulopathy, and early hemorrhage control. Traditionally, this management was only available to bleeding patients after arrival to the trauma center. However, time is critical in the hemorrhaging patient. Deaths from exsanguination occur within a few hours of injury, one third of which occur in the prehospital environment.[3]

Several studies support this and suggest blood product transfusion and adjuncts such as tranexamic acid (TXA) administered as early as possible in the prehospital setting improve survival.[4–11] The Prehospital Air Medical Plasma (PAMPer) trial demonstrated a nearly 10% absolute risk reduction in 30-day mortality for patients receiving prehospital plasma resuscitation compared with standard care.[11] However, the Control of Major Bleeding after Trauma (COMBAT) trial showed no difference in 28-day mortality for patients receiving prehospital plasma compared with crystalloid resuscitation.[12] Most interestingly, a combined analysis of these two trials showed that the mortality benefit for prehospital plasma was present only when prehospital transport times were greater than 20 minutes.[13]

From these data, it appears that early administration of plasma for hemorrhagic shock is the key factor driving the survival benefit for these patients. Furthermore, nearly all data supporting TXA in hemorrhagic shock after trauma show that earlier administration is associated with improved outcomes, particularly when given within the first hour from injury.[6,9,10] Taken together, access to early resuscitation techniques, whether at the trauma center with short transport times or in the field when prehospital times are long, is critical to improved outcomes in hemorrhagic shock patients. However, a close evaluation of the time from injury to receipt of such interventions has not been studied.

Our objective was to evaluate whether the time to availability of resuscitative interventions is associated with mortality among injured patients at risk for hemorrhagic shock. We hypothesize that increasing time to availability of packed red blood cells (pRBCs), plasma, and/or TXA will be associated with increased mortality.

PATIENTS AND METHODS

Study Design and Population

We conducted a combined secondary analysis of the PAMPer and Study of Tranexamic Acid during Air and ground Medical Prehospital transport (STAAMP) trials. The details of both trials have been published previously.[6,11,14,15] The PAMPer trial was a pragmatic multicenter cluster-randomized trial that enrolled patients at risk for hemorrhagic shock during air medical transport.

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From the Division of Trauma and General Surgery, Department of Surgery (A.-P.D., J.B.B.), and Department of Emergency Medicine (F.X.G.), University of Pittsburgh, Pittsburgh, Pennsylvania; Department of Surgery (B.J.D.), University of Tennessee Health Science Center, Knoxville, Tennessee; Department of Surgery (R.S.M.), John Peter Smith Health Network, Fort Worth, Texas; Department of Surgery (B.G.H.), University of Louisville, Louisville, Kentucky;Department of Surgery (J.A.C.), MetroHealth Medical Center/Case Western Reserve University, Cleveland, Ohio; Department of Surgery (H.A.P.), Louisiana State University Health Sciences Center—New Orleans, New Orleans, Louisiana; Department of Surgery (B.J.E.), University of Texas Health San Antonio, San Antonio, Texas; Department of Surgery (B.J., G.A.V.), University of Arizona, Tucson, Arizona; Department of Surgery (R.N.), University of Utah, Salt Lake City, Utah; Division of Trauma and General Surgery, Department of Surgery (J.L.S.), University of Pittsburgh, Pittsburgh, Pennsylvania.

This study was presented at the American Association for the Surgery of Trauma's 81st Annual Meeting, September 21–24, 2022, in Chicago, Illinois.

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Address for correspondence: Joshua B. Brown, MD, MSc, Department of Surgery, Division of Trauma and General Surgery, University of Pittsburgh Medical Center, PUH F1266.2, 200 Lothrop St, Pittsburgh, PA 15213; email: brownjb@upmc.edu.

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The intervention was randomized at the level of the air medical base, and patients received initial resuscitation with 2 U of thawed plasma or standard of care. Standard of care resuscitation included pRBCs availability at 13 of 27 participating air medical bases. Inclusion criteria were patients with systolic blood pressure (SBP) of 70 to 90 mm Hg plus heart rate (HR) of >108 beats per minute, or isolated severe hypotension with SBP of <70 mm Hg at any time before arrival at the trauma center.

The STAAMP trial was a pragmatic multicenter double-blind placebo-controlled trial that randomized patients at risk for hemorrhagic shock in the prehospital environment to receive a 1-g TXA bolus or placebo. Patients receiving TXA in the field were further randomized to three in-hospital TXA dosing regimens. Standard care for these patients also included pRBCs availability at 12 of 24 participating emergency medical services (EMS) sites. Inclusion criteria were patients with at least one episode of SBP of <90 mm Hg or HR of >110 beats per minute within 2 hours of injury.

We focused on the early timing of available resuscitative interventions after injury and therefore excluded patients who underwent interfacility transfer to the trauma center because timing and resuscitation data at the referring hospitals was unknown.

Missing Data

The proportion of missing data for analysis variables was <5% for all variables, and given this minimal degree of missingness, we elected not to use imputation methods. We also assessed the distribution of missing data across the trials and did not find substantial differences to suggest systematic bias due to missing data by trial.

Time to Early Resuscitative Intervention

For this study, we defined a time interval for each patient, termed the time to early resuscitative intervention (TERI). This time interval started at the time of EMS arrival for each patient and ended with the start of infusion of a resuscitation intervention. We defined resuscitation interventions as administration of pRBCs, plasma, and/or TXA. To ensure that we captured resuscitative interventions clinically relevant to hemorrhagic shock, we included administration of pRBCs, plasma, and/or TXA in the prehospital setting or within the first 90 minutes (median in-hospital emergency department transfusion time) of arrival at the trauma center. For patients not receiving any early resuscitative intervention in the time-frame defined previously, the TERI ended at the time of trauma center arrival. This time point was selected, as it represented the earliest possible access to a resuscitative intervention for that patient. Figure 1 graphically illustrates the TERI calculation for example patients receiving a prehospital resuscitative intervention, an in-hospital resuscitative intervention, and for those not receiving a resuscitative intervention within 90 minutes of trauma center arrival.

Propensity Score Matching

We recognize that patients who did not receive an early resuscitative intervention in the defined time frame may have not had an indication for such and likely do not represent the hemorrhagic shock population of interest for the study. Thus, we performed propensity score matching based on the probability of receiving an early resuscitative intervention (prehospital or within 90 minutes of trauma center arrival) to address this selection bias. The propensity score was estimated using age, mechanism of injury, prehospital SBP and HR, prehospital time, prehospital crystalloid volume, prehospital intubation, and trial of enrollment. A 1:1 nearest neighbor matching algorithm was used with replacement and a caliper of 0.05. Replacement allows a control patient to be matched to more than one treated patient, resulting in fewer unique control patients than number of matched pairs. This was done to minimize the difference in propensity score between matched treated and control patients and less bias in our treatment effect estimates while matching most treated patients, given the number of control

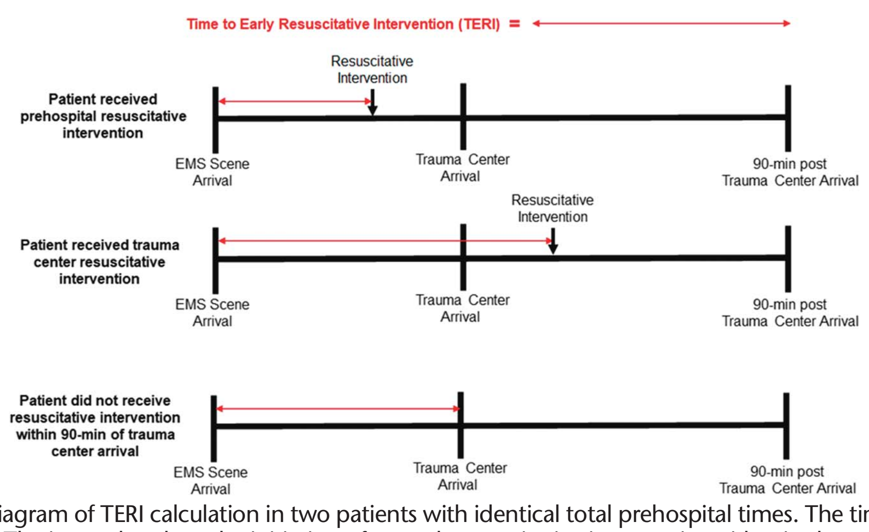

Figure 1. Conceptual diagram of TERI calculation in two patients with identical total prehospital times. The time interval begins at the arrival of EMS clinicians. The interval ends at the initiation of an early resuscitative intervention either in the prehospital setting (top scenario) or within 90-minutes of trauma center arrival (middle scenario). For patients not receiving an early resuscitative intervention (bottom scenario), the time interval ends at trauma center arrival as the first potential opportunity to receive an early resuscitative intervention. Note that this group of patients was only included if matched based on propensity score to receive an early resuscitative intervention.

patients with low propensity scores that did not overlap any treated patients.[16] Absolute standardized differences were used to assess the balance of patient characteristics between treatment groups. The standardized difference represents the difference between groups divided by the pooled SD, making it insensitive to large samples sizes, and an absolute standardized difference greater than 0.1 represents significant nonoverlap in the distributions of a given variable between groups.[17]

Statistical Analysis

Our primary outcome was 30-day mortality. Given the potential for in-hospital factors to obscure the impact of TERI on 30-day mortality, we also assessed a secondary outcome of 24-hour mortality, more proximate to the exposure of interest. To ensure that 24-hour mortality did not solely drive any association of TERI with 30-day mortality, we repeated all 30-day mortality models excluding patients who died within 24 hours. We constructed a mixed-effects logistic regression model to determine the association between mortality and TERI, analyzed as a continuous variable. Fractional polynomial analysis was performed using first- and second-degree fractional polynomials for the TERI to determine the optimal form and account for the potential of nonlinear effects. A two-level nested random effect was incorporated to account for the paired design after matching, which were then clustered within trauma centers. The postmatching models were adjusted for Injury Severity Score, admission SBR and HR, in-hospital 24-hour crystalloid, 24-hour pRBCs and plasma volumes, and head/chest/abdomen Abbreviated Injury Scale scores, and the type/setting of early resuscitative intervention received to account for residual imbalance of variables not included in the propensity score. We also included propensity score variables not achieving good balance, if any, in the adjusted models after matching. Given our use of replacement, weighted models were used, with treated patients assigned a weight of 1 and control patients assigned a weight equal to the reciprocal of the number of times the unique control was matched to a different treated patient.[18]

Data analysis was conducted using Stata v17MP (StataCorp, College Station, TX). Continuous data are presented as median (interquartile range). Continuous data were compared using Wilcoxon rank-sum tests, and categorical data were compared using χ^2. Adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) were obtained from regression models. For the treatment effect of TERI, aORs are expressed as the odds per 1-minute increase in TERI. Model discrimination was assessed using the *c* statistic, and calibration was graphically assessed using observed versus predicted calibration graphs. Variance inflation factors were used to assess for covariate collinearity, and covariates with a variance inflation factor of >10 were removed from final models. Abbreviated Injury Scale scores were explored as continuous and binary (<3 vs. ≥3) variables and models selected based on minimum Akaike and Bayesian Information Criteria. A two-tailed p value of ≤0.05 was considered statistically significant. Our institutional review board approved this study. Reporting of this study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/C826).

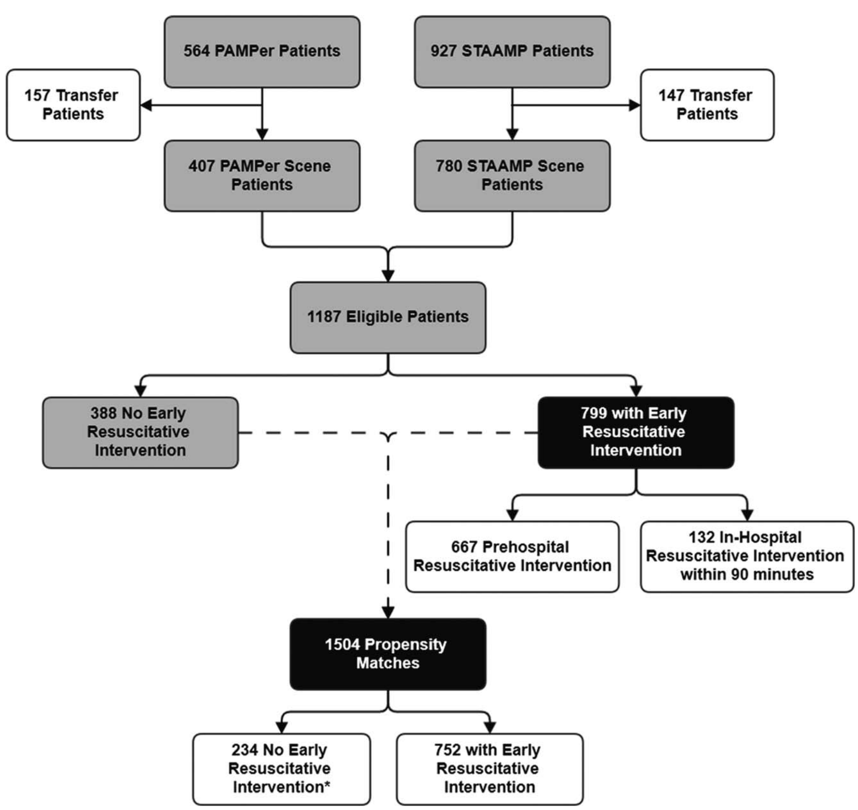

Figure 2. Patient flow diagram for enrollment from the PAMPer and STAAMP trials.

Sensitivity Analyses

We performed several sensitivity analyses to assess the robustness of our results. First, we examined the subgroup only receiving an early resuscitative intervention (prehospital or within 90 minutes of trauma center arrival), as patients not receiving an early resuscitative intervention may still be substantively different, despite propensity score matching. We constructed similar mixed-effects logistic regression model to determine the association between mortality and TERI. Because this analysis was not propensity matched, the models were adjusted for age, Injury Severity Score, prehospital and admission SBR and HR, mechanism of injury, prehospital crystalloid volume, prehospital intubation, prehospital time, in-hospital 24-hour crystalloid, 24-hour pRBCs and plasma volumes, head/chest/abdomen Abbreviated Injury Scale scores, and the type/setting of early resuscitative intervention received. A two-level nested random effect was incorporated to account for clustering by EMS site, which were then clustered within trauma centers.

Second, although the TERI includes three different resuscitative interventions to maximize power, we recognize that different components may not have equivalent effects on mortality. Thus, we independently analyzed patients receiving each of the three resuscitative interventions (pRBCs, plasma, TXA) using similar models described previously among patients receiving an early resuscitative intervention.

Interaction Testing

We tested two interactions to evaluate whether the effect of TERI on mortality was modified by other variables. First, because prehospital time has been shown to be associated with mortality in severely injured patients and hemorrhagic shock is time sensitive,[19,20] we tested the interaction between TERI and total prehospital time among patients receiving an early resuscitative intervention.

Second, because some of the resuscitative interventions were previously shown to have benefits in patients with traumatic brain injury (TBI),[9,21] we also tested the interaction between TERI and TBI. Models with significant interactions were stratified across the interaction variable. For prehospital time, we planned stratification of high/low time based on the median value. All interaction testing was performed among patients who received an early resuscitative intervention.

RESULTS

A total of 1,187 eligible patients were included; 799 (56%) received an early resuscitative intervention (Fig. 2). Propensity score matching resulted in 752 (94.1%) of treatment patients (receiving early resuscitative intervention) matched to 234 unique control patients, giving 1,504 matched pairs because of the matching with replacement design (Table 1). There was good balance among propensity score variables, with all absolute standardized differences of <0.1 (Supplemental Digital Content, Supplementary Fig. 1, http://links.lww.com/TA/C827). The distribution of TERI in minutes is shown in Supplemental Digital Content (Supplementary Fig. 2, http://links.lww.com/TA/C827). When evaluating the possibility of significant nonlinear effects of TERI on mortality using fractional polynomials, model comparison likelihood ratio testing did not reject a linear TERI model based on model deviance from a second-order fractional polynomial model ($p = 0.31$). As such, we proceeded with outcome models using TERI as a linear continuous variable. Model diagnostics are reported in Supplemental Digital Content (Supplementary

TABLE 1. Study Population Characteristics After Propensity Score Matching

	No Early Resuscitative Intervention	Early Resuscitative Intervention	Absolute Standardized Difference
N	752*	752	—
Age, median (IQR), y	38 (26–57)	40 (27–56)	0.036
Sex, n (%)			0.150
Male	584 (77.7%)	535 (71.1%)	
Female	168 (22.3%)	217 (28.9%)	
Mechanism (% blunt)	655 (87.1%)	651 (86.6%)	0.016
Prehospital time, median (IQR)	39 (32–49)	39 (30–49)	0.009
TERI, median (IQR)	39 (32–49)	22 (14–35)	0.751
Prehospital SBP, median (IQR)	86 (69.5–128)	85 (69–126.5)	0.025
Prehospital HR, median (IQR)	116.5 (109.5–128)	118 (110–128)	0.065
Prehospital crystalloid, median (IQR)	500 (0–1,050)	500 (0–1,100)	0.001
Prehospital intubation	328 (43.6%)	314 (41.8%)	0.038
Admission SBP, median (IQR)	118 (100–140)	110 (87–132)	0.288
Admission HR, median (IQR)	106 (92–121)	107 (91–121)	0.053
ISS, median (IQR)	17 (9–24)	17 (9–29)	0.271
Head AIS, median (IQR)	2 (0–3)	1 (0–3)	0.080
pRBCs 24 h, median (IQR)	0 (0–0)	2 (0–6)	0.686
Plasma 24 h, median (IQR)	0 (0–0)	0 (0–2)	0.456
Crystalloid 24 h, median (IQR)	3,047 (1,453–4,725)	4,060 (1,968–6,610)	0.318
24-h Mortality, n (%)	83 (11.0%)	92 (12.2%)	0.037
30-d Mortality, n (%)	163 (21.7%)	146 (19.4%)	0.056

*A total of 752 matches among 234 unique patients because of replacement matching technique that allows control patients to be matched more than once to different treatment patients.
GCS, Glasgow Coma Scale; IQR, interquartile range; ISS, Injury Severity Score; RR, respiratory rate.

TABLE 2. Odds Ratios and 95% CIs for 30-Day Mortality From Multivariable Multilevel Logistic Regression in Propensity-Matched Cohort

	Odds Ratio	95% CI	*p*
TERI per 1-min increase	1.020	1.006–1.033	0.004
ISS	1.052	1.021–1.084	<0.001
24-h Crystalloid volume	1.000	1.000–1.000	<0.001
Admission SBP	0.981	0.974–0.987	0.000
Admission HR	0.989	0.982–0.997	0.006
24-h Plasma volume	0.960	0.881–1.046	0.351
24-h pRBCs volume	1.168	1.091–1.249	<0.001
Head AIS	1.295	1.091–1.537	<0.001
Chest AIS	1.229	1.097–1.376	0.003
Abdomen AIS	1.130	1.007–1.269	0.038
Lower extremity AIS	0.896	0.787–1.019	0.094
Resuscitative intervention setting			
No TERI	1.000		
Prehospital	0.365	0.227–0.576	<0.001
In-hospital	0.419	0.192–0.915	0.002

95% CI, 95% confidence interval; ISS, Injury Severity Score; OR, odds ratio.

Results, Supplementary Fig. 3, and Supplementary Fig. 4, http://links.lww.com/TA/C827).

In the propensity-matched cohort, every 1-minute increase in TERI was associated with a 2% increase in the odds of 30-day mortality (aOR, 1.020; 95% CI, 1.006–1.033; $p < 0.01$; Table 2) and a 1.5% increase in odds of 24-hour mortality (aOR, 1.015; 95% CI, 1.001–1.029; $p = 0.04$; Table 3). Similar results for the association between TERI and odds of 30-day mortality were seen when excluding deaths within 24 hours (aOR, 1.016; 95% CI, 1.004–1.027; $p = 0.01$).

When evaluating only the 799 patients who underwent an early resuscitative intervention, the distribution of TERI in minutes is shown in Supplemental Digital Content (Supplementary Fig. 5, http://links.lww.com/TA/C827). In this group, every 1-minute increase in TERI was associated with a 2% increase in the odds of 30-day mortality (aOR, 1.021; 95% CI, 1.005–1.038; $p = 0.01$; Supplemental Digital Content, Supplementary Table 1, http://links.lww.com/TA/C827) and 24-hour mortality (aOR, 1.023; 95% CI, 1.005–1.042; $p = 0.01$; Supplemental Digital Content, Supplementary Table 2, http://links.lww.com/TA/C827). Again, similar results for the association between TERI and odds of 30-day mortality were seen when excluding deaths within 24 hours (aOR, 1.019; 95% CI, 1.007–1.032; $p < 0.01$). In sensitivity analysis of individual resuscitative intervention components among patients receiving an early resuscitative intervention, increasing TERI remained associated with increased odds of 30-day and 24-hour mortality (Table 4).

Prehospital time did not significantly modify the effect of TERI on 30-day mortality as observed in our interaction testing ($p = 0.73$). In the 30-day mortality model, total prehospital time was not significantly associated with mortality (aOR, 0.988; 95% CI, 0.958–1.019; $p = 0.44$), yet TERI remained associated with 30-day mortality (aOR, 1.033; 95% CI, 1.002–1.067; $p = 0.04$). Similarly, the interaction between total prehospital time and 24-hour mortality was not significant ($p = 0.20$); however, increasing total prehospital was associated with an increase in the odds of 24-hour mortality (aOR, 1.046; 95% CI, 1.001–1.093, $p = 0.04$), as was TERI (aOR, 1.055; 95% CI, 1.001–1.102; $p = 0.02$). The interaction between TERI and severe TBI was not significant for 30-day ($p = 0.63$) or 24-hour mortality ($p = 0.78$). Both increasing TERI and severe TBI were associated with increased 30-day and 24-hour mortality ($p < 0.05$).

TABLE 3. Odds Ratios and 95% Confidence Intervals for 24-Hour Mortality From Multivariable Multilevel Logistic Regression in Propensity-Matched Cohort

	Odds Ratio	95% CI	*p*
TERI per 1-min increase	1.015	1.001–1.029	0.039
ISS	1.058	1.030–1.086	<0.001
24-h Crystalloid volume	0.999	0.999–1.000	<0.001
Admission SBP	0.967	0.9547–0.976	<0.001
Admission HR	0.991	0.981–1.001	0.068
24-h Plasma volume	0.926	0.836–1.026	0.142
24-h pRBCs volume	1.242	1.142–1.350	<0.001
Head AIS	1.307	1.017–1.680	0.036
Chest AIS	1.258	1.083–1.460	0.003
Abdomen AIS	1.125	0.968–1.307	0.124
Lower extremity AIS	0.775	0.651–0.924	0.005
Resuscitative intervention setting			
No TERI	1.000		
Prehospital	0.423	0.217–0.836	0.028
In-hospital	0.588	0.197–1.753	0.341

DISCUSSION

We demonstrate that TERI is associated with both 30-day and 24-hour mortality among patients at risk for hemorrhagic shock. Total prehospital time did not modify the effect of TERI on 30-day or 24-hour mortality, suggesting that these are distinct factors to be considered independently in the prehospital care of these patients. Both total prehospital time and TERI were associated with 24-hour mortality, yet TERI alone was associated with 30-day mortality, implying that TERI may be more important than total prehospital time for this population of injured patients. Severe TBI did not modify the effect of TERI on mortality,

TABLE 4. Association of TERI on Mortality Among Individual Resuscitative Intervention Components Among Patients Receiving an Early Resuscitative Intervention

	aOR*	95% CI	*p*
pRBCs			
30-d Mortality	1.015	1.001–1.029	0.04
24-h Mortality	1.047	1.001–1.086	0.02
Plasma			
30-d Mortality	1.021	1.001–1.042	0.04
24-h Mortality	1.044	1.007–1.083	0.02
TXA**			
30-d Mortality	1.042	1.003–1.083	0.04
24-h Mortality	1.073	1.013–1.137	0.02

*Adjusted odd per 1-minute increase in TERI.
**Only available as prehospital intervention.

indicating that TERI is an important factor for 24-hour and 30-day mortality in patients at risk for hemorrhage, both with and without TBI. A similar effect of TERI on mortality was observed for the individual components of early resuscitative interventions (pRBCs, plasma, TXA), suggesting that the effect observed is not driven by a singular resuscitative component.

Physiologic perturbations and resultant trauma-induced coagulopathy occur within minutes of injury for patients at risk of hemorrhagic shock.[22,23] Left unchecked, this sets the patient on a very early and ominous trajectory. One third of exsanguinating deaths after trauma occur in the prehospital setting, underscoring the need for early resuscitation initiation especially in rural settings.[3] Given this, we are increasingly seeing the tenants of damage-control necessarily pushed into the prehospital phase of trauma care. Of note, we found that shorter times to early resuscitative intervention were associated with improved 30-day mortality even when excluding 24-hour deaths. Thus, the early introduction of blood products and/or TXA may mitigate the early immune and inflammatory effects of hemorrhagic shock including endotheliopathy that may lead to longer term improved outcomes.[24–27]

Indirect evidence of the benefits of earlier resuscitation in hemorrhagic shock after injury exists. In a secondary analysis of a randomized trial, reducing the time to massive transfusion protocol activation at the trauma center was associated with lower 24-hour and 30-day mortality, with a 5% increase for every 1-minute delay in the arrival of the first cooler of blood products.[28] Early resuscitation initiation in the form of prehospital blood product transfusion has a growing body of evidence suggesting outcome benefits. Initially shown in military settings,[29,30] civilian data corroborated a reduction in mortality at 24 hours and 30 days as well as improvements in coagulation profiles.[4,5,7] The PAMPer trial demonstrated a 10% absolute reduction in 30-day mortality for patients administered thawed plasma as compared with the standard care arm for patients with evidence of hemorrhagic shock.[11] Importantly, separation in the survival curve occurred as early as 3 hours from injury in favor of plasma, underscoring the importance of early resuscitation. In a secondary analysis of PAMPer, patients receiving combined prehospital pRBCs and plasma experienced the greatest mortality benefit after severe injury.[7]

Tranexamic acid inhibits fibrinolysis, and studies to date that demonstrate a benefit all indicate a time dependence with early administration showing improved survival.[6,9,10] Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 demonstrated a reduction in mortality from exsanguination with TXA administration within 3 hours, and the greatest effect was observed for those with receipt within 1 hour of injury.[10] Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-3 evaluated TBI patients and also showed improved mortality with early TXA administration.[31] Rowell and colleagues[9] demonstrated that prehospital TXA reduced mortality among patients with intracranial hemorrhage. Data contributing to the present study from the STAAMP trial demonstrated a mortality benefit for those who received TXA ≤1 hour, a 3-g total dose, and those with severe hypotension.[6] This benefit of early TXA intervention was corroborated by a secondary analysis of this randomized controlled trial for patients at greatest risk of hemorrhage.[32] Another analysis of STAAMP data reported potential synergy of pRBCs and TXA administration associated with a reduction in mortality.[33]

The importance of time to resuscitation in these patients is particularly reinforced by a post hoc analysis of PAMPer and COMBAT by Pusateri et al.[13] They sought to examine the disparate outcomes between these trials with seemingly similar interventions (prehospital plasma first resuscitation), with PAMPer showing a mortality benefit, while COMBAT showing to effect on mortality. By combining trial participants, they first found that the survival benefit of plasma was among patients with transport times of >20 minutes but not patients with transport times of ≤20 minutes. They then analyzed plasma and standard care patients separately, comparing mortality stratified by a 20-minute transport time. Transport time of >20 minutes was associated with increased mortality in the standard care patients, but no difference was observed in those who received plasma. This suggests that prehospital plasma may mitigate the increased mortality associated with prolonged prehospital time. Considered with our current results, we posit that early resuscitation is critical either at the trauma center with short prehospital times or in the field with prolonged prehospital times.

In the present study, we quantify the association between the TERI and mortality and highlight the impact of delays in advanced resuscitation that occur on the order of minutes for patients with hemorrhagic shock. The practical implications of our findings are dependent on individual EMS and trauma system resources. To decrease the time to initiate resuscitative interventions, storing blood products and resuscitation adjuncts in the emergency department are a common strategy at many trauma centers, as well as well-defined massive transfusion protocols with documented activation criteria.[28] In addition, as noted previously, making blood products and TXA available in the prehospital setting is a growing strategy for EMS systems. Blood products are not usually available from ground EMS agencies, although TXA is increasingly available. Urban systems with short transport times should minimize out of hospital time, rather than push prehospital resuscitative interventions, which may actually prolong prehospital time and come at the expense of fundamental interventions such as hemorrhage control. Our data should not be misconstrued; definitive hemorrhage control remains imperative, and adding resuscitative interventions that prolong definitive management is not warranted. However, in rural areas, long transport times are inevitable, and waiting to initiate resuscitation with blood products or adjuncts is not ideal for bleeding patients. These systems more frequently use air medical transport for severely injured patients, which often have greater early resuscitation capabilities.

Emergency medical services clinicians should consider initiating these resuscitative interventions when transport times are long or when there are delays in prehospital time such as with prolonged extrication. They should also consider activating air medical transport to ensure earlier initiation of resuscitative interventions for the patient in these circumstances. At a system level, support should focus on increased availability of blood products and TXA in areas with prolonged transport times, as robust logistics are necessary for a successful prehospital blood product program.[34] Finally, the TERI represents an important conceptual construct for future research and a potential quality metric to consider in EMS and trauma systems for patients with hemorrhage.

We have important limitations to acknowledge. First, our data were derived from the combination of two trials, each with different hypotheses from each other and the present study. In addition, the present results may not be generalizable to all severely injured patients given the predominance of blunt injuries and relatively long prehospital times in our study. However, we believe that the transport times are important to consider in the treatment algorithms—delayed times should necessitate early resuscitative interventions, while, with anticipated short prehospital times, the focus should be on immediate transport to the trauma center. We do not have time of injury; thus, differential time before EMS activation and arrival may impact our results. Our propensity-matched analysis cannot control for unobserved factors, and thus, residual unobserved confounders may still impact those who did and did not receive an early resuscitative intervention differently. We do not have in-hospital TXA time; however, all patients getting in-hospital TXA would likely be getting at least one transfusion, which would be captured. Furthermore, TXA is unlikely to be the first advanced resuscitation intervention for bleeding patients in-hospital given current damage-control resuscitation strategies. Finally, we explored identifying a threshold of times where availability of early resuscitative interventions made a difference in mortality; however, small sample sizes across the distribution of the early time period we focused on precluded us from drawing meaningful conclusions. This is an important next step for larger studies to investigate.

CONCLUSION

Increasing TERI is associated with 24-hour and 30-day mortality in patients at risk for hemorrhagic shock after injury. Time to early resuscitative intervention may be more important in this population than total prehospital time for long-term outcomes. Taken together, our results suggest that TERI is a crucial interval and bleeding patients need resuscitation initiated as early as possible, whether at the trauma center in systems with short prehospital transport times or in the field when prehospital time is prolonged. Emergency medical services clinicians should consider initiating available resuscitative interventions in the field when arrival at the trauma center may be delayed for patients with suspected hemorrhagic shock. Future efforts to evaluate TERI in the context of other lifesaving interventions available in the field are needed. Individual trauma and EMS systems should weigh the costs and logistics with the potential benefit for deployment of emergency department and prehospital blood products and TXA to reduce the TERI, particularly in rural communities to optimize outcomes for patients in hemorrhagic shock after injury.

AUTHORSHIP

A.-P.D. and J.B.B. participated in the literature search. A.-P.D. and J.B.B. participated in the study design. A.-P.D. and J.B.B. participated in the data collection. A.-P.D. and J.B.B. participated in the data analysis. All authors participated in data interpretation. A.-P.D. and J.B.B. participated in the writing of the manuscript. All authors participated in the critical revision of the manuscript for important intellectual content.

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DISCLOSURE

The authors declare no conflicts of interest.

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