Optimizing Outcomes in Damage Control Resuscitation: Identifying Blood Product Ratios Associated With Improved Survival

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Background: **Despite recent attention and impressive results with damage control resuscitation, the appropriate ratio of blood products to be transfused has yet to be defined. The purpose of this study was to evaluate whether suggested blood product ratios yield superior survival rates.**

Materials: **After IRB approval, a retrospective evaluation was performed on all trauma exsanguination protocol (TEP, n = 118) activations from February 1, 2006 to July 31, 2007. A comparison cohort (pre-TEP, n = 140) was selected from all trauma admissions between August 1, 2004 and January 31, 2006 that (1) underwent immediate surgery by the trauma team and (2) received greater than 10 units of PRBC in the first 24 hours. We then compared those who received FFP:RBC (2:3) and platelet:RBC (1:5) ratios with those who did not reach these ratios. Multivariate analysis was performed for independent predictors of mortality.**

Results: **A total of 259 patients were available for study. Patients receiving FFP:RBC at a ratio of 2:3 or greater (n = 64) had a significant reduction in 30-day mortality compared with those who received less than a 2:3 ratio (n = 195); 41% versus 62%, $p = 0.008$. Patients receiving platelets:RBC at a ratio of 1:5 or greater (n = 63) had a lower 30-day mortality when compared with those with who received less than this ratio (n = 196); (38% vs. 61%, $p = 0.001$). Regression model demonstrated that a ratio of FFP to PRBC is an independent predictor of 30-day mortality, controlling for age and TRISS (OR 1.78, 95% CI 1.01–3.14).**

Conclusions: **Increased FFP:PRBC and PLT:PRBC ratios during a period of massive transfusion improved survival after major trauma. Massive transfusion protocols should be designed to achieve these ratios to provide maximal benefit.**

Key Words: **Hemorrhage, Exsanguination, Trauma, Massive transfusion.**

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Hemorrhage is well-known to be a major cause of death after injury and is responsible for 30% to 40% of trauma mortalities with up to half of these deaths occurring during the prehospital period.[1] Exsanguination is a highly lethal event, second only to neurologic injury among causes of mortality after injury.[2–8] After airway management, identification of hemorrhagic shock is the most essential component of the initial management and disposition of patients after injury. Multidisciplinary hemorrhage control in a timely fashion is critical to patient survival and avoidance of the consequences of severe hemorrhage such as multiple system organ failure.[9–11]

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Recent evidence has demonstrated that 25% of trauma patients exhibit overt coagulopathy at the time of admission and that this disturbance is associated with a threefold increase in mortality.[12–14] However, current transfusion recommendations call for withholding plasma transfusions until the prothrombin or activated partial thromboplastin time is greater than or equal to 1.5 times normal.[15,16] Unfortunately, there can be significant delay between ordering the test and obtaining the results, resulting in delay in restoration of clotting factors that exacerbates the lethal triad. This "reactive" approach to hemorrhagic shock in the patient with severe injuries may result in missing the opportunity to preemptively reverse coagulopathy. With the current limitations of diagnostic measures to analyze the extent of coagulopathy, there may be no better measure than the clinical assessment of an experienced surgeon.[17]

Resuscitation of hemorrhage has evolved during the past several decades. Whole blood transfusions were frequently used up until the late 1980s, at which point there was a paradigm shift to component therapy.[18] However, there have been recent reports, primarily from the military literature, recommending component therapy transfusion in similar ratios as that found in whole blood, 1 unit blood:1 unit FFP:1 unit platelets.[19–23] The optimal ratio, if it exists, has yet to be defined for the civilian trauma population.

At our institution, we recently developed a trauma exsanguination protocol (TEP) based on a review of the current

literature, massive transfusion protocols at other institutions, and a consensus among Pathology, Anesthesiology, Hematology, and Trauma at our own institution. On the basis of previous studies, the intention of the TEP was to provide earlier clotting factor replacement and to provide a system that would facilitate early release of blood product components needed to resuscitate hemorrhagic shock.[21,24–26] Our previous work showed a mortality benefit with TEP, possibly related to earlier, intraoperative clotting factor replacement despite similar 24-hour transfusions.[27]

The purpose of this study was to analyze whether a specific ratio of blood components (in and of themselves or as part of a predefined protocol) could impact outcomes in civilian trauma patients.

MATERIALS AND METHODS

Study Setting

This study was approved by the Vanderbilt University Institutional Review Board. Vanderbilt University Medical Center (VUMC) is an academic, Level I trauma center that provides trauma care for a catchment area of approximately 65,000 square miles of the Southeastern United States. The trauma center admits approximately 3,600 acutely injured patients annually with over 800 being admitted to the trauma intensive care unit (ICU). The 14-bed trauma ICU is located within a 31-bed trauma unit. The non-ICU beds include a seven-bed acute admission area and a 10-bed subacute care unit. During the study period, no major changes in patient management were implemented in the ICU. Addition of ventilator management protocols, sepsis bundles, and glycemic control guidelines were instituted well before the initiation of the TEP.

Development of an Exsanguination Protocol

In the spring of 2005, the VUMC Blood Utilization/Transfusion Committee convened a subcommittee which consisted of faculty from the Division of Trauma, the Department of Anesthesiology, the Department of Pathology, and the Department of Hematology to address the problem of rapidly acquiring a large amount of blood products in during the initial management of severely injured patients. Specifically, the group was charged with developing a protocol that would provide blood products to hemodynamically unstable trauma patients in an immediate and sustained manner. Collectively, the committee hoped that these measures would (1) improve access to these products, (2) reduce mortality, and (3) decrease overall blood product utilization.

After an extensive literature review, an examination of established protocols at other institutions (University of Pennsylvania), and discussions with nationally recognized experts in Hematology and Transfusion Medicine, a trauma-specific exsanguination protocol was developed. Specifics regarding the ratios chosen for our protocol resulted from the above efforts and are best summarized in the works of Hirshberg et al.[24] and Ho et al.[25] This protocol was then presented and approved by the Division of Trauma, the Blood Utilization/Transfusion Committee, the Main Operating Room Committee, and the Director of the Blood Bank.

Implementation and Utilization of the Exsanguination Protocol

The VUMC TEP was implemented on February 1, 2006. Upon arrival of a severely injured patient, the attending trauma surgeon analyzes if the patient, based on physiology or injury complex, will likely warrant a blood bank response beyond routine. The attending activates the TEP by notifying the blood bank and supplying the blood bank technician with patient information and disposition. A type and screen is sent immediately to the blood bank through a pneumatic tube system. Upon receipt of phone notification of TEP, the blood bank prepares and dispenses the after blood products as part of the initial response: 10 units of nonirradiated, uncrossed packed red blood cells (PRBC), 4 units of AB negative plasma, and 2 units of single donor platelets. The blood bank then notifies the trauma team that initial response products are en route and asks whether the TEP should continue or cease. As needed, the next round of products is prepared. Subsequent round of blood products contains 6 units of nonirradiated PRBC, 4 units of thawed plasma, and 2 units of single donor platelets. This cycle of dispensing follow-up products continues until terminated by the attending trauma surgeon in the OR. All cases in which the TEP is activated are reviewed as part of the Blood Utilization Committee Performance Improvement (PI) program. Of note, recombinant factor VII (rfVII) was neither included in the protocol, nor was it given to any of the study participants.

Selection of Participants

We prospectively collected demographic, laboratory, blood product utilization, injury severity, and outcome data on all TEP activations as part of our protocol's mandatory PI/QI initiative. The data on all activations is assessed on a quarterly basis. Between February 1, 2006 and July 31, 2007, there were a total of 94 patients who received initial blood products through the TEP. To develop an 18-month comparison cohort, we then queried the institution's Trauma Registry of the American College of Surgeons (TRACS) for all trauma patients admitted from August 1, 2004 to January 31, 2006 who (1) were admitted directly to the trauma service, (2) went immediately to the OR from the trauma bay, (3) were operated on by the trauma team during this initial operation, and (4) received at least 10 units of PRBC during the initial 24 hours. One hundred seventeen patients met these criteria.

Definitions

We evaluated trauma registry data including age, gender, and mechanism of injury. Injury scores, including initial Glasgow Coma Scale (GCS), weighted Revised Trauma

Score (RTS), and Injury Severity Score (ISS) were evaluated as well.

Survival was defined at 30-day postinjury. Predicted survival based on previously described Trauma Related Injury Severity Score (TRISS) methodology was calculated and evaluated. TRISS is calculated and weighted for the patient's ISS, RTS, age, and mechanism of injury. Unexpected survivors were defined as those patients who had a TRISS probability of survival <50% yet survived to discharge from the hospital. Unexpected deaths were defined as those patients who had a TRISS probability of survival >50% yet died before discharge from the hospital. Intraoperative crystalloid administration was defined as all normal saline, lactated Ringer's solution, and Plasmalyte received during the course of the operation. Intraoperative blood products (PRBC, plasma, and platelets) were defined as those products initiated while in the operating room. Twenty-four-hour blood product calculations were defined as the total number of products received 24 hours from time of arrival to the hospital. This included blood in the trauma bay, operating room, and postoperatively up to the 24-hour postadmission mark.

Patients were separated into groups based on FFP:PRBC and PLT:PRBC ratios both intraoperatively and during the first 24 hours after admission. Based on previous work,[24,28] we chose a FFP:PRBC ratio of ≥2:3. Outcome was also evaluated for PLT:PRBC ratio ≤1:5.

Statistical Analysis

The data are represented as medians with interquartile ranges because of its distribution. Differences between groups were evaluating using Wilcoxon's rank sum test for continuous variables, and χ^2 for categorical variables. To evaluate the differences in FFP:PRBC ratios, the patients were divided into four separate groups as follows: 0:1 to 1:2.9, 1:3 to 1:1.49, 1:1.5 to 0.9:1, ≥1:1. Nonparametric analysis of variance (Kruskal-Wallis test) was performed to analyze differences between the groups.

Multivariate analysis was performed using 30-day survival as the outcome measure. Continuous variables were chosen secondary to their significance in the univariate model and clinical importance. Colinear variables were identified using nonparametric correlation tests. Logistic regression analysis was performed using TRISS, age, and intraoperative FFP:PRBC ratios. A p value of 0.05 was considered significant. Computer software was used to perform the statistical analysis (SPSS, version 15.0, Chicago, IL).

Patients were separated according to FFP:PRBC ratio and a graphical representation of unadjusted mortality was then created (GraphPad, Prism 5.0).

RESULTS

A total of 259 patients were available for this study. Demographic comparison was made between survivors and nonsurvivors. Nonsurvivors were more severely injured and were more likely to have penetrating mechanisms of injury (Table 1).

Table 1 Demographics and Clinical Features, Comparison Between 30-d Survivors and Nonsurvivors

	Nonsurvivor (n = 144)	Survivors (n = 115)	p
Median age, yrs (IQR)	34.5 (24–50)	31 (23–43)	0.08
Male patients, n (%)	108 (75)	86 (75)	0.97
Penetrating injuries, n (%)	89 (62)	54 (47)	0.02
Median ISS (IQR)	25 (18–41)	25 (16–32)	0.01
RTS (IQR)	2.1980 (1.16–3.34)	2.9304 (2.23–6.67)	<0.01
TRISS (IQR)	0.2220 (0.03–0.63)	0.6030 (0.22–0.94)	<0.01
Unexpected deaths, n (%)	34 (24)	N/A	N/A
Unexpected survivors, n (%)	N/A	27 (24)	N/A
24-h survival, n (%)	51 (35)	115 (100)	<0.01
Received TEP	56 (39%)	61 (53%)	0.02

IQR indicates interquartile range; TEP, trauma exsanguination protocol.

Transfusion data were compared between survivors and nonsurvivors. Survivors were found to have decreased intraoperative and 24-hour PRBC transfusion. FFP:PRBC and PLT:PRBC ratios were higher for survivors. The FFP:PRBC ratio remained higher at 24 hours, whereas the PLT:PRBC ratios were similar. Patients who achieved an intraoperative and first 24-hour FFP:PRBC ratio greater than or equal to 2:3 were more likely to survive. Patients who did not achieve a PLT:PRBC ratio of 1:5 or better were less likely to survive (Table 2).

Demographic data were compared between patients who did and did not receive TEP. Patients who received the transfu-

Table 2 Comparison Between 30-d Survivors and Nonsurvivors

	Nonsurvivors (n = 144)	Survivors (n = 115)	p
Median intra-op FFP:PRBC ratio (IQR)	0.41 (0.15–0.55)	0.57 (0.33–0.89)	<0.01
Median intra-op PLT:PRBC ratio (IQR)	0.05 (0–0.13)	0.11 (0–0.25)	0.01
Median 24 h FFP:PRBC ratio (IQR)	0.50 (0.26–0.77)	0.72 (0.50–1.00)	<0.01
Median 24 h PLT:PRBC ratio (IQR)	0.17 (0.41–0.36)	0.23 (0.07–0.45)	0.22
Intra-op FFP:PRBC ratio ≥2:3, n (%)	27 (19)	37 (32)	0.01
24 h FFP:PRBC: FFP ratio ≥2:3 (%)	41 (29)	57 (50)	<0.01

All blood products are measured as number of units transfused. IQR indicates interquartile range.

Table 3 Demographic and Clinical Features, Comparison Between Patients Who Did and Did Not Receive Trauma Exsanguination Protocol (TEP)

Received TEP	Pre-TEP (n = 140)	TEP (n = 119)	*p*
Median age, yrs (IQR)	36 (24–50)	30 (24–43)	0.15
Male patients, n (%)	107 (76)	88 (75)	0.73
Penetrating injuries, n (%)	86 (61)	56 (48)	0.03
Median ISS (IQR)	25 (16–34)	25 (24–41)	<0.01
Median RTS (IQR)	2.9304 (2.2–6.9)	2.9300 (1.47–6.38)	0.01
Median TRISS (IQR)	0.5440 (0.21–0.92)	0.1977 (0.04–0.77)	<0.01
Unexpected death, n (%)	26 (19)	8 (7)	0.01
Unexpected Survivors, n (%)	6 (4)	21 (18)	<0.01
24-h survival, n (%)	86 (61)	77 (65)	0.63
30-d survival, n (%)	53 (37)	61 (52)	0.02

IQR indicates interquartile range; TEP, trauma exsanguination protocol.

sion protocol were more severely injured but had a lower incidence of penetrating mechanism of injury. Although 24-hour survival was similar, 30-day survival was significantly increased in the TEP group (Table 3).

Transfusion data were compared between TEP and non-TEP. TEP patients received more intraoperative blood product of all types. The intraoperative ratio of PLT:PRBC was greater in the TEP group (0.12 vs. 0.0, $p < 0.01$). Intraoperative FFP:PRBC ratios were higher in the TEP group, but this did not reach statistical significance (0.5 vs. 0.43, $p = 0.09$). Although the chance of reaching an intraoperative FFP:PRBC ≥2:3 was similar between the groups, TEP patients were more likely to reach a PLT:PRBC ratio of 1:5 than non-TEP patients at 24 hours (58% vs. 37%, $p < 0.01$) and intraoperatively (63% vs. 42%, $p < 0.01$) (Table 4).

For the overall study group, patients receiving FFP:RBC at a ratio of 2:3 or greater (n = 64) had a significant reduction in 30-day mortality compared with those who received less than a 2:3 ratio (n = 195); 41% versus 62%, $p = 0.008$. Patients receiving platelets:RBC at a ratio of 1:5 or greater (n = 63) had a lower 30-day mortality when compared with those with who received less than this ratio (n = 196), though this did not reach statistical significance (38% vs. 61%, $p = 0.001$). Patients receiving FFP:RBC at a ratio of 1:1 or greater (n = 45) had a significant reduction in 30-day mortality compared with those who received less than a 1:1 ratio (n = 214); 49% versus 57%, $p = 0.32$. Additionally, we evaluated several ratios that have previously described (Fig. 1). The lowest 30-day mortality was noted for the intraoperative FFP:RBC between 1:1.5 and 1:1.01 (36%). This was significantly less than mortality rates for all other ratio ranges ($p < 0.001$). The majority of patients receiving ≥1:5 platelets: PRBC actually received a ratio of exactly 1:5. In fact, only 11 of the 63 patients with a ratio of 1:5 or greater actually received a ratio of ≥2:5 and only 1 patient received a ratio of ≥3:5. In light of these findings, we did not pursue a stratified ratio group evaluation for platelets.

Table 4 Transfusion Data Comparison Between Patients Who Did and Did Not Receive TEP

	Pre-TEP (n = 140)	TEP (n = 119)	*p*
Median intra-op FFP: PRBC (IQR)	0.43 (0.09–0.80)	0.50 (0.34–0.67)	0.09
Median intra-op PLT: PRBC (IQR)	0 (0–0.11)	0.12 (0.03–0.25)	<0.01
Median 24 h FFP: PRBC (IQR)	0.60 (0.31–0.97)	0.57 (0.38–0.80)	0.54
Median 24 h PLT: PRBC (IQR)	0.25 (0.04–0.50)	0.14 (0.06–0.25)	<0.01
Intra-op FFP:PRBC ratio ≥2:3, n (%)	37 (26)	27 (23)	0.47
24 h FFP:PRBC ratio ≥2:3, n (%)	56 (40)	42 (36)	0.39
Intra-op PLT:PRBC ratio ≥1:5, n (%)	61 (42)	74 (63)	<0.01

All blood products are measured as number of units transfused. TEP indicates trauma exsanguination protocol.

Odds ratios for 30-day survival were then calculated using logistic regression analysis. TRISS, intraoperative FFP: PRBC ratio, and age were entered into the regression model. Each variable was identified to be an independent predictor of 30-day survival (Table 5).

DISCUSSION

Increasing evidence has emphasized the importance of identification and treatment of coagulopathy in the early stages after trauma.[14,17,29–31] Given the inherent delays and inaccuracies involved with laboratory-guided transfusions and resuscitations, many institutions have implemented massive transfusion protocols. Our center recently addressed the problems of "reactive-resuscitation" strategies by developing

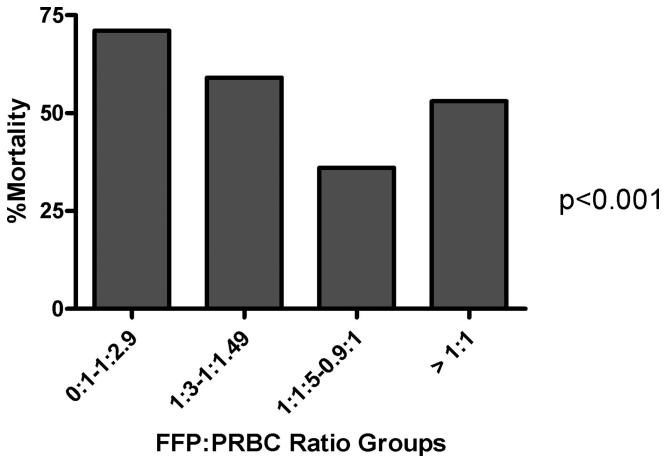

Fig. 1. *Unadjusted mortality after trauma and massive transfusion, comparison of FFP:PRBC ratios.*

Table 5 Multivariate Logistic Regression Model

Variable	Odds Ratio (95% CI)	*p*
TRISS	5.56 (2.63–11.74)	<0.01
Age	0.98 (0.97–0.99)	0.03
Intra-op FFP:PRBC ratio	1.78 (1.01–3.14)	0.04

Odds ratios predictive of 30-d survival for trauma patients requiring massive transfusion.

and implementing a "proactive" strategy aimed at rapid and continuous delivery of blood component therapy. This protocol involves the release from the blood bank of predefined ratios of PRBC, platelets, and FFP. Through the utilization of this protocol, we have previously shown a mortality benefit and a decrease in total number of blood products used in comparison with patients with similar injuries.[27] Currently, however, there is no universally accepted consensus regarding the ratios of blood components for massive transfusion.

Several authors have recently advocated the use of 1:1:1 (PRBC, plasma, platelets) in addressing patients requiring massive transfusion.[20,28,31] One such approach has been to use whole blood transfusions which deliver red blood cells, plasma, and platelets in approximately a 1:1:1 ratio. Borgman et al.[28] in a military study reviewed military trauma patients and found that the lower ratio patients had a significant improvement in survival. Interestingly though, while striving for a 1:1 ratio of FFP:PRBC, the investigators more commonly reached a ratio of 2:3. This is the ratio advocated by Hirshberg et al.[24] who developed an optimum minimal ratio by computer models of hemorrhage. Our protocol was developed on the work of this model as well as that of the protocol used at the Hospital of the University of Pennsylvania (HUP) and that of previously published recommendations of Ho et al.[25] The current findings support the use of a 2:3 ratio of FFP:PRBC and demonstrate that blood component ratios may significantly impact outcome in the civilian setting, particularly with regard to 30-day survival. However, in the current study, those patients receiving transfusions in a 1:1 (FFP:PRBC) fashion did not appear to have any greater improvement in survival above that observed in the 2:3 (FFP:PRBC).

Recently, investigators advocating the administration of FFP:PRBC in a 1:1 fashion have also recommended initiation of massive transfusion with platelet:PRBC ratios of 1:1.[20,28] This ratio was met with great skepticism and opposition by our Transfusion Medicine colleagues and by that of our Transfusion Committee. In the absence of evidence to support such a ratio, we deferred to the data available at the time and that of a successful program at another trauma center (HUP) and instead used a 1:5 ratio of platelets:PRBC. Survival was associated with a higher ratio of platelets to RPBC and early and intraoperative achievement of a 1:5 ratio significantly reduced the odds of mortality. Interestingly, this was achieved with a lower overall transfusion of platelets (at 24-hours postoperatively).

Within the current patient sample, the odds of survival increase as the FFP:PRBC ratios increase intraoperatively. This was independent of age and TRISS, which by themselves are independent predictors of mortality as well. Based on this current data, we recommend initiation of massive transfusion for any patient with hemorrhage after injury deemed likely to require in excess of 10 units of blood. FFP:PRBC ratios of 0.67 (2:3) and PLT:PRBC ratios of 0.2 (1:5) appear to be reasonable targets of early, massive transfusion.

Additionally, it remains unclear whether the presence of a protocol (not the precise ratios) is responsible for the reduction in mortality associated with protocolized transfusion strategies. The protocol at our institution currently delivers ratios of 2:5 and 1:5 for FFP:PRBC and PLT:PRBC, respectively, for the first set of products. Subsequent iterations of the protocol deliver ratios of 2:3 and 1:3 for FFP:PRBC and PLT:PRBC. A critical point is that the increased intraoperative ratios are reflective of earlier transfusion of plasma and platelets, and we think that this should be a protocolized approach at institutions that care for these types of patients. The TEP in this study did provide a greater volume of blood products which per our previous study provides a survival benefit. That it did not reach ratios that were found to predictive of survival is a matter of process improvement. Our intent is to alter the TEP within our own institution to achieve higher ratios as identified in this study and to continue strict quality control to ensure that there is adherence to the protocol.

There are several limitations to this study. Its retrospective nature brings into question the true similarity of the comparison samples, as well as whether or not the outcomes are truly a result of the studied intervention. Although the univariate analysis shows a decrease in age between survivors and nonsurvivors, this is not a clinically significant difference. A further limitation is the post hoc evaluation of varying blood product ratios, and this is an intended area of future prospective study.

CONCLUSIONS

Damage control resuscitation and the strategy aggressively addressing massive transfusion requirements has recently gained attention with impressive results reported in both the military and civilian settings. The appropriate ratio of blood products (e.g., plasma:packed red blood cells) to be transfused, however, has remained quite controversial. We have previously developed an exsanguination protocol that involves the immediate, continued release of predefined ratios of RBC, FFP, and platelets. The present study set out to identify whether our certain blood product ratios yield superior survival rates when delivered through a defined protocol. When massive transfusion is required, empiric delivery of higher, predefined FFP:PRBC and PLT:PRBC ratios improve survival. These ratio targets may be more easily reached by using a predetermined massive transfusion protocol.

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DISCUSSION

Dr. Jeffry Kashuk (Denver, Colorado): Through the 1990s to the current era, post-injury coagulopathy has remained the most prevalent and compelling reason for damage control staged laparotomy and these techniques have become standard for patients receiving massive transfusion, but despite these advances, mortality has not changed significantly over the past ten to fifteen years in this group.

A paradigm shift occurred with the current military experience, suggesting that immediate 1:1 FFP to RBC for casualties requiring greater than ten units of PRBCs in twenty-four hours, or damage control resuscitation, is independently associated with improved survival.

In fact, published consensus conferences, as well as recent civilian studies, appear to support damage control resuscitation, although the scientific basis for this policy remains to be established. Furthermore, growing concerns regarding transfusion-associated lung injury, TRALI, and multiple organ failure, MOF, associated with unbridled FFP administration must be balanced with evolving civilian massive transfusion guidelines which embrace liberal FFP administration.

The Vanderbilt group has recently re-designed their massive transfusion policy and today present their experience with optimizing outcomes in damage control resuscitation by preemptive PRBC: FFP ratios, in an effort to approach 1:1.

Dr. Cotton was kind enough to send me the manuscript well ahead of the meeting and I'll try to outline some of the salient points of the paper. The authors prospectively established a set blood delivery system, termed TEP (trauma exsanguination protocol).

The main principle of the protocol was to establish a set blood product delivery program, in an attempt to achieve a pre-defined ratio of greater than or equal to 2:3 FFP: PRBC and greater than or equal to 1:5 PRBC to platelets. The authors then evaluated retrospectively the amount of products delivered, the ratios achieved, and mortality statistics in comparison to historical controls of their prior routine resuscitation protocol.

Based upon their study, the authors found that their TEP achieved their goal ratios in about 25 percent of patients and

further concluded that the intraoperative and first twenty-four-hour ratios resulted in a reduced thirty-day mortality.

I have several questions for the authors: 1) The authors define their massive transfusion protocol as ten units or greater in twenty-four hours and evaluated ratios and their impact up to twenty-four hours, although recent data presented at the AAST by our institution and others suggest that more than 80% of transfusions in this group occur in the first six hours, suggesting that perioperative ratios are probably the most difficult to achieve, yet the most indicative of the acute hemorrhagic insult in these patients. Did the authors look at their six-hour threshold? 2) In our study in Denver, over 50% of deaths occurred secondary to exsanguinating penetrating injuries in the operating room. The authors noted that their TEP group had a statistically significant decrease in penetrating injuries in comparison to the historical group and therefore, does your data showing improved survival with improved ratios truly reflect a similar patient cohort in comparison to your TEP group? 3) Although the improved thirty-day survival in your TEP group is attributed in part to decreased blood products, no data on total products administered was provided in the manuscript. I understand that this issue was addressed in another, yet unpublished paper, but the data is inadequately presented in the current paper. 4) The authors state in the manuscript that giving a defined ratio approaching 1:1 obviates coagulation and hematological profiles. Have you really shown this? Did you evaluate coagulation studies in your patients? More importantly, can we really assume that empiric transfusion of set ratios obviates any coagulation testing, especially since POC thromboelastography is emerging as a valuable technique for rapid assessment of coagulation?

Finally, I have concerns regarding your statistical model. While univariate analysis of the data provides general data on transfusions, ratios and mortality, the complexity of factors contributing to transfusion and coagulation, including age, ISS, temperature, ph, and crystalloid administration, must be controlled for in a multiple logistic regression analysis, yet the authors only entered TRISS, intraoperative ratios, and age into their model.

For this very reason, a multi-center study led by Col. Holcomb is currently collecting data from many centers, in order to adequately power such an analysis.

Dr. Oliver Gunter (Nashville, Tennessee): With regard to the question about massive transfusions: did we look at the first six hours? No, we did not look at the first six hours after admission. The first twenty-four hours is what our data captured. We had the intraoperative numbers, which we at least would have assumed would account for the earlier transfusion and the early acute physiology including resuscitation endpoints. Again, six hours, no, we did not specifically look at six hours.

The second question was regarding the differences in the mechanisms of injury, were they the same? Again, we bring that out as a limitation of the study and we realize that in a retrospective fashion, in a non-prospective randomized study like this was, that there probably were some differences in the mechanisms and these may not be the same exact patients. We know that as a limitation of our study.

The third question was did we have data for the blood products and we actually did. As you had noted, we presented this at the AAST meeting and went through fairly briefly in this presentation that the transfusion requirements over the first twenty-four hours, the blood and platelet overall were less.

In other words, we used less blood and platelets in the TEP group, the protocol group, compared to the pre-protocol group. We think that's because we were giving them more products in the operating room, but compared to the pre and post-protocol group, we actually used less blood and less platelets after the protocol. The FFP utilization was the same.

The next question was regarding the endpoints of coagulation studies and whether the protocol actually fixed the standard coagulation parameters that we normally follow in the ICU setting when we're doing what we call a reactive transfusion.

We had some data for that, but it was incomplete and so we felt like that was probably not something that we should include with this, but another point is that we think that those studies are severely limited. I do agree that the thromboelastrogram may be something we should look into as a coagulation endpoint. The standard coagulation studies we think fall a little bit short though.

Finally, the question with regard to the statistical model, particularly the multivariate analysis, we do acknowledge that pH and temperature are important factors to consider. We do not have temperature data and we have incomplete ph data, because of the – I guess because of the emergent setting, we think. We didn't always get blood gas data on all these patients in the initial pre-operative setting but later we got it intraoperatively, from our anesthesia colleagues. Most importantly, even though this is a limited retrospective study, that this certainly sets the stage for the prospective multi-center trial.

Dr. Juan Duchesne (New Orleans, Louisiana): I really liked your presentation and we actually presented similar data at the AAST in September. Currently, in New Orleans, we've been using damage control resuscitation for the last year with improved survival in patients with severe blood loss. The key component of damage control resuscitation is early correction of coagulopathy in combination with aggressive correction of hypothermia and acidosis with damage control surgery.

Two questions. When you talk about the selection in your patients, I noticed that you didn't specify any objective score that trigger the initiation of your transfusion protocol or any other kind of clinical indicators. How this selection bias impact your outcomes?

Number two, I noticed that your ratio was actually ten to six to four or to two. Our ratio in our trauma hospital is currently six FFP, six PRBC and six platelets with inclusion of cryoprecipitate on the second transfusion run. Do you think that by having a lower number of platelets will explain your outcomes in your multivariable relationship consistent with difference?

Dr. Oliver Gunter: The question about the clinical indicators for the protocol, I think that's a limitation of this. As you can imagine, when these patients survive, they're sick. Within about a five-minute period of time, we make a clinical judgment as to whether or not we think they need massive transfusion; we activate it then right then and there.

I don't think we've perfected what the clinical indicators of massive transfusion are, but that's certainly something that we need to keep looking at and keep trying to find the answer to. The second question was did our ratios potentially affect our multivariate analysis and most certainly they could.

We think, at least at what we've looked at in other studies, that our first batch ratio was ten and four and two. We already have increased our FFP administration as part of that protocol.

The platelets, we had that fitted to the regression model and it certainly could have affected it, but thank you for your question.

Dr. Martin Schreiber (Portland, Oregon): Early on in resuscitations, patients get a low ratio of plasma to red cells and this ratio improves over time due to the logistics of getting blood products. Therefore, if a large number of your patients are dying early, by definition they're going to have a low ratio. Did you control for this problem by analyzing the time of death for your patients?

Many hospitals don't have the availability of thawed plasma and so the initial resuscitation is primarily with red cells and therefore, early deaths, by definition, will have a low ratio of plasma to red cells. You have to control for this to make your results valid.

Dr. Oliver Gunter: We did not control for the time of death. That certainly could have affected the analysis.

Dr. John B. Holcomb (San Antonio, Texas): I would like to congratulate you and your co-authors and institution for continuing to address one of the leading potentially preventable causes of death, which is bleeding, with how we resuscitate patients and I reiterate the six-hour mark that Dr. Kashuk and Dr. Schreiber were talking about. I think it's very important.

My question relates to the ''so called unbridled use of plasma'' and the associated decrease in mortality of 37 percent in your study. The question is what was your rate of multiorgan failure and TRALI in both groups?

Dr. Oliver Gunter: We currently in our dataset don't have the numbers for TRALI and for multiple organ system failure. That's something that we intend to look at in a future study.