HHS Public Access

Author manuscript

J Trauma Acute Care Surg. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

J Trauma Acute Care Surg. 2017 July ; 83(1): 19–24. doi:10.1097/TA.0000000000001531.

EVERY MINUTE COUNTS: TIME TO DELIVERY OF INITIAL MASSIVE TRANSFUSION COOLER AND ITS IMPACT ON MORTALITY

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Abstract

BACKGROUND—ACS-TQIP Best Practices recommends initial massive transfusion (MT) cooler delivery within 15 minutes of protocol activation, with a goal of 10 minutes. The current study sought to examine the impact of timing of first cooler delivery on patient outcomes.

METHODS—Patients predicted to receive MT at 12 level-1 trauma centers were randomized to two separate transfusion ratios as described in the PROPPR trial. ABC score or clinician gestalt

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The authors disclose no conflicts of interest.

To be presented in the Raymond H. Alexander, MD Resident Paper Competition of the 2017 EAST Annual Scientific Assembly.

Author Contribution: J.B.H., T.O.K., K.I., E.B., and B.A.C. contributed to study conception and design. J.B.H., T.O.K., K.I., E.B., L.A.V., and B.A.C. contributed to acquisition of data. D.E.M., L.A.V., E.E.F., and B.A.C. contributed to analysis and interpretation of data. DEM and BAC contributed to drafting the manuscript. D.E.M., J.B.H., T.O.K., K.I., E.B., E.E.F., and B.A.C. contributed to critical revision.

prediction of MT was used to randomize patients and call for initial study cooler. In this planned sub-analysis, the time to MT protocol activation and time to delivery of the initial cooler were evaluated. The impact of these times on mortality and time to hemostasis were examined using both Wilcoxon rank sum and linear and logistic regression.

RESULTS—Among 680 patients, the median time from patient arrival to MT protocol activation was 9 minutes with a median time from MT activation call to delivery of first cooler of 8 minutes. An increase in both time to MT activation and time to arrival of first cooler were associated with prolonged time to achieving hemostasis (coef 1.09, p=0.001 and coef. 1.16, p < 0.001, respectively). Increased time to MT activation and time to arrival of first cooler were associated with increased mortality (OR 1.02, p=0.009 and OR 1.02, p = 0.012, respectively). Controlling for injury severity, physiology, resuscitation intensity, and treatment arm (1:1:1 vs. 1:1:2), increased time to arrival of first cooler was associated with an increased mortality at 24-hours (OR 1.05, p = 0.035) and 30-days (OR 1.05, p = 0.016).

CONCLUSIONS—Delays in MT protocol activation and delays in initial cooler arrival were associated with prolonged time to achieve hemostasis and an increase in mortality. Independent of products ratios, every minute from time of MT protocol activation to time of initial cooler arrival increases odds of mortality by 5%.

LEVEL OF EVIDENCE—Level II, Prognostic

Keywords

massive transfusion; protocol; activation; blood product delivery

BACKGROUND

Damage control resuscitation (DCR) has dramatically changed the care of the bleeding patient. Much of the focus of recent research has been on optimizing the ratio of blood product administration and minimizing the use of crystalloid.[1] However, it is the early and timely delivery of higher balanced ratios of plasma and platelets that allows for the achievement of the ultimate goal of DCR: the rapid restoration of circulating red cells, plasma proteins and platelets, while definitive control of bleeding is achieved. The protocolization of massive transfusion (MT) was developed with DCR and has been associated with decreased mortality, decreased multi-organ failure, and an overall decrease in the amount of product transfused.[2] In part, this is because MT protocols (MTPs) are associated with a decrease in time to the availability of the first blood products.[3]

The specific timing of the delivery of these blood products, however, has not been examined thoroughly. A 2013 single-center retrospective study evaluated this variable indirectly by comparing 30-day mortality in massive transfusion patients before and after instituting an initiative to maintain a small but frequently resupplied stock of thawed plasma to the emergency department (thereby decreasing the time necessary to procure and deliver it).[4] That study found that moving thawed plasma to the emergency department (ED) resulted in cutting the time to plasma administration in half and decreased the odds of mortality at 30 days by approximately 60%. Of note, the time to first red blood cell transfusion remained the same. This suggests that timing of the administration of other blood products (plasma,

platelets) may play as crucial a role as the eventual ratio of products or limiting of crystalloid volumes.

The recent multicenter, prospective, randomized controlled trial from the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) study group sought to evaluate mortality with respect to the ratio of blood products given in massive transfusion.[5] The study found that there was a significant decrease in deaths due to bleeding in the 1:1:1 group, but the significance of the effect was not observed in overall mortality at 30 days. One possible explanation is that the PROPPR 1:1:2 group outperformed all previously reported data, with previous studies noting mortality rates in excess of 30% when a blood product ratio of 1:1:2 was utilized.[6,7,8] In PROPPR, however, the mortality rate in the 1:1:2 group was roughly 20%. It has been suggested that this dramatic improvement in mortality in PROPPR compared to other published research was the result of the rapid and balanced delivery of blood products (*i.e.,* alternating red blood cells, plasma, and platelets as opposed to previous descriptions of transfusing six units of red blood cells followed by six units of plasma, then platelets).[9] In this planned sub-analysis of the PROPPR dataset, we hypothesized that the timely delivery of blood products to the exsanguinating patient, regardless of ratio, would result in decreased mortality.

METHODS

Study Design

The PROPPR study was a pragmatic phase III, multicenter, randomized trial that compared the effectiveness of two resuscitation strategies for bleeding patients. The study began August 3, 2012 and concluded enrollment December 2, 2013. Patients were randomized to receive a ratio of 1:1:1 or 1:1:2 of platelets: plasma: red blood cells during the acute phase of resuscitation.[10] The study was approved by the US Food and Drug Administration (FDA) (Investigational New Drug No. 14929), Health Canada, NHLBI and the Department of Defense, as well as each individual site's institutional review boards. The PROPPR study used exception from informed consent (21 CFR 50.24), including community consultation with delayed patient or legally authorized representative content.

This represents a sub-analysis of the original PROPPR study, investigating the impact of time to activation of local massive transfusion protocols (MTP) and then time from activation to delivery of the first MTP cooler. These time points were specifically included in the PROPPR protocol for collection and later analysis and were audited throughout the study to evaluate compliance with study requirements. Prior to starting the study, and as part of site training and verification, each site was evaluated for the ability of its blood bank to randomize, prepare, and deliver the first MTP cooler to the bedside within ten minutes, as well as to prepare and deliver subsequent coolers on-demand.[11] As such, time of arrival, time to MTP activation and time to arrival of initial and each subsequent cooler were collected as time points of interest. The content of each MTP cooler was identical between centers, varying only by randomization group (*i.e.*, 1:1:1 vs. 1:1:2). Additionally, the sequence of transfusion was also identical between centers, so as to ensure a rapid and *balanced* transfusion strategy. Finally, as part of an ongoing quality improvement initiative, the study protocol was evaluated and reevaluated at each site and then refined as necessary

to function seamlessly within a center's specific milieu and to ensure rigorous protocol fidelity.[12]

Study Population

The PROPPR study was conducted at 12 North American level-1 trauma centers, screening those patients who were severely injured and who met local criteria for highest-level trauma activation. To meet the study's intended focus on those injured patients who were bleeding at the time of arrival, research team personnel were notified simultaneously with trauma team activation and were present prior to patient arrival. Given the aim of rapidly enrolling those patients with severe hemorrhage, inclusion criteria were as follows: (1) highest-level trauma team activation, (2) estimated age of 15 years or older or weight of 50 kg or greater if age unknown, (3) patient received directly from the injury scene, (4) having received at least one unit of any blood component transfused prior to hospital arrival or within 1 hour of admission and (5) predicted by an Assessment of Blood Consumption (ABC) score of 2 or greater or by physician judgment of the need for a massive transfusion (defined as ≥10 U of RBCs within 24 hours).[13] Patients were excluded if they: (1) did not receive at least one unit of a blood component within one hour of arrival to the hospital or during prehospital transport, (2) were expected to die within one hour of ED arrival from a devastating injury, or (3) improved during initial stabilization and did not require further transfusion. A total of 680 patients were enrolled in the original PROPPR study of blood product ratios, and all of those patients were included in this planned sub-analysis.

Outcomes and Definitions

The primary outcomes of interest in this sub-analysis were 24-hour and 30-day mortality. Secondary outcomes included time to death, time to hemostasis, and 24-hour blood product use. A clinician blinded to group assignment and external to the trial site adjudicated each death. Time to death was measured in both minutes and hours. Anatomic hemostasis in the operating room was defined as an objective assessment by the surgeon indicating that bleeding within the surgical field was controlled and no further hemostatic interventions were anticipated. This was also captured and recorded in minutes and hours. Blood product use was noted in units.

To best describe the aggressiveness of transfusion and resuscitation administered by the trauma team, independent of specific product availability and site, we utilized Resuscitation Intensity as a surrogate measurement.[14] Resuscitation Intensity is defined as the total amount of product given in the first 30 minutes after patient arrival. Each one liter of crystalloid, one 500 mL bag/bottle of colloid, one unit of red blood cells, one unit of plasma, and one six-pack (or one apheresis) platelet (= 1 unit) were defined as one Resuscitation Intensity unit. Resuscitation with four or more units of any fluid in the first 30 minutes is significantly associated with mortality as early as six hours.

The time to MTP activation was defined as the time from patient arrival until the initial phone call made to a site's Blood Bank for activation, captured and recorded in minutes. Time to initial MTP cooler arrival was defined as time from MTP activation by phone call until cooler arrival at the patient's bedside, also captured and recorded in minutes.

Statistical Analysis

Continuous data are presented with the 25th and 75th percentile interquartile range (IQR) with comparisons between groups performed by use of the Wilcoxon rank sum (Mann-Whitney U test). Categorical data are reported as proportions and, where appropriate, tested for significance using chi-2 or Fisher exact tests. All statistical tests were 2-tailed. To evaluate the above outcomes, we carefully examined the time to MTP activation and time to delivery of the initial cooler. These were specifically chosen to investigate whether (1) early recognition of the need for MT and (2) time to the delivery of MTP products impacted outcomes, regardless of transfused ratios. Initial analysis of the impact of these times on mortality and time to hemostasis were performed using Wilcoxon rank sum. This was followed by simple (univariate) linear and logistic regression, then a multivariate regression analysis. The logistic multivariate model was created through first selecting variables *a priori* based on clinical judgment that the potential confounders may be associated with recognition of bleeding and outcomes related to bleeding and mortality. These were then entered into stepwise regression to identify statistically significant variables ($p<0.05$). While this initial model included the individual site as a variable in order to evaluate for differences between centers, this was not statistically significant and was not included in the subsequent model. This model did, however, identify anatomic severity of injury (injury severity score, ISS), physiology on arrival (weighted revised trauma score, w-RTS), resuscitation intensity (RI), and randomization group as significant. These four variables were then entered into a multiple logistic regression model, along with time to MTP activation and time to arrival of initial cooler (entered separately). All analyses were performed using STATA Statistical software (version 12.1; StataCorp, College Station, TX).

RESULTS

During the study period, 14,313 highest-level trauma activations occurred at the 12 sites, with 11,185 patients undergoing screening. Among these, 680 patients were enrolled and randomized (338 to the 1:1:1 group and 342 to the 1:1:2 group). Overall, 80% of patients were male and 64% were white, with a median age of 34 (24, 51). Mechanism of injury was blunt in 53%, with an overall median ISS of 26 (17, 41) and w-RTS of 6.81 (4.09, 7.84). For the study population, 24-hour and 30-day mortality were 14.7% and 24.1%, respectively.

Dichotomizing groups by outcome of 24-hour mortality, TABLE 1 demonstrates the differences between baseline and admission variables. Patients who died within the first 24 hours had greater anatomic injury, more disturbed arrival physiology, and had more intense resuscitation in the first 30 minutes of their arrival.

Among the 680 patients enrolled, the median time from patient arrival to MTP activation was 9 minutes (IQR 3, 20). The median time from MTP activation to delivery of the first cooler was 8 minutes (IQR 5, 11). An increase in time to MTP activation in minutes was associated with prolonged time to achieving hemostasis (coef 1.09, $p=0.001$). Similarly, increased time in minutes to receipt of first cooler was associated with longer time to achieving hemostasis (coef. 1.16, $p<0.001$). More importantly, both an increased time to MTP activation and time to receipt of first MTP cooler were also associated with increased unadjusted mortality (OR 1.02, $p=0.009$ and OR 1.02, $p=0.012$, respectively). Neither time

to MTP activation nor time to receipt of initial cooler was associated with 24-hour blood product transfusion volumes.

Controlling for injury severity, admission physiology, resuscitation intensity, and treatment arm (1:1:1 vs. 1:1:2), the time to arrival of first cooler was associated with an increased mortality at 24-hours (OR 1.05, p=0.035) and 30-days (OR 1.05, p=0.016) (TABLE 2 and TABLE 3). Controlling for these same variables in a multivariate linear model demonstrated that decreased time to receiving the initial cooler was associated with a marked reduction in time to death (coef. −271.029, p=0.023)

The above model controlling for injury severity, admission physiology, resuscitation intensity, and treatment arm (1:1:1 vs. 1:1:2) was repeated to evaluate the impact of time to MTP activation. Increased time to MTP activation showed a trend, but was not significantly associated with an increase in 24-hour (OR 1.03, p=0.154) and 30-day mortality (OR 1.04, p=0.160). As well, a linear model using these same variables demonstrated that decreased time to MTP activation was associated with a trend towards reduction in time to death, but this was not statistically significant (coef. −51.098, p=0.130).

DISCUSSION

The concept of improved outcomes with decreased time to the delivery of an intervention is well-described throughout medicine. Acute myocardial infarction patients have decreased mortality with decreased time to reperfusion.[15] As a result, hospitals are now graded and ranked based on response times and “STEMI” teams have been developed to dramatically reduce “door-to-balloon times” for such patients. Similarly, hospital stroke teams have been developed based on data demonstrating improved neurologic outcomes in ischemic stroke patients with decreased time to reperfusion; “door-to-tPA” times.”[16] ICU patients with severe sepsis and septic shock have decreased mortality with decreased time to first antibiotic administration.[17] A recent study has also demonstrated decreased mortality in traumatic brain injury (TBI) patients with multifocal hemorrhage that receive early administration of plasma.[18]

The American College of Surgeons (ACS) Trauma Quality Improvement (TQIP) guidelines for MT have recently recommended delivery of the first blood product cooler within 15 minutes of activation, and the delivery of each subsequent cooler within 10 minutes of the request.[19] Yet these recommendations were based on expert opinion and not prospectively collected data. The current study, however, found a 5% increase in the odds of mortality with every minute of delay in the administration of blood products from time of MTP activation. This suggests that even the availability of blood within 10–15 minutes may be too long for many critically injured patients. Furthermore, decreasing the time to delivery of blood products may be one of the modifiable risk factors that impacts mortality in the trauma patient.

In order to improve the timeliness of blood product delivery, several challenges must be overcome. One challenge is to decrease the time to activation of MTP by decreasing the time to physician recognition of the need for blood product administration. There are several clear

opportunities for improving this variable. One is simply physician awareness that timing of blood administration is of critical importance. Additionally, clinical adjuncts can be used to predict the need for MT. The ABC score, for example, is a rapid bedside clinical scoring system that is 75% sensitive and 86% specific for predicting the need for MT.[10] Another challenge is to decrease the physical distance between the blood and the patient. To this end, many trauma centers have transitioned to having a small reserve of thawed/liquid blood products immediately available within the emergency department: The Mayo Clinic (Rochester, MN) has a full MTP cooler at all times within their ED; the R Adams Cowley Shock Trauma Center (Baltimore, MD) maintains an entire MTP refrigerator within their ED; Memorial Hermann- Texas Medical Center also maintains a blood product refrigerator within the ED, with RBCs and liquid plasma. Another way to significantly decrease the distance (and therefore time to administration) of blood products is to make them available in the pre-hospital setting. Memorial Hermann Hospital and the Mayo Clinic, as examples, have maintained red blood cells and plasma on-board every air ambulance since 2011. Blood product administration pre-hospital is protocolized, and the administration of any pre-hospital blood products automatically activates the hospital's MTP. A full MTP cooler is then present at the bedside in the ED prior to the arrival of the patient.

Several limitations are apparent in this study. First, while the data regarding time to blood cooler delivery was collected prospectively, and intended for sub-analysis, patients were not randomized by time nor were evaluation of time to activation and time to initial cooler designated primary outcomes. Second, the actual time of administration of the first blood product was not used but rather time to arrival of first cooler. While it seems unlikely that MTP would be activated for any trauma patient and blood products not given immediately, this cannot be explicitly stated. Finally, this study may not be easily generalizable. Prior to beginning the PROPPR study, each of the twelve North American Level-1 trauma centers was vetted for its ability to provide blood products within the strict, predetermined time criteria. Further, periodic assessments of each center's ability to continue to meet these goals were continued throughout the data acquisition phase. Smaller hospitals with fewer resources may find it more difficult to consistently meet stringent time criteria. It is difficult to calculate the cost of such an effort, especially when measuring against the value of a life saved. However, research suggests that the protocolization of massive transfusion actually decreases both product wastage and costs.[20] Further, provision of timely blood products is a benchmark of quality that should be continuously reevaluated at every trauma center. "Door-to-balloon" times are measured for cardiac referral centers; no less should be expected for trauma centers.

CONCLUSIONS

Delays in the activation of MTP and delays in the delivery of the first blood product cooler were both associated with increased time to hemostasis and increased mortality. In the PROPPR dataset, every minute of delay between the activation of MTP and the arrival of the first blood cooler regardless of ratio, resulted in a 5% increase in the odds of mortality. In fact, it appears that decreasing the time to blood product administration is one of the modifiable risk factors that affect mortality in the exsanguinating trauma patient. Every

effort should be made to decrease the time to recognition of the need for MTP and the time to administration of the first blood product.

Acknowledgments

This work was supported with grant U01HL077863 from the US National Heart, Lung, and Blood Institute and funding from the US Department of Defense, the Defence Research and Development Canada in partnership with the Canadian Institutes of Health Research-Institute of Circulatory and Respiratory Health (grant CRR-120612).

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Table 1

Baseline and arrival data by those who live and die within 24-hours

	Death within 24 hours (n=100)	Alive at 24 hours (n=580)	p-value
Male gender	77%	81%	0.352
Median age in years	39 (24, 56)	34 (25, 49)	0.223
White race	68%	63%	0.336
Blunt mechanism	62%	51%	0.042
Median ISS	36 (25, 48)	25 (17, 37)	<0.001
Median w-RTS	4.09 (3.80, 6.37)	6.90 (4.09, 7.84)	<0.001
Median Resuscitation Intensity	6 (4, 9)	4 (3, 6)	<0.001

Medians are expressed with 25^{th} and 75^{th} interquartile range; ISS: injury severity score; w-RTS: weighted revised trauma score

Table 2

Multivariate regression predicting 24-hour mortality

	Odds ratio	95% C.I.	p-value
Time to receipt of first cooler (min)	1.05	1.01–1.10	0.035
Anatomic injury severity (ISS)	1.03	1.02–1.05	<0.001
Disturbed arrival physiology (w-RTS)	0.69	0.60–0.81	<0.001
Randomization group (1:1:2)	1.69	1.01–2.86	0.047
Resuscitation Intensity (units)	1.12	0.60–2.05	0.719

95% C.I.: 95% confidence interval; min: minutes; ISS: injury severity score; w-RTS: weighted revised trauma score

Table 3

Multivariate regression predicting 30-day mortality

	Odds ratio	95% C.I.	p-value
Time to receipt of first cooler (min)	1.05	1.01–1.09	0.016
Anatomic injury severity (ISS)	1.05	1.03–1.06	<0.001
Disturbed arrival physiology (w-RTS)	0.61	0.53–0.69	<0.001
Randomization group (1:1:2)	1.46	0.92–2.29	0.102
Resuscitation Intensity (units)	1.03	0.60–1.44	0.184

95% C.I.: 95% confidence interval; min: minutes; ISS: injury severity score; w-RTS: weighted revised trauma score