

Early Aggressive Use of Fresh Frozen Plasma Does Not Improve Outcome in Critically Injured Trauma Patients

Thomas M. Scalea, MD, Kelly M. Bochicchio, RN, BSN, MS, Kim Lumpkins, MD,
John R. Hess, MD, MPH, Richard Dutton, MD, Anne Pyle, RN, BSN, MS,
and Grant V. Bochicchio, MD, MPH

Objectives: Recent data from Iraq supporting early aggressive use of fresh frozen plasma (FFP) in a 1:1 ratio to packed red blood cells (PRBCs) has led many civilian trauma centers to adopt this resource intensive strategy.

Methods: Prospective data were collected on 806 consecutive trauma patients admitted to the intensive care unit over 2 years. Patients were stratified by PRBC:FFP transfusion ratio over the first 24 hours. Stepwise regression models were performed controlling for age, gender, mechanism of injury, injury severity, and acute physiology and chronic health evaluation (APACHE) 2 score to determine if early aggressive use of PRBC:FFP improved outcome.

Results: Seventy-seven percent of patients were male ($N = 617$) and 85% sustained blunt injury ($n = 680$). Mean age, injury severity score (ISS), and APACHE score were 43 ± 20 years, 29 ± 13 , and 13 ± 7 , respectively. Mean number of PRBCs and FFP transfused were 7.7 ± 12 U, 6 U, and 5 ± 12 U, respectively. Three hundred sixty-five (45%) patients were transfused in the first 24 hours. Sixty-eight percent ($n = 250$) of them received both PRBCs and FFP. Analyzing these patients by stepwise regression controlling for all significant variables, the PRBC:FFP ratio did not predict intensive care unit days, hospital days, or mortality even in patients who received massive transfusion (≥ 10 U). Furthermore, there was no significant difference in outcome when comparing patients who had a 1:1 PRBC:FFP ratio with those who did not receive any FFP.

Conclusion: Early and aggressive use of FFP does not improve outcome after civilian injury. This may reflect inherent differences compared with military injury; however, this practice should be reevaluated.

(*Ann Surg* 2008;248: 578–584)

Critically injured trauma patients presenting in hemorrhagic shock who are unresponsive to crystalloid resuscitation have an absolute indication for early packed red

blood cell (PRBC) transfusion. Signs and symptoms such as hypotension, tachycardia, oliguria, lactic acidosis, and significant base deficit indicate that oxygen consumption is hemoglobin-dependent or at the state of critical oxygen delivery. The prompt transfusion of PRBCs in conjunction with early hemorrhage control can be life saving in this situation.^{1,2}

Patients in hemorrhagic shock who have been identified to have the altered physiologic signs as listed above have been shown to require an increased volume of PRBCs and plasma transfusions.^{3–5} In a study of 5645 patients who sustained acute trauma, we have previously shown that the majority of transfusions (64%) were administered in the first 24 hours of care.³ Only 3% of these patients received more than 10 U of RBCs. Almost all of these patients received plasma and platelet transfusions to treat actual or anticipated dilutional coagulopathy.

Coagulopathy is a common occurrence post injury as patients bleed and undergo aggressive resuscitation. Numerous strategies in regards to the use of fresh frozen plasma (FFP) in critically injured patients exist, which include 1 unit of FFP for every 4 to 10 U of PRBCs transfused and a minimum of 2 U of FFP if the PT is greater than or equal to 1.8 times control. Recently, these strategies have been challenged. Ho et al⁶ recently reported on a pharmacokinetic model to simulate the dilutional component of coagulopathy during hemorrhage and compared various FFP transfusion strategies for the prevention or correction of dilutional coagulopathy. This study documented that once excessive deficiency of factors has developed and bleeding is unabated, 1 to 1.5 U of FFP must be given for every unit of PRBCs transfused. Most recently, Borgman et al⁷ reported a retrospective study of patients with combat-related trauma who required massive transfusion. A high plasma to RBC ratio (1:1.4 U) was independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage.

The adaptation of an early and aggressive transfusion practice that mandates a 1:1 ratio of FFP to PRBCs would clearly impact blood bank resources across the country. Therefore, our goal of the current study was to evaluate the impact of early aggressive FFP transfusion on outcome in critically injured trauma patients who are admitted to the intensive care unit (ICU).

From the R Adams Cowley Shock Trauma Center, Division of Clinical and Outcomes Research, Departments of Surgery, Anesthesiology, and Pathology, University of Maryland School of Medicine, Baltimore, MD. Partial funding was provided by NIH Grant 1T32GM075767. Reprints: Thomas M. Scalea, MD, Room T3R32, R Adams Cowley Shock Trauma Center, 22 South Greene Street, Baltimore, MD 21201. E-mail: tscalea@umm.edu.

Copyright © 2008 by Lippincott Williams & Wilkins
ISSN: 0003-4932/08/24804-0578
DOI: 10.1097/SLA.0b013e31818990ed

MATERIALS AND METHODS

Subject Selection

This prospective cohort study was performed at the R Adams Cowley Shock Trauma Center, the Primary Adult Resource Center (PARC) for the State of Maryland. Appropriate Institutional Review Board approval was obtained before study initiation. Subjects were screened for enrollment over a 28-month period (July 2004–November 2006). Patients were included in this study if they presented to the trauma resuscitation unit within 24 hours of injury and required intensive care unit admission. The exclusion criterion was a nontraumatic reason for admission and transfers from other hospitals.

Data Collection

Prospective data collection included all units of FFP, PRBC, and platelets administered throughout the hospital stay. Transfusion data were ascertained by examining signed transfusion receipts from administered units. Demographic data including age, gender, race, and mechanism of injury were collected on admission. Anatomic injuries were recorded from both clinical documentation and radiographic findings. The injury severity score, admission acute physiology and chronic health evaluation II (APACHE) score, and Glasgow Coma Score (GCS) were calculated in standard fashion. The diagnosis of infection including site and organism was recorded; all infections were diagnosed by infectious disease specialists using Centers for Disease Control criteria when applicable. Data collection was terminated at the time of hospital discharge or death. No postdischarge follow-up was conducted.

Determination of Study Groups

Subjects were subsequently classified according to the need for transfusion of at least 1 unit of PRBC within 24 hours of admission, at least 1 unit of PRBC, and 1 unit of FFP, or no transfusion requirement. For patients receiving both FFP and PRBC within the first 24 hours, a PRBC to FFP ratio was calculated by dividing the number of units of PRBC received by the number of units of FFP received, yielding a low ratio in cases where FFP units predominated and a high ratio in cases where PRBC units predominated. A secondary outcome was defined as the presence or absence of a 1:1 PRBC to FFP ratio (a binary variable), defined as a ratio between 0.9 and 1.1.

Transfusion Policy During Resuscitation

A massive transfusion institutional protocol was in place during the study period that did not include FFP at a 1:1 ratio until after 5 U of PRBCs had been transfused. However, during the course of the study period, early and aggressive use of FFP became more common but was at the discretion of the trauma team on call.

Statistical Analysis

Bivariate analysis was performed using Student *t* test, Wilcoxon rank sum test, and Pearson's χ^2 test as appropriate for continuous and categorical variables. Significance was set at $P < 0.05$. Logistic regression analysis was performed for categorical outcome variables using stepwise methodology to

control for demographic variables and other potential confounders; the same methodology was employed for linear regression of continuous outcome variables. All variables significant to $P < 0.20$ for the outcome of interest were included in the initial model. Entry was set at $P = 0.10$ and removal was set at $P = 0.15$. Age and injury severity score (ISS) were forced to be retained in all models. All analysis was performed using Stata 9.2 (Stata Corporation, Lakewood, TX).

RESULTS

Study Population

Eight hundred six critically injured patients were enrolled in this study. The cohort demographics are described in Table 1. Figure 1 illustrates the breakdown of the study cohort by transfusion in the first 24 hours. Two hundred fifty patients (31%) received both FFP and PRBCs in the first 24 hours ("dual transfusion" group); 115 patients (14%) received PRBCs but no FFP during this period ("PRBC only" group). Thus, 365 total patients (45.6%) received PRBC within the first 24 hours. Forty-one patients (5%) received FFP without PRBC during the first 24 hours (not shown in Fig. 1).

Patients who received any PRBCs during the first 24 hours had a significantly greater number of units transfused over the entire hospital stay than those who did not (median number 9 U PRBC vs. 2 U; P value < 0.001). Similar results were found when examining cumulative FFP units over the hospital stay (median 6 in patients receiving initial RBC transfusion vs. 0 without; $P < 0.001$). Patients receiving PRBC transfusion within the first 24 hours had significantly greater injury severity scores, worse admission glucose and APACHE, higher rates of penetrating trauma, longer hospital and ICU lengths of stay, and a greater rate of nosocomial infection (Table 2) than patients who were not transfused in the first 24 hours. The median number of units of PRBCs given in the PRBC only group was 2, as compared with 6 units for patients in the dual transfusion group ($P < 0.01$). There was no significant difference in demographic factors between the dual transfusion group and the PRBC only group

TABLE 1. Demographics of the Entire Study Cohort

Age	42.5 ± 20
Gender (% male)	77% (N = 617)
Race (% African American)	33% (N = 262)
Mechanism of injury (% blunt)	84.7% (N = 680)
ISS	29 ± 13
PRBC units (entire hospitalization)	7.7 ± 12
FFP units (entire hospitalization)	6.5 ± 12
ICU LOS (d)	13.5 ± 11
Ventilator (d)	13.2 ± 13
Hospital LOS (d)	19.1 ± 14
Nosocomial infection	49% (N = 398)
Mortality	12.8% (N = 102)

Mean ± SD.

ISS indicates injury severity score; PRBC, packed red blood cell; FFP, fresh frozen plasma; LOS, length of stay.

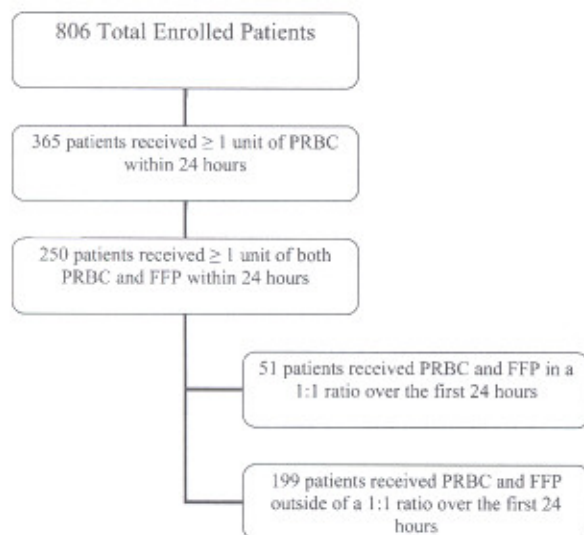


FIGURE 1. Flow diagram of enrolled patients.

with the exception of a significantly higher laparotomy rate in the dual transfusion group (46% vs. 21%; $P < 0.001$).

PRBC to FFP Ratio

Within the dual transfusion group, the mean PRBC to FFP ratio was 1.35 ± 0.90 , the mean number of PRBCs transfused in the first 24 hours was 7 ± 8 , and the mean number of units of FFP transfused was 5 ± 5 . Fifty-one patients (20%) received PRBC and FFP in a 1:1 ratio as described above; 199 patients (80%) did not. Within the non-1:1 group, 72 patients had PRBC to FFP ratios below 0.9, whereas 127 patients had ratios above 1.1. The number of PRBC units transfused in the 1:1 PRBC to FFP ratio group was significantly less than the number transfused in the non-1:1 ratio group (6.5 ± 5.7 vs. 9.3 ± 9.3 ; $P = 0.02$).

Higher admission glucose and the presence of traumatic brain injury were associated with a higher PRBC to FFP ratio

($P < 0.05$); higher admission APACHE, the presence of pelvic fractures, and having a laparotomy were associated with higher PRBC to FFP ratios, but this was not significant (all $P < 0.2$ but > 0.05). No other variable was significantly related to the ratio.

Predictors of Mortality

In the 365 patient cohort who received PRBCs in the first 24 hours, age, hospital length of stay, ICU length of stay, admission APACHE, and brain injury were all significantly related to mortality (all $P < 0.05$) on bivariate analysis. Admission GCS was associated with mortality with $P = 0.19$ and therefore was maintained for subsequent regression analysis. Hospital length of stay (LOS) and ICU LOS were highly correlated ($r = 0.86$) and therefore only ICU LOS was retained for further analysis.

Logistic Regression Analysis Using PRBC to FFP Ratio

A stepwise logistic regression analysis was performed utilizing all variables with P value < 0.20 for predicting the PRBC to FFP ratio or mortality with the exception of the diagnosis of nosocomial infection. The initial model included gender, ISS, age, admission APACHE, pelvic fracture, laparotomy, ICU length of stay, diagnosis of nosocomial infection, admission GCS, and closed head injury. Admission GCS, pelvic fracture, and the diagnosis of nosocomial infection did not reach significance and were eliminated from the model. The final model is presented in Table 3. For a given patient, controlling for age, gender, ISS, head injury (HAIS ≥ 3), mechanism of injury, laparotomy, admission APACHE, and ICU length of stay, the PRBC to FFP ratio given in the first 24 hours had no impact on the risk of death.

Logistic Regression for Mortality Using 1:1 Ratio

A 1:1 PRBC to FFP ratio has previously been suggested to be most beneficial, and extremely high or low ratios may plausibly be detrimental. Therefore, the logistic regression analysis described above was repeated using the 1:1 PRBC to

TABLE 2. Demographics of the Patients Who Received Packed Red Blood Cell Transfusions Versus Patients Who Were Not Transfused in the First 24 Hours

	No Transfusion (N = 441)	PRBC Transfusion (N = 365)	P
Age	42.4 $\pm$ 20	42.6 $\pm$ 20	0.90
Gender (% male)	79% (N = 347)	74% (N = 269)	0.10
Race (% African American)	33% (N = 144)	33% (N = 118)	0.94
Mechanism of injury (% blunt)	90.5% (N = 394)	77.6% (N = 286)	<0.01*
ISS	27 $\pm$ 13	31 $\pm$ 13	<0.01*
Admission glucose	158 $\pm$ 60	193 $\pm$ 75	<0.01*
Admission APACHE	12 $\pm$ 7	15 $\pm$ 7	<0.01*
ICU LOS (d)	12.5 $\pm$ 10.4	14.6 $\pm$ 12.2	<0.01
Ventilator (d)	12.4 $\pm$ 12.1	14.0 $\pm$ 13.0	0.08
Hospital LOS (d)	17.4 $\pm$ 12.8	21.2 $\pm$ 14.8	<0.01*
Nosocomial infection	44.5% (N = 196)	55.0% (N = 201)	0.003*
Mortality	11.5% (N = 50)	14.0% (N = 51)	0.26

* $P < 0.05$.

TABLE 3. Logistic Regression Model Examining the Impact of Packed Red Blood Cell to Fresh Frozen Plasma Ratio on Mortality

	Odds Ratio	95% CI	P
PRBC to FFP ratio	1.23	0.81–1.87	0.34
Age	1.04	1.02–1.07	<0.01*
ISS	1.00	0.97–1.04	0.92
Gender	0.63	0.24–1.66	0.35
Admission APACHE	1.08	1.02–1.15	0.01*
Closed head injury	2.92	1.13–7.55	0.03*
Laparotomy	3.38	1.31–8.72	0.01*
ICU (d)	0.90	0.85–0.95	<0.01*

*P < 0.05.

CI indicates confidence interval.

TABLE 4. Logistic Regression Model Examining the Impact of a 1:1 Packed Red Blood Cell to Fresh Frozen Plasma Ratio on Mortality

	Odds Ratio	95% CI	P
1:1 Ratio	0.57	0.19–1.66	0.34
Age	1.05	1.02–1.07	<0.01*
ISS	1.00	0.97–1.04	0.92
Gender	0.66	0.25–1.78	0.35
Admission APACHE	1.08	1.02–1.15	0.01*
Closed head injury	2.72	1.08–6.84	0.03*
Laparotomy	3.37	1.30–8.74	0.01*
ICU (d)	0.90	0.85–0.95	<0.01*

*P < 0.05.

FFP ratio binary variable instead of the PRBC to FFP ratio itself (Table 4). Again, the presence of a 1:1 ratio was not associated with any protective effect against mortality when controlling for other significant predictors of death.

Massive Transfusion Subgroup

Eighty-one patients were identified from the dual transfusion group who required at least 10 U of PRBC within 24 hours of admission, and the above regression analyses were repeated on this subgroup. No significant effect on mortality was identified for either the PRBC to FFP ratio as a continuous variable (odds ratio (OR), 1.49; 95% CI, 0.63–3.53; $P = 0.37$) or 1:1 ratio as a binary variable (OR, 0.60; 95% CI, 0.21–1.75; $P = 0.35$) when controlling for age, gender, ISS, closed head injury, laparotomy status, and ICU length of stay.

Length of Stay

In bivariate analysis of the dual transfusion group, higher ISS, having a laparotomy, and the diagnosis of nosocomial infection were associated with significantly increased HLOS (all $P < 0.05$). Higher admission APACHE and admission glucose demonstrated a nonsignificant trend towards longer HLOS ($P < 0.2$ but >0.05). Factors associated with increased ICU LOS were similar with the exception of additional nonsignificant trends towards higher ICU LOS with increased age ($P = 0.11$) and blunt mechanism of injury ($P = 0.06$). Stepwise linear regression models were subse-

quently constructed using PRBC to FFP ratio as a predictor for each LOS outcome variable, incorporating the related covariates described above. PRBC to FFP ratio in the first 24 hours was not predictive of increased HLOS (OR, 0.64; 95% CI, –1.23 to 2.51; $P = 0.50$) or ICU LOS (OR, 0.57; 95% CI, –1.07 to 2.22; $P = 0.49$). Using the binary 1:1 ratio variable instead of the continuous PRBC to FFP ratio, no significant relationship was found between a 1:1 ratio and either HLOS (OR, 0.75; 95% CI, –3.5 to 5.0; 0.73) or ICU LOS (OR, 2.09; 95% CI, –1.60 to 5.78; $P = 0.27$).

DISCUSSION

Hemorrhagic shock has been clearly shown to be predictive of early mortality and overall poor outcome in critically injured trauma patients.^{8–16} Hypotension (defined as a systolic blood pressure below 90 mm Hg) in the field or upon arrival to the trauma center in combination with hemorrhage is associated with the systemic inflammatory response syndrome (SIRS), risk of infection (sepsis), and multiple system organ failure.^{6,16–22} Early management of hemorrhagic shock relies heavily on the transfusion of PRBCs, which by itself has been shown to have an exponential increase in infection rate, multiple organ failure (MODS), ICU and hospital length of stay, and mortality.^{6,20–22}

Coagulopathy of Trauma

Critically injured hemorrhagic patients undergo massive resuscitation with a combination of crystalloid and blood products. This process begins in the field by prehospital providers and becomes augmented when they arrive to the trauma center. The lethal triad of hemodilution, hypothermia, and acidosis ensues creating the “blood vicious cycle” unless an intervention is performed that can stop it.^{23–28} If this cycle is not broken, there is a clear pathway to coagulopathic exsanguination. Numerous attempts to interrupt this fatal cycle included damage control surgery or truncated laparotomy, hypotensive resuscitation, effective warming of resuscitation fluids (including allogeneic and shed blood), and innovative products such as Factor VIIa.²⁸ Recently efforts have been focused on the early aggressive use of fresh frozen plasma as a resuscitation strategy as studies have shown that most severely injured patients are coagulopathic at admission, and that traditional massive transfusion practices grossly underestimate the needs for further therapy.⁷

Early Aggressive FFP Strategy

Ho et al⁶ reported on a pharmacokinetic model to simulate the dilutional component of coagulopathy during hemorrhage and compared various FFP transfusion strategies for the prevention or correction of dilutional coagulopathy. This study documented that once excessive deficiency of factors has developed and bleeding is unabated, 1 to 1.5 U of FFP must be given for every unit of PRBCs transfused. This model, however, does not take into account factors such as hypothermia, acidosis, thrombocytopenia, or DIC. Gonzalez et al²⁹ evaluated whether their preintensive care unit massive transfusion protocol adequately corrected coagulopathy (normalization of INR) and impacted mortality. Ninety-seven patients admitted over a 51-month period of time underwent

protocol resuscitation (>10 U of PRBCs) during hospital day 1. All patients did not receive FFP until 6 U of PRBCs were transfused, and the ratio of PRBCs to FFP was greater than 2 to 1. Coagulopathy that was present on admission persisted at ICU admission. The ICU resuscitation protocol used a more aggressive approach to FFP transfusion with a ratio of FFP to PRBCs of 1:1. The mean pH became normal within 8 hours and temperature increased from 35°C to 37°C (within 4 hours). Mean INR decreased from 1.6 to 1.4 within 8 hours and remained constant for the remaining 16 hours of resuscitation. Univariate logistic regression analysis demonstrated that severity of coagulopathy early after ICU admission was predictive of mortality. There was an overall mortality of 29% as 6 patients died during the first 24 hours of ICU admission, 4 died on ICU day 2, and the remaining 19 died later during their hospitalization due to complications. The authors however, presented no evidence that correction of coagulopathy improved survival.

In a retrospective study of 246 patients at a US Army Combat support hospital, each who have received a massive transfusion (>10 U of PRBCs), patients were stratified by ratio (median) of FFP to PRBCs, which were defined as low (1:8), medium (1:2.5) and high (1:1.4).⁷ Median ISS was 18 for all 3 groups with mortality rates of 65% (low), 34% (medium), and 19% (high). In addition, hemorrhage mortality rates were 92.5%, 78%, and 37%, respectively. The authors concluded that a high plasma to RBC ratio is independently associated with survival, and for all practical purposes, massive transfusion protocols should use a 1:1 ratio of plasma to RBCs for all patients who are hypocoagulable with traumatic injuries.

In the current study, for any given patient, controlling for age, gender, ISS, head injury, laparotomy, admission APACHE, and ICU length of stay, the PRBC to FFP ratio given in the first 24 hours had no impact on the risk of death. This held true even in massive transfusion patients (>10 U of PRBCs) despite a high degree of injury as defined by ISS in our study population.

One must ask then why our data seems so different than the data available in the military and possibly even some of the early data from civilian trauma centers. Trauma care during a war is perhaps the best example of an uncontrollable environment. Injury patterns may be different and certainly resources available in most American trauma centers are not always available in the field. Injured soldiers are typically young men with penetrating injury. Using ISS as a marker may well underestimate the true injury severity. Thus, it is possible then that differences in resuscitation strategies that may help save lives in combat troops simply do not reach statistical significance in civilian practice.

Additionally, we studied patients who survived to get to the ICU. One might theorize that patients who would have benefited from a one to one RBC FFP resuscitation scheme simply did not survive to be entered into our study. During our study period, the overall mortality in the first 24 hours after admission was 4%. This increased to 6% for patients who received 10 U or more of PRBCs. The majority of our early deaths were due to either lethal brain injury (55%) or

death immediately upon arrival (25%, median = 36 minutes). These mortality rates are quite lower than those reported by Holcomb and coworkers. Thus, it seems that these patient populations are different, as the number of patients that may have "potentially" survived if given FFP at a higher ratio at our institution in our opinion would be very few.

In addition, the timing of transfusion needs may be more important than the total number of units given. For instance, receiving 10 U of blood over the first 12 hours of hospitalization is far different then requiring 10 U of blood over the first 90 minutes of resuscitation. Conversely, patients that arrive with a mortality in excess of 90% are unlikely to survive, no matter what resuscitation strategy is employed.

It is very likely that a group of patients exists who will benefit from utilizing plasma and red cells in a way different from traditional resuscitation schemes. We have simply not yet defined that patient population. It is likely a combination of anatomic severity and physiologic dysfunction would help identify such a group. However, blind adoption of one to one ratio of red cells to plasma seems unwise. Even patients who come in hemorrhagic shock from isolated splenic injury should be able to have expeditious hemostasis and transfusion as needed but likely do not need plasma. In our own institution and others, we assume patients with steady but not torrential bleeding, such as those undergoing fracture fixation, often receive unnecessary plasma with the needed red cell transfusions. There are clear risks to plasma transfusion and one must at least begin to consider the costs as well.

Taking all of these things into consideration, the authors seriously question whether it is prudent to adopt this resource intensive strategy for all critically injured patients to benefit an undefined select few, at least in the civilian setting. Further research should be directed to identify the patients who may benefit.

REFERENCES

- Napolitano L. Transfusion: management of blood and blood products in trauma. In: Asesio JA, Trunkey DD, eds. *Current Therapy of Trauma and Surgical Critical Care*. Philadelphia, PA: Mosby-Elsevier; 2008: 648–658.
- Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. *Crit Care Clin*. 2004;20:255–268.
- Como JJ, Dutton RP, Scalet TM, et al. Blood transfusion rates in the care of acute trauma. *Transfusion*. 2004;44:809–813.
- Dutton RP, Shih D, Edelman BB, et al. Safety of uncrossmatched type-O red cells for resuscitation from hemorrhagic shock. *J Trauma*. 2005;59: 1445–1449.
- Ruchholtz S, Pehle B, Lewan U, et al. The emergency room transfusion score (ETS): prediction of blood transfusion requirement in initial resuscitation after severe trauma. *Transfus Med*. 2006;16:49–56.
- Ho AM, Dion PW, Cheng CA, et al. A mathematical model for fresh frozen plasma transfusion strategies during major trauma resuscitation with ongoing hemorrhage. *Can J Surg*. 2005;48:470–478.
- Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007;63:805–813.
- El-Masri MM, Hammad TA, Fox-Wasylyshyn SM, et al. Predicting nosocomial bloodstream infections using surrogate markers of injury severity: clinical and methodological perspectives. *Nurs Res*. 2005;54: 273–279.
- Gervin AS, Fischer RP, Gervin AS, et al. Resuscitation of trauma patients with type-specific uncrossmatched blood. *J Trauma*. 1984;24: 327–331.

10. Hamilton SM, Hamilton SM. The use of blood in resuscitation of the trauma patient [comment] [erratum appears in *Can J Surg*. 1993;36:114]. *Can J Surg*. 1993;36:21-27.
11. Hardy JF, de MP, Samama CM, et al. The coagulopathy of massive transfusion. *Vox Sang*. 2005;89:123-127.
12. Harrigan C, Lucas CE, Ledgerwood AM, et al. Primary hemostasis after massive transfusion for injury. *Am Surg*. 1982;48:393-396.
13. Hess JR, Zimrin AB, Hess JR, et al. Massive blood transfusion for trauma. *Curr Opin Hematol*. 2005;12:488-492.
14. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma*. 2007;62:307-310.
15. Malone DL, Hess JR, Fingerhut A, et al. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *J Trauma*. 2006;60:S91-S96.
16. Moore FA, Moore EE, Sauaia A, et al. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Arch Surg*. 1997;132:620-624.
17. Agarwal N, Murphy JG, Cayten CG, et al. Blood transfusion increases the risk of infection after trauma. *Arch Surg*. 1993;128:171-176.
18. Dunne JR, Malone DL, Tracy JK, et al. Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. *Surg Infect (Larchmt)*. 2004;5:395-404.
19. Dunne JR, Riddle MS, Danko J, et al. Blood transfusion is associated with infection and increased resource utilization in combat casualties. *Am Surg*. 2006;72:619-625.
20. Bochiocchio GV, Napolitano LM, Joshi M, et al. Systemic inflammatory response score at admission independently predicts infection in blunt trauma patients. *J Trauma*. 2001;50:817-820.
21. Bochiocchio GV, Napolitano L, Joshi M, et al. Blood product transfusion and ventilator-associated pneumonia in trauma patients. *Surg Infect*. In press.
22. Bochiocchio GV, Napolitano L, Joshi M, et al. Outcome analysis of blood product transfusion in trauma patients: a prospective risk-adjusted study. *World J Surg*. In press.
23. Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. *J Trauma*. 2003;54:1127-1130.
24. Staab DB, Sorensen VJ, Fath JJ, et al. Coagulation defects resulting from ambient temperature-induced hypothermia. *J Trauma*. 1994;36:634-638.
25. Cosgriff N, Moore EE, Sauaia A, et al. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidosis revisited. *J Trauma*. 1997;42:857-861.
26. Ferrara A, MacArthur JD, Wright HK, et al. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg*. 1990;160:515-518.
27. Watts DD, Trask A, Soeken K, et al. Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. *J Trauma*. 1998;44:846-854.
28. Kauvar DS, Kauer CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. *Crit Care*. 2005;9(suppl 5):S1-S9.
29. Gonzalez EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma*. 2007;62:112-119.

Discussions

DR. GRACE S. ROZYCKI (ATLANTA, GEORGIA): This prospective cohort study included patients who presented to the trauma resuscitation unit within 24 hours of admission. Would your conclusions be different if patients with severe traumatic brain injury were excluded, as these patients frequently present with an abnormal coagulation profile? Similarly, what about patients with penetrating trauma?

A recent study by Perkins and coworkers found that their early administration of recombinant factor VII-A de-

creased the use of red blood cells by at least 20% in trauma patients. Did you examine the use of fibrinogen and factor VII-A used in your study population?

Considering your trauma's large attachment area, did time from injury to arrival make a difference in outcome? That is, did a delay in transfusion translate to a greater need for blood? Were these patients more acidotic and hypothermic, clearly factors that could affect their outcome?

Finally, your data indicate that the greatest likelihood of transfusion occurred within the first 24 hours of admission. Considering your high volume trauma center, how does your blood bank maintain the demand for these expensive resources, especially that of thawed plasma? Has this changed your massive transfusion protocol at all?

DR. A. BRENT EASTMAN (SAN DIEGO, CALIFORNIA): Dr. Rozycki addressed an issue that I would like to enlarge upon. Neither you nor Dr. Holcomb specifically mentioned controlling for hypothermia and acidosis, which we know are critical factors in the initial resuscitation process. My question is, did you control for these factors, and was there any difference in your ability to warm Crystalloid versus 1:1:1 during the high volume infusions in this protocol?

DR. HOWARD R. CHAMPION (BETHESDA, MARYLAND): It seems to me that the target of opportunity for this therapeutic regimen (early aggressive use of FFP) is the patient presenting in shock with a coagulopathy on arrival and who is in the process of exsanguinating. This approach is not warranted in the patient who is opting for an elective procedure 24 hours later. To that end, you seem to say that a small patient population may benefit from aggressive use of FFP, specifically only 81 of the patients that you studied. From my estimate, that is, less than 1% of the patient population coming through the Baltimore Shock Trauma Unit per year (this was a 28-month period, 81 patients, and you see 4000 to 5000 patients a year). Given the rarity of this patient even in your unit, can you comment on the powering and the logistics of performing an adequate study to reach a valid scientific conclusion as to the value of early aggressive use of FFP in the critically injured patient?

DR. CHARLES E. LUCAS (DETROIT, MICHIGAN): All of the coagulation factors can be monitored for both activity and for protein content. What is the objective that we are trying to achieve? A deficiency of any one factor to 25% of normal activity will be associated with bleeding, and when multiple factors are deficient to 50%, there will be bleeding. Are we monitoring these factors and are we looking at this scientifically to define our end point?

Secondly, all of our proteins are also present in the interstitial fluid space. Albumin is more in the interstitial space than it is in the plasma volume. This is also true for the coagulation factors. For example, factor VIII, which has a

molecular weight of 800,000, is present in the lymphatic system after it goes through the interstitial space. Therefore, when you give large volumes of plasma you can predict that these proteins will relocate to and slowly egress from the interstitial space. Do you see any differences in the central filling pressure to cardiac work ratios when you give more plasma?

DR. DONALD D. TRUNKEY (PORTLAND, OREGON): It seems to me, going back to the time when I was in San Francisco, that we had a major advantage in blood replacement for trauma because the blood bank was run by physicians; by the San Francisco Medical Society. They would save one third of every day's procurement to be used in the trauma center at night. The next day, if we did not use that blood, they could still get components, except for the platelets.

Why do we not consider forming a uniform study group that looks at this from a nationwide standpoint? We could compare components to whole blood. Another issue is the bank age of the blood, and my belief is that we should use blood that is relatively fresh, less than 24 hours old.

DR. KEITH D. LILLEMOR (BALTIMORE, MARYLAND): Most of us here are not trauma surgeons, but we lose blood performing vascular, GI, or transplant cases. Is there any message that we, who are not trauma surgeons, who require transfusions for our patients can draw from these last 2 articles?

DR. THOMAS M. SCALEA (BALTIMORE, MARYLAND): Rather than addressing each question let me try to make summary comments. This study was a retrospective study review of our practice.

A number of years ago, we adopted a 1:1:1 transfusion strategy. It made so much sense and the preliminary data

from the military was sufficient for us to change our practice. We undertook this study to prove that this change in practice was wise. In fact, we were unable to do so. One reason for this is that we may already have realized all of the advantages of adopting this strategy. For the study, we define 1:1 as being between 0.9 and 1.1:1, which is obviously a very tight range. If we were more liberal, perhaps the results would have been different.

There is no question in my mind that a 1:1 resuscitation is wise in some patients, but we have not yet defined who those patients are. There is also no question in my mind that the most important principle in homeostasis after trauma is rapid identification and treatment of the bleeding sites. No transfusion strategy can substitute for that. In our institution, patients who present with active hemorrhage and are rapidly taken to the operating room for hemostasis often get between 5 and 10 U of blood. Do these patients need a 1:1 transfusion ratio? I would submit to you that the answer is probably not.

There are a number of other factors for which we did not control that may also impact the result. Hypothermia and acidosis resuscitation strategies using platelets, the use of Factor VIIa, and coagulopathy from severe brain injury all could affect our results. I think we all would prefer to use fresh whole blood since this is what patients are bleeding. Unfortunately, this is not available in Baltimore, and I do not believe it is available anywhere else in the United States.

The issues that were defined in this manuscript and the work by Colonel Holcomb are almost certainly translatable to bleeding patients from every discipline. After all, coagulopathy complicates significant blood loss regardless of the cause. There are a number of questions we must continue to ask. This current manuscript was an attempt to add to the discussion on a provocative and very important subject.