Predefined Massive Transfusion Protocols are Associated With a Reduction in Organ Failure and Postinjury Complications

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Introduction: **Massive transfusion (MT) protocols have been shown to improve survival in severely injured patients. However, others have noted that these higher fresh frozen plasma (FFP): red blood cell (RBC) ratios are associated with increased risk of organ failure. The purpose of this study was to determine whether MT protocols are associated with increased organ failure and complications.**

Methods: **Our institution's exsanguination protocol (TEP) involves the immediate delivery of products in a 3:2 ratio of RBC:FFP and 5:1 for RBC:platelets. All patients receiving TEP between February 2006 and January 2008 were compared with a cohort (pre-TEP) of all patients from February 2004 to January 2006 that (1) went immediately to the operating room and (2) received MT (≥10 units of RBC in first 24 hours).**

Results: **Two hundred sixty-four patients met inclusion (125 in the TEP group, 141 in the pre-TEP). Demographics and Injury Severity Score were similar. TEP received more intraoperative FFP and platelets but less in first 24 hours ($p < 0.01$). There was no difference in renal failure or systemic inflammatory response syndrome, but pneumonia, pulmonary failure, open abdomens, and abdominal compartment syndrome were lower in TEP. In addition, severe sepsis or septic shock and multiorgan failure were both lower in the TEP patients (9% vs. 20%, $p = 0.011$ and 16% vs. 37%, $p < 0.001$, respectively).**

Conclusions: **Although MT has been associated with higher organ failure and complication rates, this risk appears to be reduced when blood products are delivered early in the resuscitation through a predefined protocol. Our institution's TEP was associated with a reduction in multiorgan failure and infectious complications, as well as an increase in ventilator-free days. In addition, implementation of this protocol was followed by a dramatic reduction in development of abdominal compartment syndrome and the incidence of open abdomens.**

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

J Trauma. 2009;66:41–49.

Massive transfusion (MT) protocols provide large amounts of blood products to critically injured patients in an immediate and sustained manner.[1] The delivery of these products in predefined ratios of plasma and platelets to packed red blood cells (PRBC) reduces the severity of trauma-associated coagulopathy.[2] The concept of damage control resuscitation combines early delivery of blood component therapy (PRBC, plasma, and platelets) with permissive hypotension and minimizing of crystalloid based resuscitation.[3–5] Both military and civilian investigators have reported that this proactive approach to resuscitation results in a significant reduction in trauma-related mortalities.[5,6]

Submitted for publication August 20, 2008.

Accepted for publication October 28, 2008.

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Presented at the 67th Annual Meeting of the American Association for the Surgery of Trauma, September 24–27, 2008, Maui, Hawaii.

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DOI: 10.1097/TA.0b013e31819313bb

The dramatic reduction in mortality associated with these MT protocols has been primarily attributed to the empiric delivery of higher, predefined plasma: RBC and platelet concentrates (PLT):PRBC ratios.[7–10] These ratio targets are more readily achieved when part of a well-defined, predetermined protocol.[6,7,11,12] Stinger et al. noted that transfusion of an increased fibrinogen (plasma):PRBC ratio was independently associated with improved survival to hospital discharge, primarily through a reduction in death from hemorrhage.[6] Similarly, Gunter et al. demonstrated that transfusion of higher plasma:PRBC and platelet:PRBC ratios improved survival in patients undergoing MT.[7] The survival benefit remained even after adjusting for age, mechanism, injury severity, and physiologic instability.

Although an increased body of literature would support the use of higher ratios of plasma and platelets in the patient receiving MT, other investigators have noted that these blood components may be associated with an increased risk of infection and organ failure.[13–15] In a study of surgical intensive care patients, Sarani et al. noted that transfusion of plasma was associated with an increased risk of infectious complications, with a 4% increase in the odds risk of infection per unit of plasma.[15] Similarly, Vamvakas and Carven found the risk of pneumonia was increased by 5% percent per unit of PRBC or platelets transfused.[16] Though neither of

these studies was conducted in a trauma population, the results are of definite concern to those ordering the transfusion of large amounts of these products to the critically injured patient. The purpose of this study was to analyze whether MT protocols and their large amounts of plasma and platelets are associated with increased organ failure and complications.

PATIENTS AND METHODS

Study Setting

The Vanderbilt University Institutional Review Board approved this study. Vanderbilt University Medical Center (VUMC) is a state verified Level I trauma center that provides care for a catchment area of approximately 65,000 square miles of the Southeastern United States. The trauma center cares for approximately 3,900 acutely injured patients annually, 2,500 of which are admitted to the Trauma service, with 800 patients 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.

Development of an Exsanguination Protocol

In the spring of 2005, the VUMC Blood Utilization/Transfusion Committee convened a subcommittee to address the problem of rapidly acquiring a large amount of blood products 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. Additionally, it was thought that the delivery of these blood products in a predefined ratio would prevent the development or at least decrease the severity of traumatic coagulopathy. This last goal would in theory obviate the need for and dependence on serial coagulation and hematological profiles. Collectively, the committee hoped that these measures would (1) improve access to these products, (2) reduce mortality, and (3) decrease overall blood product utilization. This subcommittee consisted of faculty from the Division of Trauma, the Department of Anesthesiology, the Department of Pathology (Transfusion Medicine), and the Department of Hematology. The resulting protocol was presented and approved by the Division of Trauma, the Blood Utilization/Transfusion Committee, the Main Operating Room Committee, and the Director of the Transfusion Service. Finally, the protocol was presented and approved at the VUMC Perioperative Enterprise Committee, chaired by the Departmental Chiefs of the Section of Surgical Sciences and Anesthesiology.

Implementation and Utilization of the Exsanguination Protocol

The VUMC Trauma Exsanguination Protocol (TEP) was implemented on February 1, 2006. The steps and process of the protocol are as follows: upon arrival of a severely injured patient, the attending trauma surgeon determines 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 the following information: the attending surgeon's name and the patient's "Stat" name, patient sex, medical record number, and the operating room (OR) location where blood products are to be delivered. A type and screen is sent immediately to the blood bank through a pneumatic tube system. Upon receipt of phone notification of TEP (by the trauma attending only), the Blood Bank prepares and dispenses the following blood products as part of the initial response: 10 units of nonirradiated, uncrossed PRBC, 4 units of AB-negative plasma, and 2 units of single donor platelets or two apheresis packs (both equivalent to traditional 10 packs of pooled platelets). The Blood Bank then notifies the trauma team that initial response products are en route and ascertains whether the TEP should continue or cease. If the blood bank personnel are told to continue, the next round of products is prepared. If the protocol is to continue the following products will be delivered as soon as they are prepared: 6 units of nonirradiated PRBC, 4 units of thawed plasma, and 2 units of single donor platelets. This cycle of dispensing follow-up products will continue until terminated by the attending trauma surgeon in the OR. Cryoprecipitate is made available for all cycles upon physician request. For each new cycle of products generated, the Blood Bank contacts the OR to notify them that the next round of products is en route and to get the trauma attending's direction as to whether or not to continue the protocol. TEP activation is a quality performance indicator at our institution as mandated by the Perioperative Committee. All cases in which the TEP is activated are reviewed as part of the Blood Utilization Committee Performance Improvement (PI) program.

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 initiative. The data on all activations are assessed on a quarterly basis. Between February 1, 2006 and January 31, 2008, there were a total of 125 patients who received initial blood products through the TEP. To develop a 24-month comparison cohort (pre-TEP), we attempted to choose what we thought would be the most comparable group with those who had, in the experience of our PI/QI group, been receiving the TEP in the previous 2 years. These were patients that were (1) taken directly to the OR from the trauma bay, (2) went to the OR with the trauma team, and (3) those receiving at least 10 units of blood. To this end, we then queried the institution's Trauma Registry of the American College of Surgeons 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 forty-one patients met these criteria.

Definitions and Outcomes

We evaluated trauma registry data including age, gender, and mechanism of injury. Injury scores, including initial Glasgow Coma Scale, weighted Revised Trauma Score (w-RTS), and Injury Severity Score (ISS) were evaluated as well. The w-RTS incorporates the initial Glasgow Coma Scale, systolic blood pressure, and respiratory rate, using coded and weighted values that range from 4 (normal) to 0 (poor) for each of the physiologic variables (yielding a high of 7.841 and a low of 0). Abbreviated Injury Scale (AIS) is an anatomic injury scoring system that quantifies injuries in various body regions from a score of 1 (minor injury) to 6 (nonsurvivable). ISS is calculated by summing the squares of the three highest AIS scores in three different body regions (values range from 1 to 75).

The primary outcomes of interest were the development of single system and multiple organ failures (MOFs). Organ dysfunction and MOF were defined using the Denver MOF scoring system.[17–19] This system evaluates four organ systems: pulmonary, hepatic, renal, and cardiac. Organ dysfunction is graded on a scale from 0 to 3. The pulmonary score is determined by the Pao_2/FIO2 (P/F) ratio. P/F ratios greater than 208 received 0 points, whereas ratios of 208 to 165, 165 to 83, and 83 received 1, 2, and 3 points, respectively. The renal system was graded by serum creatinine level in mg/dL: 0 points for $<$1.8, 1 point for 1.8 to 2.5, 2 points for 2.5 to 5.0, and 3 points for $>$5.0 mg/dL. The hepatic score was calculated by total serum bilirubin level in mg/dL: 0 points for bilirubin $<$2.0, 1 point for 2.0 to 4.0, 2 points for 4.0 to 8.0, and 3 points for bilirubin $>$8.0 mg/dL. Cardiac dysfunction was graded based on inotropic support and cardiac index (CI). No inotropes and cardiac index $>$3.0 L/min per meter squared yielded a score of 0, whereas minimal inotropic support or CI $<$3.0 yielded a score of 1. Moderate and high-dose inotropic received scores of 2 and 3, respectively. For MOF, the MOF score was calculated as the sum of the simultaneously obtained individual organ scores on each hospital day. Single system organ failure was defined as an organ failure grade greater than 0, and MOF was defined as a total score of 4 or higher.[18,19] However, organ dysfunction occurring in the first 48 hours of admission was not considered to be single system organ failure nor was it used to calculate MOF score. This is in keeping with the concept put forth by Ciesla et al. that multiple organ dysfunction (not organ failure) occurring within the first 48 hours of injury represents reversible physiologic responses to injury and resuscitation that have the potential for resolution once resuscitation is complete.[20]

Secondary outcomes evaluated include infectious complication, lengths of stay, and abdominal wall complications. Systemic inflammatory response syndrome was defined as two or more of the following variables in the absence of an infectious source: (1) core body temperature of more than 38°C or less than 36°C, (2) heart rate of more than 90 beats per minute, (3) respiratory rate of more than 20 breaths per minute or a $Paco_2$ level of less than 32 mm Hg, or (4) abnormal white blood cell count ($>$12,000/μL or $<$4,000/μL or $>$10% bands). Infectious complications were defined as clinical or culture positive diagnosis of ventilator-associated pneumonia, bacteremia, surgical site infection, or intra-abdominal infection, in accordance with the guidelines of the American College of Chest Physicians and the Society of Critical Care Medicine.[21,22] As well, severe sepsis and septic shock were defined according to standard accepted criteria from a consensus statement of the American College of Chest Physicians and the Society of Critical Care Medicine. Hospital length of stay (in days), ICU length of stay (in days), and ventilator days, are expressed in calendar days. Ventilator-dependent respiratory failure was defined as the need for mechanical ventilation greater than 72 hours. Abdominal Compartment Syndrome (ACS) was defined as intra-abdominal pressure greater than 25 mm Hg, at least one organ system failure that was not identified before abdominal hypertension, and attending surgeon documentation of concern for ACS before decompressive celiotomy. Open abdomen was defined as failure to achieve primary fascial closure by postinjury day 7.

The incidences of 24-hour and 30-day mortality were recorded and evaluated. 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, w-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 OR. 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, OR, and postoperatively up to the 24-hour postadmission mark.

Statistical Analysis

Continuous data are presented as means $\pm$ SD with comparisons between groups performed using the Student's *t* test or the Mann-Whitney *U* test, as appropriate. Categorical data are reported as proportions and, where appropriate, tested for significance using χ^2 or Fisher's exact tests. The primary data analysis evaluated single system and MOF between the pre-TEP and TEP groups using univariate, fol-

Table 1 Demographic and Injury Score Differences Between Groups

	Pre-TEP (n = 141)	TEP (n = 125)	*p*
Age, yr (±SD)	38.5 (±17.8)	35.6 (±15.5)	0.101
Male (%)	86	94	0.367
Penetrating mechanism (%)	40	51	0.034
ISS (±SD)	28.0 (±15.5)	33.3 (±15.9)	0.006
w-RTS (±SD)	4.29 (±2.5)	3.48 (±2.6)	0.010
Predicted survival by TRISS, % (±SD)	52	35	<0.001

ISS, Injury severity score; w-RTS, weighted revised trauma score; TRISS, Trauma related Injury Severity Score.

lowed by multivariable logistic regression model. The variables included in the multivariate analysis of MOF were age, gender, w-RTS, ISS, TEP activation, and total 24-hour blood product utilization (i.e. the number of units of PRBC, plasma, and platelets transfused). Analyses comparing development of ACS and open abdomen status between the two groups were performed using multivariable logistic regression models as well. To meet the normality of residuals assumption required of linear regression analysis, the values for overall and specific blood component (i.e. PRBC, plasma, and platelet) consumption were log-transformed. In an effort to minimize the risk of falsely identifying significant results with multiple comparisons, all multivariate regression models were prespecified and judged a priori to be clinically sound. All statistical tests were two-tailed with $p < 0.05$ set as significant. STATA Statistical software (version 10.0; College Station, TX) was used for analysis.

RESULTS

Study Group

A total of 266 patients met inclusion criteria. These patients were divided into two groups for the purpose of this study: pre-TEP (n = 141) and TEP (n = 125).

Univariate Analysis

Demographics

Demographic comparison was made between the two groups. Age and gender were similar between the groups. However, the TEP group was more severely injured (ISS 33.3 vs. 28.0, $p = 0.006$) and demonstrated a higher physiologic severity (lower w-RTS) on arrival (3.48 vs. 4.29, $p = 0.01$). With respect to the individual components of the ISS, mean head AIS in the TEP group was 2.1 (3.1 in the blunt population and 0.9 in penetrating) versus 2.9 in the pre-TEP (3.4 in the blunt population and 1.1 in the penetrating group). In addition, the predicted survival (by TRISS) was significantly lower in the TEP group (35% vs. 52%, respectively; $p < 0.001$). The TEP group also had a higher percentage of patients with penetrating injuries (51% vs. 40%, $p = 0.03$). Descriptive data are shown in Table 1.

Table 2 Outcome and Resuscitation Comparison Between Groups

	Pre-TEP (n = 141)	TEP (n = 125)	*p*
24-h survival (%)	61	69	0.185
30-d survival (%)	37.6	56.8	0.001
Hospital length of stay, d (±SD)	16.4 (±20.1)	12.0 (±12.1)	0.049
ICU length of stay, d (±SD)	6.6 (±9.4)	5.0 (±8.3)	0.239
Ventilator days, d (±SD)	8.2 (±9.7)	5.7 (±7.2)	0.017
IO blood products, units (±SD)	11.0 U (±SD)	14.7 U (±SD)	0.001
IO crystalloid, L (±SD)	7.0 L (±SD)	4.8 L (±SD)	<0.001
24-h blood products (±SD)	38.7 U (±SD)	31.2 U (±SD)	0.050

SD, standard deviation; IO, intraoperative.

Penetrating patients had lower head AIS in both TEP and pre-TEP cohorts compared with blunt patients (0.9 vs. 3.1 and 1.1 vs. 3.4, respectively). However, penetrating and blunt patients had similar abdominal AIS in the TEP group (3.9 vs. 3.6) and in the pre-TEP group (3.6 vs. 3.5, p = NS). Chest AIS was also similar regardless of mechanism in the TEP cohort (3.6 vs. 3.9, p = NS) and in the pre-TEP cohort (3.9 vs. 3.7, p = NS). ISS for penetrating patients was significantly lower than that for blunt patients in both the pre-TEP cohort (20.8 vs. 32.4, $p < 0.001$) and the TEP cohort (24.3 vs. 42.8, $p < 0.001$). As those with blunt mechanism were more likely to arrive intubated, patients with penetrating injuries arrived with less physiologic severity (by w-RTS) than blunt patients in the TEP cohort (4.0 vs. 2.9, $p = 0.023$). There was no difference in physiologic severity scores between those with penetrating and blunt mechanism in the pre-TEP cohort (4.2 vs. 4.3, $p = 0.741$). Accordingly, TRISS predicted survival for patients with penetrating mechanism was similar to that of blunt trauma mechanism in the pre-TEP cohort (55.6% vs. 51.0%, $p = 0.451$), whereas patients with penetrating mechanism in the TEP cohort had a significantly higher TRISS predicted survival compared with penetrating patients (46.1% vs. 29.9%, $p < 0.001$).

Outcomes

Although there was no statistical difference in 24-hour survival by group, the TEP patients had higher 30-day survival (56.8% vs. 37.6%, $p = 0.001$) (Table 2). The overall length of stay was lower in those patients who received TEP (12 days vs. 16 days, $p = 0.049$) and this group also had less ventilator days (5.7 days vs. 8.2 days, $p = 0.017$). Patients in the TEP group received more intraoperative blood products of all types (PRBC, fresh frozen plasma, and PLT) while receiving less intraoperative crystalloid administration (4.8 vs. 7.0 L, $p < 0.001$). Postoperative blood products (0–24 hours) transfusions were lower in the TEP group (31 vs. 39 units, $p = 0.05$).

Table 3 Complications Rates Between Groups

	Pre-TEP (n = 141)	TEP (n = 125)	p
SIRS (%)	55.3	52.8	0.682
Severe sepsis/septic shock (%)	19.8	10.0	0.019
Ventilator-dependent respiratory failure (%)	62.4	60.8	0.787
Ventilator associated pneumonia (%)	39.0	27.2	0.041
Abdominal compartment syndrome (%)	9.9	0.0	<0.001
Open abdomen (%)	30.5	6.4	<0.001
Need for renal replacement therapy (%)	2.8	3.2	0.826

SIRS, systemic inflammatory response syndrome; open abdomen, failure to achieve primary fascial closure by hospital day 7.

Table 4 Differences in Single System and Multiple Organ Failures

	Pre-TEP (n = 141)	TEP (n = 125)	p
Respiratory failure (%)	62.4	56.0	0.287
Cardiac failure (%)	39.0	12.8	<0.001
Hepatic failure (%)	9.2	3.2	0.045
Renal failure (%)	6.4	5.6	0.801
Multiple organ failure (%)	37.2	15.6	<0.001

Complications

Inhospital complication rates were compared between the groups (Table 3). There was no difference in the development of systemic inflammatory response syndrome, ventilator-dependent respiratory failure, or need for renal replacement therapy. However, severe sepsis or septic shock and ventilator-associated pneumonia were both lower in those receiving TEP (10% vs. 20%, $p = 0.019$ and 27% vs. 39%, $p = 0.041$, respectively). Simple logistic regression confirmed these findings with TEP being associated with a 58% odds reduction in severe sepsis or septic shock (OR 0.428, $p = 0.022$, CI 0.207–0.884) and 51% odds reduction in ventilator-associated pneumonia (OR 0.491, $p = 0.005$, CI 0.299–0.807). In addition, abdominal complications were significantly lower in the TEP group ($p < 0.001$), with regards to both ACS and failure to close abdominal fascia by 7 days ("open abdomen").

As well, simple logistic regression identified a greater than sixfold reduction in the risk of abdominal fascia not being primarily approximated by 7 days in patients who received the TEP.

Organ Failure and Dysfunction

Univariate analysis demonstrated no difference in respiratory failure and renal failure rates between the two groups (Table 4). However, both cardiac and hepatic failure rates were significantly lower in the TEP patients (12.8% vs. 39.0%, $p < 0.001$ and 3.2% vs. 9.2%, $p = 0.04$). Simple logistic regression noted an almost 80% reduction in the odds of cardiac failure (OR 0.197, $p < 0.001$, CI 0.102–0.378) in patients who received TEP.

Patients who received the TEP were significantly less likely to develop MOF by both univariate analysis (15.6% vs. 37.2%, $p < 0.001$) and simple logistic regression (OR 0.189, $p < 0.001$, CI 0.100–0.357).

Table 5 Multivariate Regression Model for Odds of Developing Multiple Organ Failure

	Odds Ratio	95% CI	p
Received TEP	**0.20**	**0.106–0.395**	**<0.001**
Age	1.00	0.986–1.020	0.732
Gender	1.00	0.795–1.267	0.971
ISS	0.997	0.979–1.017	0.831
w-RTS	0.999	0.891–1.120	0.996
Total 24-h blood products (units)	1.01	1.000–1.024	0.045

TEP, trauma exsanguination protocol; ISS, Injury severity score; w-RTS, weighted revised trauma score.

Table 6 Multivariate Regression Model for the Odds of Achieving Primary Abdominal Fascial Closure by Day 7

	Odds Ratio	95% CI	p
Received TEP	**5.61**	**2.476–12.723**	**<0.001**
Age	1.00	0.981–1.019	0.992
Male	0.99	0.725–1.355	0.959
ISS	1.00	0.986–1.032	0.414
w-RTS	0.88	0.773–1.002	0.056
Total 24-h blood products (units)	0.98	0.957–1.039	0.208

TEP, trauma exsanguination protocol; ISS, Injury Severity Score; w-RTS, weighted revised trauma score.

Multivariate Analysis

Using multivariable logistic regression analysis, we sought to identify predictors of MOF (Table 5). Adjustment was made for the following variables: age, gender, ISS, w-RTS, and 24-hour transfusion of PRBC, fresh frozen plasma, and PLT. After adjusting for these variables, TEP was found to be a predictor of a reduction in the risk of MOF (OR 0.203, $p < 0.001$, CI 0.105–0.392).

Multivariate logistic regression analysis was then performed to evaluate the impact of TEP on achieving primary closure of the abdominal fascia by hospital day 7 (Table 6). Controlling for age, gender, ISS, w-RTS, and total 24-hour transfusions, patients receiving the TEP were more than five times more likely to achieve primary fascial closure by day 7 (OR 5.61, $p < 0.001$, CI 2.476–12.723).

DISCUSSION

Several investigators have recently demonstrated improved survival with damage control resuscitation strategies.[4,5] This approach involves less crystalloid during the early resuscitation,

lower tolerated blood pressure measurements, and, most importantly, higher ratios of plasma and platelets to RBC. Although these investigators and their associated MT or exsanguination protocols have generated great interest, other authors have raised concern of the potential increase in morbidity associated with such large number of blood products being transfused.[13–16] The current study, however, confirmed the survival benefit of this protocol noted in previous investigations and also demonstrated a dramatic reduction in many of the complications and organ failures associated with critically injured patients receiving MTs.[5,7]

RBC transfusions have long been associated with immunosuppression and subsequent increased risk of postinjury and postoperative bacterial infections. Although the majority of the data are related to patients with cancer and postsurgical patients, data in the critically injured population appears to support these findings.[23,24] Unfortunately, many of these studies are quite flawed and only when grouped together into a meta-analysis do they gain enough power to support this association.[24–27] As well, patients receiving transfusions appear to be more severely injured and hemodynamically unstable on arrival. Norda et al. recently evaluated risks of plasma and platelet transfusions and did not find a significant infectious risk associated with their transfusion in the absence of a contaminated product.[28] Recently, Sarani et al. demonstrated a significant dose-response relationship between plasma and infectious complications. Of note, the infectious risk was only observed in those patients receiving only plasma and no other blood products (RBCs, platelets).[15] In the current study, we found a greater than 50% odds reduction in development of severe sepsis, septic shock, and ventilator-associated pneumonia in patients receiving our institution's exsanguination protocol.

Blood and component therapy transfusions have been implicated in the development of MOF in several retrospective and nonrandomized trials. Biological plausibility of this interaction centers on the potential for lipid and cytokine mediators present in packed RBC to augment postinjury inflammatory responses, worsening multiple organ dysfunction, and subsequent development of MOF. In addition to increased age and injury severity, investigators from Denver identified transfusion of 6 or more units of RBCs in the first 12 hours as an early independent predictor of MOF.[18,29] As with other studies, however, patients receiving large amounts of blood early in their resuscitation were more likely to arrive with severe physiologic disturbances. Not surprisingly, both base deficit (>8 mEq/L) and lactate (>2.5 mmol/L) were independent predictors of developing MOF. Of note, we eliminated all patients who did not survive at least 48 hours. Although the group has since differentiated early organ dysfunction from organ failure, removing a large and severely ill cohort (likely to have received a large number of blood products) could alter the results quite dramatically.[20] The result may very well be the "survivor's curse" of being successfully resuscitated from hemorrhagic shock and living long enough to develop MOF. We noted a dramatic reduction in single system and MOF since implementation of the TEP. Moreover, when controlling for injury and physiologic severity, as well as overall blood products transfused, our MT protocol was associated with an 80% reduction in the odds of developing MOF.

MT has long been associated with the development of abdominal wall complications in severely injured patients; most notably, ACS and the chronic open abdomen.[30–32] Both Balogh et al. and Madigan et al. identified early, aggressive resuscitation strategies as independent risk factors for ACS.[31,32] This applied to early transfusion of blood as well as use of large volumes of crystalloid. As with infectious complications and organ failure, however, it is difficult to delineate whether these variables were causative or merely surrogate markers for the most severely injured and severely ill patients. Despite receiving a large number of blood products, the current study noted an 80% higher likelihood of primary abdominal wall closure in patients receiving these components as part of a predefined MT protocol.

Although on the surface these results would seem to fly in the face of conventional wisdom, a closer look shows our findings are consistent with those of investigators who have identified blood transfusions as independent risk factors for infectious complications and MOF.[13,18,24,29] Though they received a "MT," patients in the TEP group experienced less infectious complications and less single system and MOF than those resuscitated before its implementation. Key to understanding these findings is remembering that the TEP group, although receiving more RBC, plasma, and platelets in the OR and early in their resuscitation, received significantly less products overall. Given that the risks of infectious complications and organ failure have both been shown to be "dose-dependent" per unit of product transfused, our findings are actually consistent with those of previous investigators. In addition, the products delivered through the TEP were transfused earlier in the process, potentially achieving hemostasis more rapidly and restoring shock indices (such as lactate and base deficit) toward normal values more quickly.[5,7] Finally, the TEP resuscitation process was associated with a dramatic reduction in intraoperative and early crystalloid resuscitation volumes. This likely not had a insignificant impact on observed outcomes as more cautious and restrictive crystalloid based resuscitation strategies have been associated with a decrease in MOF and acute respiratory distress syndrome.[3,33,34]

Limitations to this study include the relatively small sample size for each cohort and the retrospective design. Although the TEP group was collected in a prospective cohort fashion, the comparison cohort was obtained using data collected via a trauma registry database and computerized patient chart. In addition, a notable limitation is the fact that the population is not homogenous and the cohort is not identically matched. These issues, however, were addressed with the use of multivariable regression strategies. As we did not collect data on prehospital fluid and blood product administration, the potential impact of these variables on the initial physiologic presentation and eventual outcomes may

have been omitted. Both populations also include many individuals that died intraoperatively. Though we speculate that a fairly similar number exists between the two groups, patients who died in the OR would likely skew the data toward increased blood component utilization in the survivors. Finally, we only assessed a limited number of organ failures based on a single classification system and did not evaluate or express the variables in a disease-free method (e.g., ventilator-free days). Such a method may have been preferred as it takes into consideration early deaths not developing organ failures and complications. However, a survival bias, if it were present, would likely only strengthen our hypothesis and findings that suggest better outcome with the use of TEP.

CONCLUSION

Blood product-based resuscitation strategies, especially those involving MTs, have been associated with higher organ failure and complication rates. When blood component therapies are delivered through predefined MT protocols, however, this risk appears to be dramatically reduced. Our institution's TEP was associated with an 80% reduction in the odds of developing MOF and infectious complications. These findings, although significant, are less surprising when one appreciates the dramatic reduction in overall blood products transfused in the TEP cohort.

In addition, implementation of this protocol was followed by a dramatic reduction in development of ACS and the incidence of open abdomens. The open abdomen is a potentially preventable complication with extraordinary costs and high risk of further morbidities associated with attempts at abdominal wall reconstruction. Our findings are encouraging and lend promise to potentially reducing the development of ACS and increasing the chances for earlier, primary fascial closure by rethinking resuscitation strategies of patients in hemorrhagic shock.

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DISCUSSION

Dr. Kazuhiko Sekine (Keio University, Japan): In this historical control study, Dr. Cotton and his colleagues have reported their predefined trauma exsanguinating protocol, TEP, for prospectively collected patients with severe injury requiring massive transfusion.

The study results clearly demonstrated the usefulness of TEP in reducing the risk of developing infectious complications and multiple organ dysfunction syndrome, as well as in reducing the risk of developing abdominal compartment syndrome and open abdomen.

A multivariate regression analysis after adjustment for confounding factors revealed the use of TEP as an independent factor reducing the risk of multiple organ failures.

The results appear to be robust, and I agree with their conclusions. However, I have a couple of concerns and questions regarding the method used.

Number 1. It is unclear how the patients were selected to activate the TEP after the protocol was implemented. The authors indicated that this selection was dependent on the patient's physiology and complexity of the patient's injury. However, this inclusion or exclusion criteria were not described in detail in the paper.

Number 2. It is to be noted that the mechanism of injuries would also influence the patients' outcome. From our experience of treating with coagulopathy, it is observed that patients with penetrating injuries may sometimes show a better chance of survival, compared to than those with the same ISS due to blunt injuries.

As observed in this paper, the TEP group had more patients with penetrating injuries than the pre-TEP group. This difference might have contributed to the better outcomes, in terms of survival and complications rate in the TEP group.

Number 3. Concurrent severe head injury has been reported as a risk factor for mortality in patients with polytrauma. Also, respiratory failure due to pneumonia often occurs as a complication in cases of severe head trauma.

Therefore, it is necessary to assess the effect of head injuries on early death and pulmonary infections in the TEP and the pre-TEP groups.

Number 4. The damage-control resuscitation strategy for the control of coagulopathy consists of early blood transfusions and low-volume crystalloid injection. In addition, a hypotensive resuscitation or a Factor VIIa administration may have been available for some patients. These factors could also have showed an effect on the outcomes in this study. In view of these factors, I would like to know if there are any differences between the two groups.

As a closing statement, I would like to congratulate the authors for addressing one of the most important topics in the field of trauma patient resuscitation.

Dr. John B. Holcomb (Houston, Texas): I'd like to congratulate the authors for a very nice study addressing one of the questions that people have raised about hemostatic resuscitation that is by giving increased blood products are you increasing multi-organ failure and sepsis.

You published last week in *Annals of Surgery* the largest transfusion trial done in the United States from 17 centers. And the answer to that in that retrospective study was similar to this one, no, it does not.

These authors in their single center study have driven into the data in a fairly large study of over 200 patients shown a decrease in multi-organ failure.

I would suggest that what we're doing is reprising the paper from 1976 of Carrico and Shires that said give whole blood and a little bit of crystalloid. That was the message from our real fathers of modern resuscitation of hemorrhagic shock patients.

That's what we're starting to relearn right now is what they told us in 1976. Our equivalent to whole blood is one-to-one-to-one. That's what we can do because it's hard to get whole blood.

My question for the authors is as you've looked at your ratios of less than one-to-one-to-one are you starting to change your opinions and maybe give even less crystalloid and more plasma and more platelets?

Where will you end up in seeing this effect? Are you continuing to push the envelope?

Dr. Frederick A. Moore (Houston, Texas): We recently reported that when we changed our massive transfusion protocol to ensure a ratio of one-to-one FFP to packed red blood cells that we showed a reduction in mortality with massive transfusion from 30 to 15 percent.

And when we were analyzing this data obviously we were focused on the FFP but it became obvious that when you

use that massive transfusion protocol you're also using less crystalloids.

We also demonstrated the patients got to the intensive care unit two hours sooner. So that means that we were getting hemorrhage control done sooner.

We've also shown that when we became less aggressive with our ICU resuscitation that we reduced the incidence of abdominal compartment syndrome. And then, lastly, if you leave the abdomen open it's kind of hard to get abdominal compartment syndrome.

So I want you to address how other things that might have changed when you were trying to improve your massive transfusion. It's inherent that when you try to change the process of care that other behaviors differ.

Dr. Juan Duchesne (New Orleans, Louisiana): Good job Bryan, I am not really that surprise with your findings. At New Orleans Charity Hospital we've been doing damage control resuscitation for one-year-and-a-half now and we have the same results that you actually talked about here today.

When you submit this paper for publication I will encourage you to please add in your logistic regression, the impact of crystalloids in damage control resuscitation ratios on multiple system organ failure. Our preliminary data from Charity hospital have shown to us the detrimental impact on outcomes during the era before damage control resuscitation and the era of damage control resuscitation when less unnecessary crystalloids were utilized in patients with severe hemorrhage.

If you can find that in your logistic regression that's going to be a big plus so people will understand the negative impact of unnecessary crystalloid resuscitation in patients with severe hemorrhage.

Dr. Martin Schreiber (Portland, Oregon): We know that now that TRALI is a leading cause of blood transfusion related deaths.

TRALI occurs from plasma products and it's nine times more common in products obtained from females. In our center we no longer use plasma products from females.

Do you use plasma products from females? And do you think it's possible that you may have missed the incidence of TRALI in your study because it wasn't part of the definition that you were looking for?

Dr. Michael L. Hawkins (Augusta, Georgia): Both my questions have actually been touched on. You showed more blood and blood products intra-op and less later on.

Aren't you really showing that early, aggressive resuscitation is far better than stalling around and resuscitating later?

Dr. Zsolt J. Balogh (Newcastle, Australia): Your experience is similar to ours that we hardly see any more ACS these days. But we really don't know what is causing the single factor or multiple factor, the reduction.

If you want to conclude in your paper that you reduce ACS I would recommend to break it up to primary and secondary because your strategy with the massive transfusion protocol should reduce the incidence of secondary ACS which is resuscitation related rather than the primary which is usually reduced by leaving the abdomen open.

My second question is that in the last five years we've seen that ACS is a real driver these days of post-injury MOF. And how many of your MOF patients have actually ACS as well?

Dr. Bryan A. Cotton (Nashville, Tennessee): Thank you, again. To address Dr. Sekine's comments, the activations were based on attending clinical acumen.

We've tried to standardize that through a massive transfusion activation score which we're presenting in the poster session and hope that that will help even out the activations among the attendings which, again, there is some clinical variability among our faculty.

Benefit from blunt versus penetrating, we seem to get a benefit from both. To our surprise, however, if you weigh the two separately the benefit in the blunt camp seemed to be higher than that in the penetrating, although both were significant.

No differences in groups with respect to TBI. Did not have a lot of TBIs get in this massive transfusion protocol. And no Factor VII used in the TEP group. It was off-label and prohibited by our institution during that study period.

To Dr. Holcomb's, again, we are constantly changing it through our PI process and are getting closer to a one-to-one. We are already at one-to-one for our platelets. And we're at a three-to-two for FFP. That may continue to change.

To Dr. Moore's comments, we are definitely using less fluids. And, yes, we are leaving them open but I think that the abdominal compartment syndrome finding is less important than the closure by seven days which, again, previously we were doing a miserable job with.

To Dr. Hawkins' comments, again, we would agree and have found a decreased mortality. And when they're getting those products sooner we have even found a better mortality within our own TEP group if those ratios are given in a very short timeframe, again, intra-operatively and minimizing anything post-op.

To Dr. Schreiber's, we did not look at the female plasma issue and that absolutely could be one of our drivers for our acute lung injury although we did not find a difference with respect to respiratory failure between the groups.

To Dr. Balogh's, again, we did not look at a link between the ACS and multi-organ failure but that would be a very good thing to do in the future and we will try to address some of these things in the manuscript.

And, finally to Dr. Duchesne, we did find, again, with the products had a higher risk of getting multiple organ failure. However, when you break it down to the TEP they got less fluid and less products and we think that that mechanism is, appears to be protective.