
Massive Transfusion Protocols: The Role of Aggressive Resuscitation Versus Product Ratio in Mortality Reduction

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- BACKGROUND:** Exsanguinating hemorrhage necessitating massive blood product transfusion is associated with high mortality rates. Recent data suggest that altering the fresh frozen plasma to packed red blood cell ratio (FFP:PRBC) results in significant mortality reductions. Our purpose was to evaluate mortality and blood product use in the context of a newly initiated massive transfusion protocol (MTP).
- STUDY DESIGN:** In July 2005, our American College of Surgeons-verified Level I trauma center implemented an MTP supporting a 1:1.5 FFP:PRBC ratio, improved communications, and enhanced systems flow to optimize rapid blood product availability. During the 4 years surrounding protocol implementation, we reviewed data on trauma patients directly admitted through the emergency department and requiring 10 or more units PRBCs during the first 24 hours.
- RESULTS:** For the 2 years before and subsequent to MTP initiation, there were 4,223 and 4,414 trauma activations, of which 40 and 37 patients, respectively, met study criteria. The FFP:PRBC ratios were identical, at 1:1.8 and 1:1.8 ($p = 0.97$). Despite no change in FFP:PRBC ratio, mortality decreased from 45% to 19% ($p = 0.02$). Other significant findings included decreased mean time to first product: cross-matched RBCs (115 to 71 minutes; $p = 0.02$), FFP (254 to 169 minutes; $p = 0.04$), and platelets (418 to 241 minutes; $p = 0.01$).
- CONCLUSIONS:** MTP implementation is associated with mortality reductions that have been ascribed principally to increased plasma use and decreased FFP:PRBC ratios. Our study found a significant reduction in mortality despite unchanged FFP:PRBC ratios and equivalent overall mean numbers of transfusions. Our data underscore the importance of expeditious product availability and emphasize that massive transfusion is a complex process in which product ratio and time to transfusion represent only the beginning of understanding. (*J Am Coll Surg* 2009;209:198–205. © 2009 by the American College of Surgeons)
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Hemorrhage has been identified as a major cause of death in trauma patients, causing most trauma-related mortality within hours of admission to the emergency room.¹⁻³ Massive transfusion has been defined as greater than 10 units of packed red blood cells (PRBCs) in a 24-hour period.⁴ When first discussed in the 1970s, massive transfusion was associated with mortality rates higher than 90%.⁵ Since then, advances in critical and surgical care of trauma patients requiring massive transfusion have led to dramatic

decreases in mortality. Mortality rates between 30% and 70% are commonly reported.⁶ Improved survival has been attributed to damage-control techniques, appreciation and correction of coagulopathy, patient rewarming, and improved overall resuscitation.⁶ The institution of massive transfusion protocols (MTP) has reduced mortality, with the benefit primarily ascribed to an increased ratio of fresh frozen plasma (FFP):PRBCs.^{7,8} But the precise contributing factors responsible for improved outcomes remain unclear.

Many retrospective analyses and some prospective studies have explored the role of FFP, recombinant activated factor VII (rFVIIa), and whole blood in improving outcomes in the context of MTPs.⁹⁻¹¹ Exsanguinating hemorrhage results in acidosis, hypothermia, and coagulopathy, which represent a “lethal triad.”¹² The importance of avoid-

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Abbreviations and Acronyms

FFP	=	fresh frozen plasma
MTP	=	massive transfusion protocol
PRBCs	=	packed red blood cells
rFVIIa	=	recombinant activated factor VII

ing this triad has been validated by military and civilian data.¹³ Aggressive correction of coagulopathy with FFP improves outcomes.^{9,10,14-16} In cases of coagulopathy, administration of rFVIIa decreases transfusion requirements and may affect mortality.^{11,17,18} Although massive transfusion has been replaced by component therapy in civilian practice, whole blood has been shown to be beneficial in military practice.¹⁹

The emphasis on rapidly correcting coagulopathy from the US military experience in Iraq has led to recommendations of fixed ratios of FFP:PRBCs in massive transfusion protocols at trauma centers, suggesting that a fixed ratio of 1:1 is optimal.^{14,20,21} In civilian practice, the evidence has been conflicting. Although recent studies have suggested that high FFP:PRBC ratios do not translate to decreased mortality,^{10,22} others have shown improved mortality with high FFP:PRBC ratios.^{23,24} Additionally, although the analysis of FFP:PRBC ratio has occurred mainly within the context of protocol-based care, the benefits of MTP beyond component ratios are rarely discussed. Overuse of blood products may be associated with systemic inflammatory response syndrome, transfusion-related acute lung injury, and infection;²⁴⁻²⁷ early product use may actually reduce these complications,²⁸ prompting the need to further define MTP strategies and goals.

Accordingly, the goal of this study was to evaluate the process and outcomes measures of massive transfusion trauma patients at a Level I trauma center for the 2 years before and 2 years after implementation of an MTP. Our hypothesis was that increasing the product ratio of FFP:PRBCs by instituting a formal system for MTP activation would be associated with better outcomes and improved mortality rates in the trauma patient population.

METHODS

Stanford University Medical Center is a county-designated and American College of Surgeons Committee on Trauma-verified Level I trauma center. The Stanford MTP was fully implemented in July 2005 with the start of the academic year. Goals of the protocol included increasing the FFP:PRBC ratio to 1:1.5, while also providing for rapid product availability and improved distribution.

Of note, the number of 1 to 2 activations per week in the attached algorithm reflecting our MTP (Fig. 1) refers to all

activations across the various services within the hospital: ie, trauma, vascular, transplantation, OB/GYN, cardiothoracic, severe gastrointestinal bleeding, and general surgery, and surgical subspecialties that might use the MTP on rare occasions, such as urology, plastics, or orthopaedics. Although the overall protocol was designed to meet the needs of multiple services within the hospital, our goal was to evaluate the particular impact of the MTP on trauma patients.

Within the protocol, an MTP leader is designated, and defined roles for physicians, nurses, transfusion services, and laboratory staff are established. MTP activation is at the discretion of the attending physician. In most cases, MTP is activated by the attending trauma surgeon, who also serves as the MTP leader. But the MTP does not necessarily have to be activated by the attending surgeon. Emergency department and attending physicians and other physicians, including senior residents from either the emergency department or the trauma team, can activate the MTP. Activation is recommended for greater than 4 units PRBCs transfused in the first hour or expected transfusion requirements in excess of 10 units in a 12-hour period. At minimum, four units of thawed FFP are kept available at all times by the blood bank in anticipation of MTP activation and any unforeseen need for rapid correction of coagulopathy. Upon activation of the MTP, a set of six units PRBCs, four units FFP, and one apheresis pack of platelets (formerly called a "six-pack") is sent to the patient's bedside. This 6:4:1 pack is continually delivered each time blood is requested until the protocol is "deactivated." Cryoprecipitate is not incorporated into the massive transfusion guidelines, nor is cryoprecipitate customarily administered to our exsanguinating trauma patients. Goal hematocrit is not explicitly described within the protocol, because resuscitation to hemodynamic stability is used without hematocrit-based transfusion triggers. The protocol is shown in Figure 1.

To best assess outcomes differences and related variables, a retrospective cohort study format was selected. Patients were grouped into two cohorts: before and after implementation of the protocol. The first cohort (Pre-MTP) included patients who presented within the 2 years before July 1, 2005; the second cohort (Post-MTP) included patients who presented within the 2 years including and after July 1, 2005. Definitions of massive transfusion ranged from 10 units in a 6-, 12-, or 24-hour period.^{23,24} To use the broadest definition, the study inclusion criteria were direct admittance through the emergency department and requiring ≥ 10 units PRBCs over the first 24 hours, which remains the most commonly used definition of massive transfusion in the literature. Exclusion criteria included preadmission care at an outside hospital, age less than 16

Massive Transfusion Guidelines (Estimated activation 1-2/week)

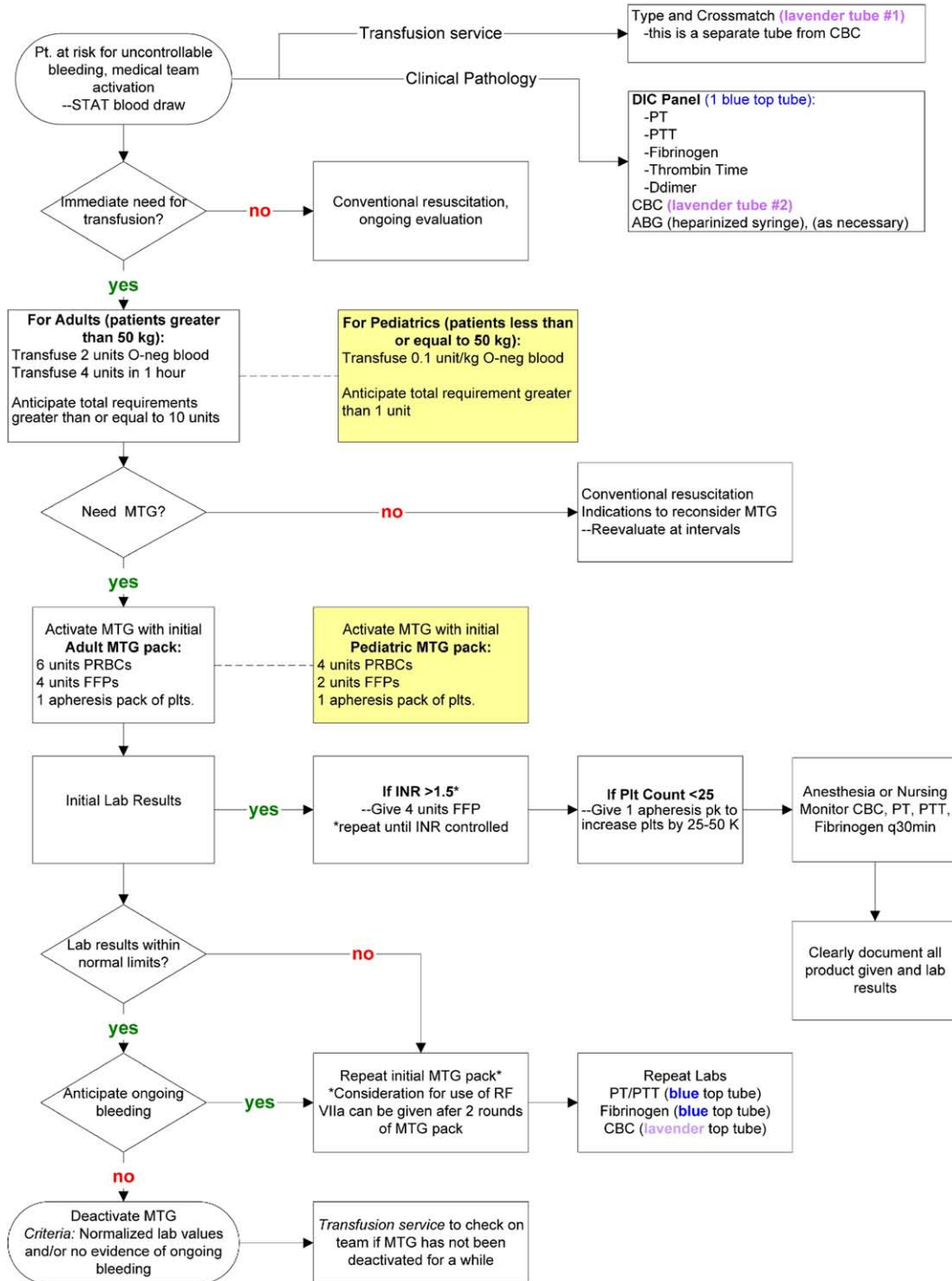


Figure 1. Stanford massive transfusion protocol. ABG, arterial blood gases; CBC, complete blood count; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; INR, international normalized ratio; MTG, massive transfusion guidelines; PRBCs, packed red blood cells; PT, prothrombin time; PTT, partial thromboplastin time; rFVIIa, recombinant activated factor VII.

Table 1. Patient Demographics

Variable	Pre-MTP (n = 40)	Post-MTP (n = 37)	p Value
Mean age, y	42	45	0.94
Male, n (%)	29 (73)	25 (62)	0.77
Blunt trauma, n (%)	35/40 (88)	28/37 (76)	0.18
ISS	32	28	0.27
Head AIS	1.6	1.5	0.81
Chest AIS	2.3	2.2	0.85
Abdomen AIS	2.5	2.1	0.37
Presenting GCS	10.5	11.8	0.27

AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; MTP, massive transfusion protocol.

years, greater than 5 minutes of prehospital cardiopulmonary resuscitation, emergency department thoracotomy performed for blunt injury, and pregnancy.

Admission records identified trauma patients with any blood transfusion requirements, who were then categorized as receiving greater than 10 units of PRBCs during their hospitalization. These patients were cross-referenced with blood bank data and trauma registry data to select those who met MTP criteria. Information on transfusion products, volume, and timing were confirmed directly from the original patient record. Because four units of uncross-matched PRBCs have been available at all major trauma activations both before and after MTP implementation, the impact of the protocol is found in subsequent, patient-specific transfusions. To highlight differences resulting from protocol intervention, our process defines time to product as time from patient presentation to first patient-specific cross-matched product delivered from the blood bank, transfused, and documented.

Dichotomous and continuous variables were examined by chi-square analyses and Student's *t*-test, respectively. Logistic regression analysis was applied to blood quantity transfused and mortality, correcting for potential confounders. The model was evaluated using the goodness-of-fit statistic. All analyses were performed using STATA software (StataCorp 2001 statistical software, release 7.0; Stata Corp).

RESULTS

The cohorts were similar in age ($p = 0.94$) and gender ($p = 0.77$). There was no difference in percentage of blunt trauma between the pre- and post-MTP cohorts: 88% and 76%, respectively ($p = 0.18$). There was also no difference in Injury Severity Score (ISS): 32 and 28, respectively ($p = 0.27$). Patients from both cohorts experienced similar admission rates to the operating room (pre-MTP, 70.0%; post-MTP, 70.2%) and the ICU (pre-MTP, 27.5%; post-

Table 2. Mean Units and Ratios of Product Used, Pre- and Postmassive Transfusion Protocol Implementation

Product and ratio	Pre-MTP, mean (95% CI)	Post-MTP, mean (95% CI)	p Value
PRBCs	23.9 (18.7–29.1)	20.5 (15.5–25.5)	0.34
FFP	12.3 (9.6–15.0)	10.7 (7.8–13.6)	0.42
Plt	2.3 (1.7–2.9)	2.8 (1.8–3.7)	0.41
FFP:PRBCs	1:1.8 (1:1.5–1:2.2)	1:1.8 (1:1.5–1:2.1)	0.97
Plt:PRBCs	1:1.7 (1:1.4–1:2.1)	1:1.3 (1:1.1–1:1.5)	0.05*

*Statistically significant; $p \leq 0.05$.

FFP, fresh frozen plasma; MTP, massive transfusion protocol; Plt, platelets; PRBCs, packed red blood cells.

MTP, 27.0%). Comparisons of demographics for pre- and post-MTP implementation are found in Table 1.

During the pre-MTP cohort period (July 1, 2003, to June 30, 2005) there were 4,223 trauma activations; 1,878 patients were admitted and 40 met study inclusion criteria. Of these 40, 35 had blunt trauma and 5 were penetrating injuries. The mean units of product transfused for PRBCs, FFP, and platelets were 24.0, 12.3, and 2.3, respectively. The ratio of FFP:PRBCs infused was 1:1.8. The mean times in minutes to first documented cross-matched product transfused for PRBCs, FFP, and platelets were 115, 254, and 418, respectively.

During the post-MTP cohort period (July 1, 2005, to June 30, 2007) there were 4,414 trauma activations; 1,970 patients were admitted and 37 met study inclusion criteria. Of these 37, 28 were blunt trauma and 9 were penetrating trauma. The number of mean units of product transfused for PRBCs, FFP, and platelets were 20.4, 10.7, and 2.8, respectively. The ratio of FFP:PRBCs infused was 1:1.8. The mean times in minutes to first documented cross-matched product transfused for PRBCs, FFP, and platelets were 71, 169, and 241, respectively. Comparisons of the number and ratio of blood products used are found in Table 2, with mean time to transfusion in Table 3.

There was a significant difference in mortality: 18 of 40 patients in the pre-MTP cohort compared with 7 of 37 patients in the post-MTP cohort (45% versus 19%, respectively; $p = 0.02$; Table 4; Fig. 2). In comparing product

Table 3. Mean Minutes to First Transfusion of Type-Specific Blood Products Before and after Implementation of Massive Transfusion Protocol

Product	Pre-MTP, mean (95% CI)	Post-MTP, mean (95% CI)	p Value
PRBCs	115 (85–146)	71 (49–93)	0.02*
FFP	254 (185–323)	169 (130–209)	0.04*
Platelets	418 (316–519)	241 (169–311)	0.01*

*Statistically significant; $p \leq 0.05$.

FFP, fresh frozen plasma; MTP, massive transfusion protocol; PRBCs, packed red blood cells.

Table 4. Mortality Rates Between Cohorts

Variable	Pre-MTP	Post-MTP	p Value
Patients, n	40	37	
Deaths, n	18	7	
Mortality, %	45	19	0.02*

*Statistically significant; $p \leq 0.05$.

MTP, massive transfusion protocol.

given, the quantities of product administered before and after MTP implementation were similar, except for a higher platelet:PRBC ratio, which changed from 1:1.8 to 1:1.3 with implementation of the protocol ($p = 0.05$). A logistic regression model was built to predict the risk of mortality using blood transfusion quantities as the independent variables, with results outlined in Table 5. The goodness-of-fit statistic indicated the model was well fit (p value = 0.3743), and the model yielded an area under the curve of 0.8269. The model controlled for confounding variables: age, Injury Severity Score, Glasgow Coma Scale < 3, and type of injury. Significant predictors of mortality were number of units of PRBCs and platelets transfused. An increase in units of PRBCs transfused was associated with increased mortality, with an odds ratio of 1.21 (95% CI, 1.06 to 1.38); increased units of platelets transfused were associated with decreased mortality, with an odds ratio of 0.43 (95% CI, 0.20 to 0.93).

DISCUSSION

This study evaluated massive transfusion trauma patients at a Level I trauma center for the 2 years before and 2 years after implementation of an MTP. The combined mortality rate for the 2 years preceding implementation was 45%, compared with only 19% mortality in the 2 years postimplementation ($p = 0.02$). The mortality difference noted is consistent with experience in military and civilian trauma in implementation of an MTP.^{4,13,23,29} Our data are unique compared with those from other studies in that mortality decreased despite no significant alteration in the ratio of blood components used for resuscitation.

Much discussion in the current trauma literature focuses on changes in blood product ratio as a means to affect mortality.²⁰ In fact, our protocol was designed to target a 1:1.5 ratio of FFP:PRBCs. A second goal of our protocol was to improve communication with the blood bank and decrease the time needed to have components available for transfusion. It is unclear why the FFP:PRBC ratio did not alter with protocol implementation. The primary reason was likely a surgical and anesthesia culture that already actively practiced aggressive resuscitation targeted to combat dilutional coagulopathy in the major trauma patient before implementation of the MTP. This rationale is fur-

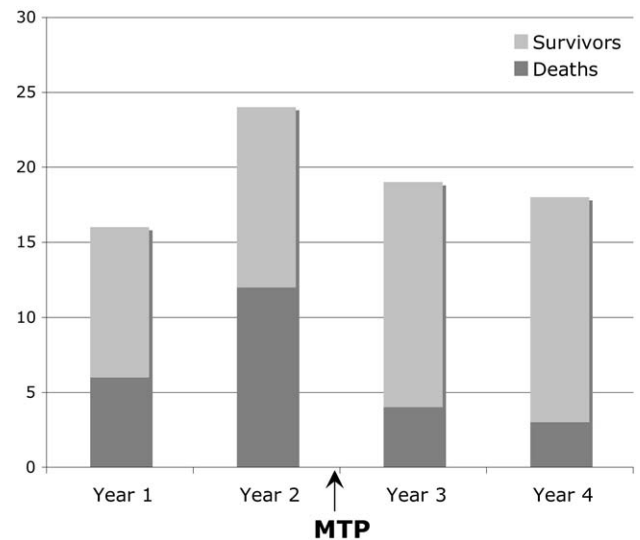


Figure 2. Patient survival by year. MTP, massive transfusion protocol.

ther supported by our findings that the overall volume of product was also unchanged.

The second goal of MTP implementation was met. Communication with the blood bank and product availability improved. Time to blood product resuscitation, indicated by times to first transfusion for cross-matched PRBCs, FFP, and platelets, was dramatically decreased after implementation of MTP. Times to first documented transfusion for cross-matched PRBCs, FFP, and platelets were reduced 39%, 33%, and 42% ($p \leq 0.04$), respectively. Notably, overall numbers of blood products given did not significantly change.

A valid definition of massive transfusion is evolving. In regard to timing, is the definition of massive transfusion 10 units in the first 24 hours, 10 units in 12 hours, 10 units in 6 hours or less? Alternatively, perhaps intention to treat rather than transfusion requirements themselves should define massive transfusion. At the time of the initiation and construction of our study design, we chose our inclusion and exclusion criteria (10 units in 24 hours) to be consistent with those in the literature, so we did not use intention to treat analysis. The trauma community is currently hotly debating the “valid” criteria for massive transfusion. The definition of massive resuscitation based on volume resuscitation ignores patients who may have required less product in the late cohort because of improved procedures. The definition of massive transfusion as 10 units in 24 hours used in our study design was chosen for consistency with definitions in previously published literature. Because most of the published reports refer to product ratios rather than timing, the suggestion of our data that the impact of timing

Table 5. Predictors of Mortality from Multiple Regression

Predictor	Odds ratio	Standard error	p Value	Lower 95% CI	Upper 95% CI
PRBCs*	1.2	0.07	0.01*	1.05	1.32
FFP	1.0	0.08	0.80	0.87	1.19
Platelets*	0.5	0.16	0.04*	0.30	0.98
Age	1.0	0.02	0.38	0.98	1.06
ISS	1.0	0.06	0.73	0.86	1.11
Injury (blunt)	2.8	4.11	0.48	0.16	49.16
Head AIS	1.5	0.54	0.25	0.75	3.05
Chest AIS	1.1	0.32	0.86	0.58	1.93
Abdomen AIS	1.0	0.33	1.00	0.52	1.92
ED GCS	0.9	0.07	0.12	0.76	1.03

*Statistically significant; $p < 0.05$.

AIS, Abbreviated Injury Scale; ED GCS, emergency department Glasgow Coma Scale; FFP, fresh frozen plasma; ISS, Injury Severity Score; PRBCs, packed red blood cells.

rather than ratio is an indicator of improved mortality is a vital contribution of our findings. Although we were not able to bear out our original hypothesis of higher FFP: PRBC ratio associated with improved mortality, we were able to show that protocolization and the resultant improved access and availability of blood product are likely as important as, if not more important than, ratios. Our data ultimately argue that, in fact, we should not use 10 units in the first 24 hours as a definition, and even 10 units in the first 6 hours might not be an adequate definition or goal. As is stated by Trunkey³⁰ in his seminal article on the trimodal distribution of trauma and the role of formalized trauma systems in intervening against potential death as the “Golden Hour,” our data underscore that the utility and impact of massive transfusion should correspondingly be considered not only in product ratios but also measured in minutes, not hours or days.

Because institution of an MTP attempts to standardize multiple variables, previous studies have been unable to separate changes in product ratio and time to transfusion. In fact, at least one study suggested that product ratio, representing aggressiveness of resuscitation, may not influence outcomes.²² Because no study has previously evaluated improved product availability in isolation from changes in product ratio, these data represent a unique view of mortality changes in MTP implementation. The improved efficiency of process resulting in decreased time to transfusion, in turn leading to rapid correction of coagulopathy, may be the principal factor by which mortality was decreased. Additionally, critical care literature has consistently shown mortality benefit through protocol implementation over ad hoc systems of care.⁷ Perhaps it is not surprising that there is similar benefit seen in the trauma population.

STUDY LIMITATIONS

There are several notable limitations in this study. An important aspect of care that our study did not address is end points of resuscitation. The initial goal of massive hemorrhage treatment is reversal of shock with adequate tissue perfusion. Treatment requires fluid resuscitation and rapid hemostasis through surgical control of bleeding.³¹ Measured end points, as described by advanced trauma life support, include normalization of blood pressure, heart rate, central venous pressure, and urine output.³² These physiologic parameters have traditionally augmented clinical judgment as soft end points for resuscitation. Other intermediate markers suggestive of resuscitation adequacy include normalization of mixed venous oxygen saturation and lactate and base deficit measurements. Recent studies have suggested central venous pressure and mixed venous oxygen as markers of hemodynamic improvement in the setting of hemorrhagic shock.^{33,34} Despite the increased research on MTP, there is no consensus on end points of resuscitation.³¹ Few data exist to support outcomes differences based on resuscitation end points.^{33,34} The Eastern Association for the Surgery of Trauma “Clinical Practice Guidelines: End points Of Resuscitation”³¹ finds insufficient data to formulate a Level I recommendation regarding end points. Our existing MTP does not specify end points for resuscitation beyond clinical judgment, and this study regrettably cannot address this question. Given that nonclinical determinations of end points of resuscitation were not incorporated into the MTP, and this study design was unlikely to show a meaningful difference in such measures, this information was neither collected nor analyzed.

Retrospective design and small sample size limit interpretation and confer risk of type II error for mortality assessment despite a p value of 0.02. Because of changes in information technology systems and data collection prac-

tices during the study period, serial hematocrit, platelet count, and international normalized ratio were not analyzed. Because our institution is in the process of implementing fully computerized electronic medical records, the ability in the future to capture basic information accurately, time-specific values, such as laboratory results and exact determinations of physiologic parameters, will be significantly enhanced. Ultimately, the expectation is that full implementation of electronic medical records will result in significant enhancements in both bedside patient care and the ability to comprehensively capture and analyze data for research purposes. Unfortunately, restricted resources, because our medical records department is in the midst of this transition, prohibit access to such information from the previous handwritten and scanned medical records documents. But the absence of these specific values in our study should not detract from our principal finding that outcomes—specifically, a significant decrease in mortality—appear to be associated with time to PRBCs and plasma product as a surrogate for adequate resuscitation rather than the specific ratio of PRBCs:FFP, as previous studies have postulated.

Further limitations of this study include lack of analysis of clinical sequelae of potential transfusion-related complications, such as ARDS, multiple organ failure, abdominal compartment syndrome, and damage control surgery, because our primary end point was mortality. An additional limitation is a lack of analysis of the effects of factor rVIIa. Factor rVIIa was not routinely administered in our MTP so was not included as a variable. Finally, it is possible that awareness and education of the need to correct hypothermia and acidosis and the importance of rapid resuscitation may have changed during the study period and have a Hawthorne effect on our ultimate findings. In defense of this possibility, it is notable that during the 4 years for which data were reviewed, there was little alteration in broad patterns of care noted, and there was no change in the emergency department and trauma surgery faculty or the anesthesiologists providing care.

In conclusion, initiation of an MTP was associated with a significant decrease in mortality at our Level 1 trauma center. The survival benefit does not appear to have been related to any alteration in the volume or ratio of blood components used. The protocol did result in a significant decrease in time to transfusion of PRBCs, FFP, and platelets. In the absence of altering transfusion ratios, the presence of a protocol itself, with the concurrent quicker access to products, may be the primary factor behind our finding of improved survival. This improved survival is likely the result of increased awareness of, communication with, and access to, transfusion services. This is a marked departure

from previous literature citing ratio change as the main determinant of mortality difference. Our data underscore that the impact, as well as the definition, of massive transfusions should be measured in minutes, not hours or days.

Although we did not alter the ratio of blood components used in resuscitation, our data provide unique insight into previously unidentified and undefined benefits of transfusion protocols and suggest that protocol implementation in trauma resuscitation warrants further discussion and prospective investigation.

Author Contributions

Study conception and design: DJ Riskin, Hernandez-Boussard, Purtill, Maggio, Spain, Brundage
 Acquisition of data: Tsai, L Riskin
 Analysis and interpretation of data: DJ Riskin, Brundage, Tsai, L Riskin
 Drafting of manuscript: DJ Riskin, Tsai, L Riskin
 Critical revision: Hernandez-Boussard, Purtill, Maggio, Spain, Brundage

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