The Ratio of Fibrinogen to Red Cells Transfused Affects Survival in Casualties Receiving Massive Transfusions at an Army Combat Support Hospital

Harry K. Stinger, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Jose Salinas, PhD, Wenjun Z. Martini, PhD, John R. Hess, MD, Michael A. Dubick, PhD, Clayton D. Simon, MD, Alec C. Beekley, MD, Steven E. Wolf, MD, Charles E. Wade, PhD, and COL John B. Holcomb, MC

Background: **To treat the coagulopathy of trauma, some have suggested early and aggressive use of cryoprecipitate as a source of fibrinogen. Our objective was to determine whether increased ratios of fibrinogen to red blood cells (RBCs) decreased mortality in combat casualties requiring massive transfusion.**

Methods: **We performed a retrospective chart review of 252 patients at a U.S. Army combat support hospital who received a massive transfusion (≥10 units of RBCs in 24 hours). The typical amount of fibrinogen within each blood product was used to calculate the fibrinogen-to-RBC (F:R) ratio transfused for each patient. Two groups of patients who received either a low (<0.2 g fibrinogen/RBC Unit) or high (≥0.2 g fibrinogen/RBC Unit) F:R ratio were identified. Mortality rates and the cause of death were compared between these groups, and logistic regression was used to determine if the F:R ratio was independently associated with survival.**

Results: **Two-hundred and fifty-two patients who received a massive transfusion with a mean (SD) ISS of 21 (±10) and an overall mortality of 75 of 252 (30%) were included. The mean (SD) F:R ratios transfused for the low and high groups were 0.1 grams/Unit (±0.06), and 0.48 grams/Unit (±0.2), respectively ($p < 0.001$). Mortality was 27 of 52 (52%) and 48 of 200 (24%) in the low and high F:R ratio groups respectively ($p < 0.001$). Additional variables associated with survival were admission temperature, systolic blood pressure, hemoglobin, International Normalized Ratio (INR), base deficit, platelet concentration and Combined Injury Severity Score (ISS). Upon logistic regression, the F:R ratio was independently associated with mortality (odds ratio 0.37, 95% confidence interval 0.171–0.812, $p = 0.013$). The incidence of death from hemorrhage was higher in the low F:R group, 23/27 (85%), compared to the high F:R group, 21/48 (44%) ($p < 0.001$).**

Conclusions: **In patients with combat-related trauma requiring massive transfusion, the transfusion of an increased fibrinogen: RBC ratio was independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage. Prospective studies are needed to evaluate the best source of fibrinogen and the optimal empiric ratio of fibrinogen to RBCs in patients requiring massive transfusion.**

Key Words: **Massive transfusion, Trauma, Coagulopathy, Fibrinogen, Cryoprecipitate.**

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Hemorrhage remains the most common preventable cause of combat death.[1] Upon autopsy review, 80% to 85% of deaths in combat are classified as nonsurvivable as the result of devastating injury.[1,2] Of the remaining 15% to 20% of survivable deaths, 66% to 80% of patients die from hemorrhage.[1,2] Severe trauma, defined as an Injury Severity Score (ISS) of greater than 15,[3] is common during combat, representing 20% of all trauma admissions at one U.S. Army combat support hospital in Baghdad in 2004.[4] Recent combat operations in the Middle East have refocused attention on the early coagulopathy of trauma present on hospital admission.[5–7] Trauma and shock severity correlate with the degree of coagulopathy,[6–9] which in turn has been associated with mortality. The most severely injured 10% of patients[10] may require massive transfusion, defined as the transfusion of 10 or more red blood cell (RBC) units in a 24-hour period.[11–13] In civilian trauma centers, the incidence of patients with traumatic injuries requiring massive transfusion ranges between 1% and 3%,[13–15]

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From the Brooke Army Medical Center (H.K.S., K.W.G., C.D.S.); U.S. Army Institute of Surgical Research (P.C.S., J.S., W.Z.M., M.A.D., C.E.W., J.B.H.); University of Texas Health Science Center at San Antonio (S.E.W.), San Antonio Texas; Walter Reed Army Medical Center (J.G.P.), Washington, DC; University of Maryland School of Medicine (J.R.H.), Baltimore, Maryland; and Madigan Army Medical Center (A.C.B.), Tacoma, Washington.
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Address for reprints: Harry K. Stinger, MD, BAMC/USAISR, Bldg. 3611, 3400 Rawley E. Chambers Ave., Fort Sam Houston, San Antonio, TX 78234-6200; email: harry.stinger@us.army.mil.

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with an incidence of massive transfusion reported as high as 15% in patients with the most severe injuries.[5,16] The majority of massive transfusion patients die within 6 to 12 hours of hospital arrival,[4,17,18] mortality rates for patients requiring massive transfusion range between 20% and 50%,[11,16,19] and massive transfusion has been shown to be independently associated with increased mortality.[14] The high mortality risk in massive transfusion patients largely results from the well-described "lethal triad" characterized by hypothermia, acidosis, and coagulopathy.[20–23]

Damage control resuscitation addresses that lethal triad immediately at admission to the combat hospital or civilian trauma center.[10] Intravascular volume resuscitation is accomplished using thawed human plasma as primary resuscitation fluid in a 1:1 or 1:2 ratio with RBCs.[5,11,24–27] For patients who require continued resuscitation, a massive transfusion protocol is activated and the blood bank delivers an additional 6 units of RBCs, 6 packs of platelets, 6 units of plasma, and one 10-unit bag of cryoprecipitate to the operating room.[10]

Cryoprecipitate is a human blood product derived from the precipitate fraction of cold-thawed human plasma.[28] It typically contains about 2.5 g of fibrinogen per 10-unit bag. Among all clotting factors in human plasma, fibrinogen is the first to decrease to pathophysiologic levels in hypocoagulable patients who have undergone major elective abdominal surgery with blood loss exceeding 20% of their calculated blood volume.[29] This hypofibrinogenemia does not seem to be completely explained by blood loss and resuscitation alone.[30,31] After moderate hemorrhagic shock in pigs, we reported that fibrinogen decreases as a result of constant production and increased consumption and hyperfibrinolysis, which results in prolonged blood clotting times.[32,33] Additionally, fibrinogen replacement has been shown to restore normal coagulation times in both coagulopathic pigs in hemorrhagic shock[34] and in diluted coagulopathic in vitro human blood.[35]

Our hypothesis was that early administration of fibrinogen to patients with severe injuries requiring a massive transfusion would decrease death from hemorrhage as a result of minimizing coagulopathy, excessive bleeding, and shock. Our objective in this retrospective study was to determine whether an increased ratio of fibrinogen to RBCs transfused would improve survival to hospital discharge in patients with severe traumatic injuries requiring massive transfusion at a combat support hospital by decreasing death from hemorrhage.

PATIENTS AND METHODS

The data presented here were obtained under a human use protocol that received Institutional Review Board approval through the Department of Clinical Investigation at Brooke Army Medical Center at Fort Sam Houston in San Antonio, TX. Using the Joint Theater Trauma Registry (JTTR) maintained at the U.S. Army Institute of Surgical Research (USAIR) at Fort Sam Houston in San Antonio, Texas, we performed a retrospective analysis of data for trauma patients admitted to two combat support hospitals in Iraq between January 2004 and October 2005. The JTTR is a database established by the Department of Defense to capture data prospectively from military hospitals for coalition and foreign national patients and from point of injury through rehabilitation for the U.S. casualties.[36]

The JTTR was queried for patients who received a massive transfusion, defined as 10 or more RBC units [including both RBCs and fresh whole blood (FWB) units] within a 24-hour period, between January 2004 to October 2005. Data analyzed from the JTTR in this study were age, combined ISS, recombinant Factor VIIa use, overall mortality at hospital discharge, mortality resulting from hemorrhage, and laboratory values and vital signs at admission to the combat support hospital (temperature, systolic blood pressure, hemoglobin, platelet level, international normalized ratio [INR], and base deficit) as well as the number in units and type of blood products administered within 24 hours of hospital admission. Numbers of units of blood products tabulated were packed red blood cell (RBC) units, fresh whole blood (FWB) units, fresh frozen plasma (FFP) units, cryoprecipitate (Cryo) 10-unit bags, and apheresis platelet (aPLT) units. Fibrinogen levels on hospital admission were not available in theater.

We calculated the F:R ratio (Fig. 1) according to standard amounts of fibrinogen contained in each blood component (Table 1). In the numerator of the ratio, each blood product is multiplied by a conversion factor that converts the units of that blood product transfused to grams of fibrinogen in that blood product (Fig. 1). Note that cryoprecipitate contains 2.5 g of fibrinogen per 10-unit bag, and FWB contains

$$\frac{\text{FFP (.4)} + \text{FWB (1.0)} + \text{Cryo (2.5)} + \text{aPLT(.3)}}{\text{RBC} + \text{FWB}}$$

Actual (F:R) Ratio Units:

$$\frac{\text{Grams Fibrinogen Transfused}}{\text{Total Units of Red Cells (RBC + FWB) Transfused}}$$

(FFP, Fresh Frozen Plasma; FWB, Fresh Whole Blood; Cryo, Cryoprecipitate; aPLT, Apheresis Platelets; RBC, Red Blood Cells)

Fig. 1. *Fibrinogen-to-red cell (F:R) ratio. FFP indicates fresh frozen plasma; FWB, fresh whole blood; Cryo, cryoprecipitate; aPLT, apheresis platelets; RBC, red blood cells.*

Table 1 Fibrinogen Content in Various Blood Products

1 unit of FFP	400 mg fibrinogen in 200–250 mL
1 six-pack of platelets	80 mg × 6 units = 480 mg in 300 mL
1 unit of apheresis platelets	300 mg in 200–250 mL
1 10-unit bag of cryoprecipitate	2,500 mg fibrinogen in about 150 mL
1 unit of fresh whole blood	1,000 mg fibrinogen
1 unit of PRBCs	<100 mg fibrinogen

Source: Dr. John Hess, Pathologist, University of Maryland School of Medicine and R. Adams Cowley Shock Trauma Center; Dr. Clayton Simon, Blood Bank Pathologist, Brooke Army Medical Center.

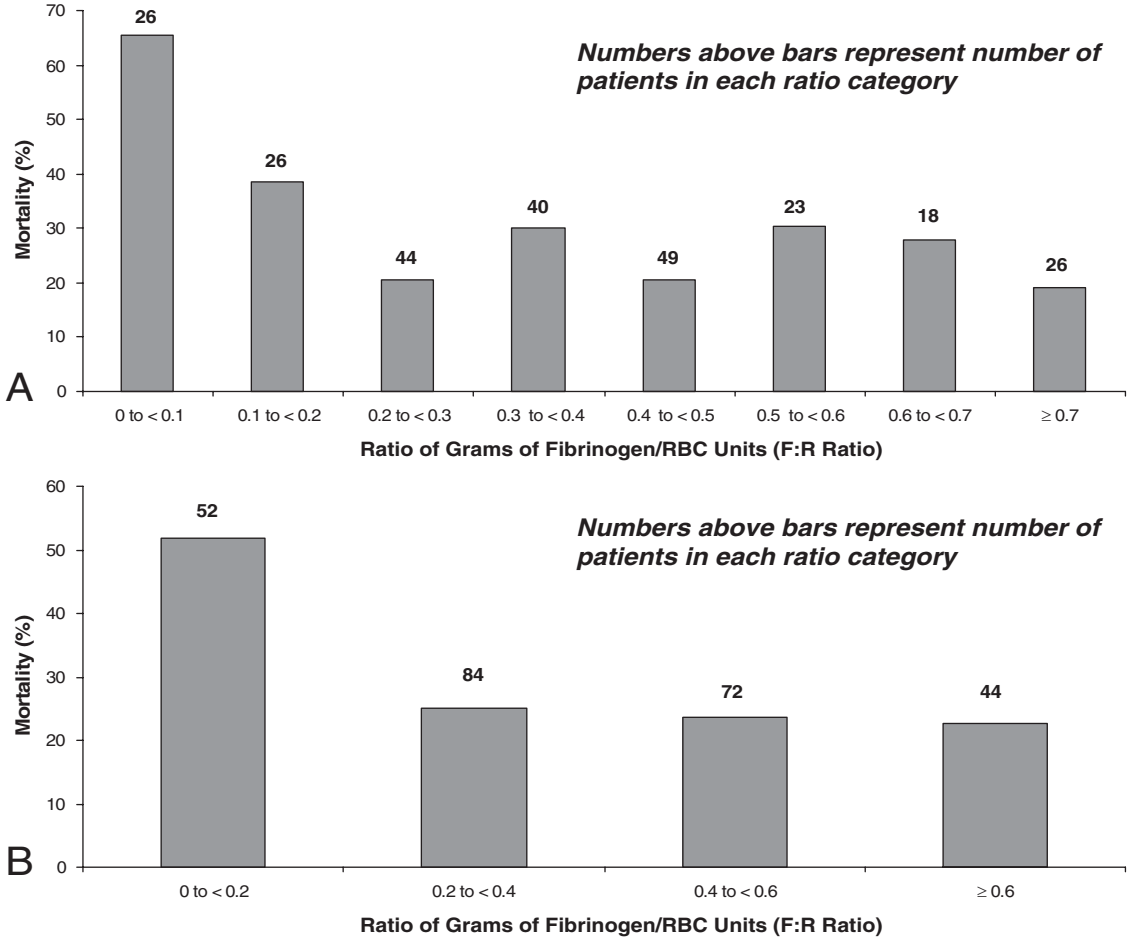

Fig. 2. (A) *Initial plot of mortality versus fibrinogen-to-red cell (F:R) ratio.* (B) *Quartile plot of mortality versus fibrinogen-to-red cell (F:R) ratio.*

1 g of fibrinogen per unit. The FWB appearing in the numerator of the F:R ratio thus actually represents grams of fibrinogen, not whole blood units transfused.

To analyze the effect of fibrinogen-to-red cell (F:R) ratios on mortality, patients were initially divided into eight ratio groups (Fig. 2A) and then into quartiles (Fig. 2B) based on the ratio of F:R units transfused. The first quartile consisted of patients with F:R ratios of 0 to ≤0.2 g/unit, the second 0.2 to ≤0.4 g/unit, the third 0.4 to ≤0.6 g/unit, and the fourth ≥0.6 g/unit. A sharp drop in mortality was noted at 0.2 g/unit between the first and second quartile, so the four ratio groups were combined into two groups, with a low F:R ratio of <0.2 g/unit and a high F:R ratio of ≥0.2 g/unit. We then plotted both mortality and death resulting from hemorrhage as a function of low F:R ratio (<0.2 g/unit) and high F:R ratio (≥0.2 g/unit; Fig. 3).

All continuous parametric data are described as mean (±SD). Comparisons were performed with Student's *t* test for continuous data and with Fisher's exact test for categorical data. Statistical analysis was performed with SPSS 14.0 (Chicago, IL). Significant differences were determined at $p < 0.05$. A logistic regression model was developed using multivariate

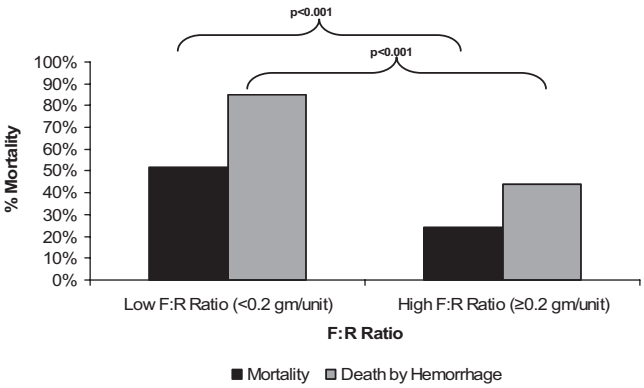

Fig. 3. *Plot of overall mortality versus fibrinogen ratio category.*

logistic regression analysis to determine which sets of variables were independent predictors of mortality. Correlation analysis was performed using both Pearson's and Spearman's correlation analysis with mortality as the dependent correlation factor. Values with greater than 0.15 correlation coefficients were considered candidates for model development. Regression analysis was performed using a backward likelihood ratio logistic regression. Results were validated using a forward stepwise regression

Table 2 Analysis of Variables Associated With Low and High F:R Ratio Tabulated on 252 Massive Transfusion Casualties

Variable	Low F:R Ratio (n = 52)*	High F:R Ratio (n = 200)*	p
F:R ratio (g/unit)	0.1 ± 0.06 (52)	0.48 ± 0.2 (200)	<0.001
RBCs (units)	15.9 ± 7.4 (52)	15.9 ± 7.4 (200)	NS
FWB (units)	0.6 ± 0.31 (52)	2.9 ± 4.6 (200)	<0.001
FFP (units)	3.5 ± 2.9 (52)	11.2 ± 7.4 (200)	<0.001
Cryoprecipitate (units)	0.77 ± 2.6 (52)	9.33 ± 10.9 (200)	<0.001
Platelets (cells/mm^3)	0.0 ± 0.0 (52)	0.72 ± 1.4 (200)	<0.001
Hemoglobin (g/dL)	9.8 ± 2.8 (43)	10.9 ± 2.7 (196)	<0.05
Base deficit	9.3 ± 7.1 (38)	9.4 ± 6.7 (168)	NS
INR	1.9 ± 1.8 (25)	2.0 ± 1.4 (143)	NS
Temperature (°F)	96.1 ± 2.6 (33)	95.7 ± 2.6 (166)	NS
Systolic blood pressure (mm Hg)	96.6 ± 27.8 (49)	101.0 ± 31.6 (188)	NS
ISS	21.5 ± 10.1 (52)	20.6 ± 9.7 (200)	NS
Mortality (%)	51.9 (27/52)	24.0 (48/200)	<0.001
Death by hemorrhage (%)	85.2 (23/27)	43.8 (21/48)	<0.001

Data presented as mean ± SD.

p values generated by Student's *t* test, Fisher's exact test, or χ^2 analysis, as appropriate.

* Values in parentheses indicate no. patients with data available.

INR indicates international normalized ratio; F:R ratio, fibrinogen-to-red cell ratio; NS, no significant difference; both group percentages equal.

of the same candidate variables. Variables comprised of single blood products alone were excluded to eliminate any collinear effects on the model.

RESULTS

During the 22-month period between January 2004 and October 2005, the combat support hospital received 5,586 patients from both military and civilian populations with traumatic injuries. The JTTR identified 252 of those 5,586 casualties (4.5%) who required massive transfusions. The mean age of the patients studied was 26 (±7.5) years. The mean ISS was 21 (±9.8). The overall mortality was 30% (75 of 252). The mean (SD) F:R ratios transfused for the low and high groups were 0.1 g/unit (±0.06) and 0.48 g/unit (±0.2), respectively ($p < 0.001$). Mortality was 27 of 52 (52%) and 48 of 200 (24%) in the low and high F:R ratio groups, respectively ($p < 0.001$; Fig. 3). The incidence of death from hemorrhage was higher in the low F:R group, 23 of 27 (85%), compared with the high F:R group, 21 of 48 (44%) ($p < 0.001$; Table 2). Additional comparisons of variables between patients in the low F:R ratio (<0.2 g/unit) and the high F:R ratio (≥0.2 g/unit) groups are summarized in Table 2. Upon multiple logistic regression, base deficit, ISS, and high F:R ratio (≥0.2 g fibrinogen per red cell unit [RBC or FWB] transfused) were noted to be independently associated with survival (Table 3).

Correlation analysis of variables resulted in eight variables as candidates for further multivariate analysis. These included hemoglobin, platelets, INR, base deficit, FFP, ISS, F:R ratio (continuous), and F:R ratio (high/low). The F:R ratio (high/low) variable had a higher correlation coefficient than F:R ratio (continuous) variable (−0.247 vs. −0.178) and was, therefore, chosen for multivariate analysis over the continuous F:R ratio variable. The INR variable showed a significant positive correlation (0.290) to mortality, but was excluded for low sample size (168 of 252). Recombinant Factor VIIa use was not correlated with mortality in this analysis and was therefore not a candidate for multivariate logistic regression.

Table 3 Multivariate Logistic Regression Analysis Results of Variables Associated With Mortality

Variable	Odds Ratio (95% CI)	p
Base deficit	1.075 (1.02–1.129)	0.003
ISS	1.049 (1.014–1.084)	0.005
F:R ratio	0.372 (0.171–0.812)	0.013

Backward and forward regression analysis resulted in the base deficit, ISS, and F:R ratio (high/low), as the best predictors of mortality with a receiver operating characteristic curve area of 0.71 (95% confidence interval 0.63–0.79; Fig. 4 and Table 3). Hosmer and Lemeshow tests showed a good model fit with a χ^2 of 3.17 ($p = 0.92$). The model correctly predicted 93% (10 of 147) of survivors and 29% (17 of 50) of deaths in the sample set using a 0.5 predictive positive cutoff. Mortality rate predicted increased to 56% (33 of 59) using a 0.3 positive cutoff value (survival rate decreased to 76%, correct predictions were obtained in 36 of 147).

DISCUSSION

Previous studies have shown that fibrinogen levels fall early in elective surgical patients with significant blood loss,[29] and in pigs[32,33] subjected to blood loss, but neither blood loss nor resuscitation[30,31] completely explains this decrease in fibrinogen levels. Acidosis in a swine model caused

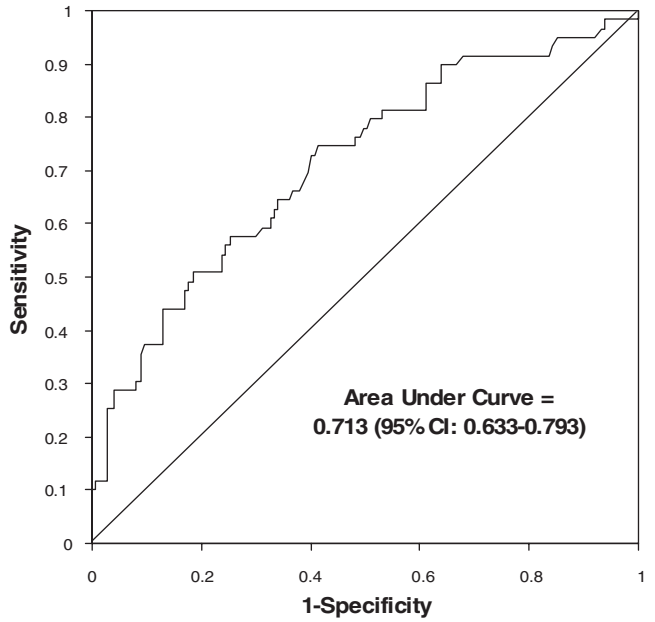

Fig. 4. *Receiver operating characteristic (ROC) curve for regression analysis model.*

a near twofold increase in fibrinogen degradation but no changes in fibrinogen synthesis.[37] Furthermore, neither bicarbonate[38] nor tris-hydroxymethyl-aminomethane[39] pH neutralization in similar swine models immediately corrected an acidosis-induced coagulopathy. On the other hand, replenishment of fibrinogen restored normal coagulation times in coagulopathic pigs in hemorrhagic shock[34] and in diluted coagulopathic in vitro human blood.[35]

Our results are consistent with the studies above in that they demonstrate that an increased amount of fibrinogen in relation to the amount of RBCs transfused was independently associated with survival in combat casualties requiring massive transfusions. This is important since the majority of preventable deaths in combat are due to hemorrhage and strategies that can decrease death from hemorrhage in combat will significantly impact survival in this population. To the best of our knowledge, this is the first article to demonstrate the association of high levels of transfused fibrinogen on the survival of casualties requiring massive transfusion.

High concentrations of fibrinogen are available not only from cryoprecipitate but also from plasma-derived fibrinogen concentrates. Fibrinogen is also now being produced using recombinant techniques and is available in a lyophilized powder form (Pharming Group, Leiden, The Netherlands). The ability to reconstitute recombinant fibrinogen from a lyophilized powder form surmounts the logistical hurdle that burdens FFP administration in military operations, i.e., the need to transport frozen human plasma thousands of miles from home station to military hospitals in the combat zone. Future trials comparing equal amounts of fibrinogen in FFP, cryoprecipitate, and fibrinogen concentrates for coagulopathic patients are needed.

Recombinant Factor VIIa (NovoSeven, NovoNordisk, Princeton, NJ) is another clotting factor available in lyophilized powder form that many trauma centers have recently integrated into their massive transfusion protocols. Recombinant Factor VIIa reduces the total number of red cell units transfused in combat casualties,[36] decreases death in combat casualties requiring massive transfusion,[4] and requires adequate levels of platelets and fibrinogen in place to achieve hemostasis.[40,41] Administering recombinant Factor VIIa in the face of low fibrinogen levels may not produce the desired hemostatic effect; in addition, acidosis should be reversed and platelet deficiencies corrected either simultaneously with or before recombinant Factor VIIa administration.[41]

Although our data reveal a strong association between a high F:R transfusion ratio and survival, that association does not necessarily imply causation. During the data collection period from January 2004 through October 2005, platelet availability varied, and deployed U.S. military medical personnel shifted progressively away from crystalloid toward more plasma and whole blood in factor-specific targeted resuscitation of combat casualties. Progressively smaller amounts of crystalloid infused may also have contributed to these results.[42,43]

Although compelling, our results are limited by the fact that fibrinogen was administered as cryoprecipitate, plasma, platelets, and whole blood, with each product containing other coagulation factors in varying amounts. Could those nonfibrinogen clotting factors—especially in plasma, because 239 of 252 casualties in our study received plasma—be responsible for the lowered mortality seen in the high F:R ratio group? Unfortunately, our sample size of 252 massive transfusion patients is not large enough to make valid comparisons between fibrinogen sources: plasma, cryoprecipitate, whole blood, etc., or to ascertain precisely where the mortality benefit came from: fibrinogen or from fibrinogen in addition to other clotting factors. A prospective randomized trial on massive transfusion casualties using cryoprecipitate, plasma, platelets, and whole blood as sole fibrinogen sources in separate treatment arms would come closer to answering that question; the likelihood of such a trial being conducted, however, may be remote for ethical reasons.

CONCLUSION

Although the sample size in this study is small, our data demonstrate that transfusion of a high F:R ratio (≥0.2 g of fibrinogen per red cell unit transfused) was independently associated with survival to hospital discharge, primarily by decreasing death from hemorrhage. One 15-mL cryoprecipitate bag containing 250 mg of fibrinogen can be transfused per unit of RBCs to achieve this ratio; plasma and whole blood seem to be just as capable of supplying the needed fibrinogen. Clinicians can meet this requirement by (1) transfusing 1 unit of FFP for every 2 units of red cells transfused, or (2) transfusing 1 unit of whole blood for every 4 units of red cells transfused (Table 1), or (3) transfusing one 10-unit

bag of cryoprecipitate for every 10 units of red cells transfused. Whether the survival benefit of the increased F:R ratio is a result of fibrinogen alone or to fibrinogen working with the other clotting factors present in plasma and whole blood is unknown. More prospective studies are needed to evaluate the best source of fibrinogen and the optimal empiric ratio of fibrinogen to RBCs in patients requiring massive transfusion.

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DISCUSSION

Dr. Myung S. Park (Wilford Hall Medical Center, San Antonio, TX): I would like to thank Dr. Stinger and his co-authors for tackling the much debated issue of how much of which blood components do we give to an exsanguinating trauma patient requiring massive transfusion. In their review of 252 patients who received massive transfusions (10 or more RBC units within 24-hour period) at the combat support hospital in Baghdad, they found that the ratio of fibrinogen per unit of RBCs transfused (F:R ratio) differed significantly between survivors and nonsurvivors. Specifically, patients who received <200 mg of fibrinogen per unit of RBC had a mortality rate of 52% versus 24% in those who received >200 mg of fibrinogen per unit of RBC. The percentage of death by hemorrhage was even more striking with mortality rate of 85% versus 44%, respectively. Furthermore, in multiple logistic regression, they found that the high fibrinogen-to-RBC ratio (>200 mg/unit) was an independent additive predictor of survival. Thus far, this is the first clinical study that has shown the survival benefit of fibrinogen during massive transfusions. This study supports the important concept of damage control hemostatic resuscitation as currently practiced in military combat support hospitals where plasma (containing 400 mg fibrinogen per unit) is given in 1:1 ratio to RBCs.

Based on this study, the authors recommend that we give at least 200 mg fibrinogen per unit of RBC transfused. As the authors note, "Although compelling, our results are limited by the fact that fibrinogen was administered as cryoprecipitate, plasma, platelets, and whole blood, with each product containing other coagulation factors in varying amounts." Because of their small sample size of 252 patients, comparisons between different fibrinogen sources were not made. Despite this shortcoming, I think this study delineates the importance of adequate fibrinogen supplementation in massive transfusions.

I have two questions: (1) Significant number of patients in this study received rFVIIa, especially in those who received the high F:R ratio. How can you attribute the improvement in survival to the latter when rFVIIa may be a contributor to increased survival? It is likely that both are important factors in improving the outcome of the exsanguinating trauma patients, but it is hard to discern the two based on the study presented. (2) Will the authors look into any mortality difference between patients who received fibrinogen from different sources, i.e., cryoprecipitate, plasma, whole blood, etc. using a larger cohort of patients?

Again, I would like to commend the authors for sharing with us their data that support fibrinogen is one of the key components in the resuscitation strategy.

Dr. Harry K. Stinger (Brooke Army Medical Center, Fort Sam Houston, TX): Thanks for your comments, Dr. Park. This analysis documented rFVIIa use versus nonuse in the 252 massive transfusion patients; it did not assess the timing or the dose of rFVIIa administered. In our analysis, the rate of rFVIIa use was similar (between survivors [51 of 177, 29%] and nonsurvivors [22 of 75, 29%]). However, a much higher percentage of patients in the high F:R ratio group (77 of 200, 38.5%) received rFVIIa than in the low F:R ratio group (5 of 52, 9.6%; $p < 0.001$). This issue is one limitation mentioned in the discussion section above, that is, was it the fibrinogen in the various blood products that positively impacted survival, or was it the other clotting factors present in those blood products—especially in plasma and in whole blood—that conferred the survival advantage? Recombinant Factor VIIa is a clotting factor that, along with fibrinogen, may have conferred a survival benefit.

At least in theory, rFVIIa needs adequate serum levels of fibrinogen and platelets in a normothermic, nonacidotic patient to work. I suspect that at least part of the survival benefit in the high F:R ratio category was the synergistic result of high serum levels of rFVIIa, plasma clotting factors, platelets and fibrinogen all working together to achieve hemostasis, and not the result of any single clotting factor operating alone. Separating out the effects of each factor individually is a challenge that would require a prospective randomized trial of massive transfusion casualties, hypothetically by assigning the various fibrinogen sources to separate treatment arms. Recombinant Factor VIIa use could then be evaluated by further subdividing each treatment arm into Factor VIIa use and nonuse categories, and looking at the effect of mortality in each group. Again, as stated in the article, the likelihood of such a trial being conducted is low for ethical reasons.

With regard to fibrinogen administration, based on these preliminary findings, we recommend transfusing a minimum of 200 mg of fibrinogen per red cell unit. Clinicians can meet this requirement by (1) transfusing 1 unit of FFP for every 2 units of red cells, (2) transfusing 1 unit of whole blood for every 4 units of red cells, or (3) transfusing one 10-unit bag of cryoprecipitate initially and then just before every subsequent 10th unit of red cells. Keep in mind that this is a preliminary recommendation based on this analysis only; we plan to analyze larger JTTR data sets in the near future to further refine this recommendation.