The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

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Background: **Patients with severe traumatic injuries often present with coagulopathy and require massive transfusion. The risk of death from hemorrhagic shock increases in this population. To treat the coagulopathy of trauma, some have suggested early, aggressive correction using a 1:1 ratio of plasma to red blood cell (RBC) units.**

Methods: **We performed a retrospective chart review of 246 patients at a US Army combat support hospital, each of who received a massive transfusion (≥10 units of RBCs in 24 hours). Three groups of patients were constructed according to the plasma to RBC ratio transfused during massive transfusion. Mortality rates and the cause of death were compared among groups.**

Results: **For the low ratio group the plasma to RBC median ratio was 1:8 (interquartile range, 0:12–1:5), for the medium ratio group, 1:2.5 (interquartile range, 1:3.0–1:2.3), and for the high ratio group, 1:1.4 (interquartile range, 1:1.7–1:1.2) ($p < 0.001$). Median Injury Severity Score (ISS) was 18 for all groups (interquartile range, 14–25). For low, medium, and high plasma to RBC ratios, overall mortality rates were 65%, 34%, and 19%, ($p < 0.001$); and hemorrhage mortality rates were 92.5%, 78%, and 37%, respectively, ($p < 0.001$). Upon logistic regression, plasma to RBC ratio was independently associated with survival (odds ratio 8.6, 95% confidence interval 2.1–35.2).**

Conclusions: **In patients with combat-related trauma requiring massive transfusion, a high 1:1.4 plasma to RBC ratio is independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage. For practical purposes, massive transfusion protocols should utilize a 1:1 ratio of plasma to RBCs for all patients who are hypocoagulable with traumatic injuries.**

Key Words: **Blood components, Fresh frozen plasma, Trauma, Coagulopathy.**

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Massive transfusion is defined as the transfusion of 10 or more red blood cell (RBC) units in a 24-hour period.[1–3] In civilian trauma centers, the incidence of patients with traumatic injuries receiving massive transfusion ranges between 1% and 3%,[3–5] with an incidence reported as high as 15% in patients with the most severe injuries.[6] Mortality rates for massive transfusion patients ranges between 20% and 50%.[1,6,7] Currently, 5% of all patients admitted to US combat support hospitals in Iraq require massive transfusions. Mortality rates among these patients is more than 30%.[8] The high risk of mortality in massive transfusion patients largely results from the "lethal triad" or "bloody vicious cycle" characterized by hypothermia, metabolic acidosis, and coagulopathy.[9–12] In approximately 30% of patients who have received a blood transfusion, coagulopathy results directly from the trauma itself. These patients present in the hypocoagulable state known as the coagulopathy of trauma.[13] The coagulopathy of trauma is multifactorial; it is consumptive because of widespread tissue trauma, is augmented by dilution of hemostatic factors from crystalloid, colloid, and component therapy resuscitation, and exacerbated by hemorrhagic shock, metabolic acidosis, hypothermia, hyperfibrinolysis, hypocalcemia, and anemia.[11,14–19] Alternatively, coagulopathy can develop independent of acidosis and hypothermia secondary to trauma.[20]

Historically, whole blood was commonly used for patients suffering massive trauma.[21,22] By the late 1980s, however, component therapy had almost completely replaced whole blood therapy.[23] The primary purpose of component therapy was to improve resource utilization and reduce infectious disease transmission. This was accomplished by replacing blood component deficiencies individually based upon rigorous laboratory analysis. This approach of replacing specific hematologic deficits based upon laboratory analysis extended into the guidelines developed for patients requiring massive transfusion after injury. However, proof of the efficacy of this change in practice was lacking. Current transfusion recommendations were extrapolated from the setting of elective surgery, and may not be applicable to patients with severe trauma who are hypocoagulable, acidotic, and in hemorrhagic shock. Recently, published reports now recommend a 1:1:1 ratio (i.e. equal parts RBCs, fresh frozen plasma [FFP], and platelets) for component therapy based on a more physiologic regimen and is more similar to the composition of whole blood.[1,15,24–28] These recommendations, however,

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have been based on anecdotal evidence and not on outcome studies examining the effect of blood product transfusion ratios for trauma patients requiring massive transfusion.

Most deaths (80% to 85%) that occur during combat are not preventable. Sixty-six to 80% of the 15% to 20% of potentially survivable combat-related deaths are a result of hemorrhagic shock.[27,29] Scoring systems and predictive models that are able to rapidly identify who is at risk for massive transfusion have been recently published.[30,31] Expeditious recognition and treatment of coagulopathy is important because most patients requiring massive transfusion die within 6 hours of admission.[30] Resuscitation strategies that rapidly identify risk of massive transfusion and quickly address the coagulopathy of trauma should prevent deaths from uncontrolled hemorrhage and improve survival of potentially preventable deaths on the battlefield. Our objective in this retrospective study of patients with severe traumatic injuries requiring massive transfusion at a combat support hospital was to determine whether the ratio of plasma to RBCs transfused would affect survival by decreasing death from hemorrhage.

METHODS

The data presented here were obtained under a human use protocol that the Institutional Review Board at Brooke Army Medical Center in San Antonio, TX approved. Using the Joint Theater Trauma Registry (JTTR) maintained at the US Army Institute of Surgical Research (USAISR) at Ft. Sam Houston in San Antonio, TX, we performed a retrospective analysis of data for trauma patients admitted to a combat support hospital (CSH) in Iraq between November 2003 and September 2005. The JTTR database was established by the Department of Defense to capture data prospectively from multiple nonintegrated clinical and administrative systems. This database provides comprehensive data collection from the point of injury through discharge from military treatment facilities for non-US military patients and from point of injury through rehabilitation for US patients. Non-US military patients are defined to include coalition soldiers and foreign national patients.

The JTTR was queried for patients who received a massive transfusion, defined as 10 or more RBC units (including both stored RBC and fresh whole blood units) in 24 hours from admission. Data analyzed from the JTTR in this study were Injury Severity Score (ISS), Abbreviated Injury Scale (AIS) scores, primary cause of death, time of death, mortality at hospital discharge, laboratory values, and vital signs at admission to the CSH, (hemoglobin, platelet level, base deficit, International Normalized Ratio [INR], systolic blood pressure, temperature, heart rate), and total crystalloid and blood products (RBC, FFP, cryoprecipitate, recombinant FVIIa [rFVIIa], apheresis platelet [aPLT], and fresh whole blood [FWB] units) administered within 24 hours from admission to the combat support hospital. Because 1 unit of FWB has approximately 1 unit of RBCs, plasma, and platelets, the amount of RBC units transfused was calculated as the number of both stored RBC and FWB units transfused and plasma as FFP plus FWB units. One apheresis platelet unit is equal in number to approximately 6 to 10 units of leukocyte-reduced platelets.[32] The platelet contribution from FWB was not included in the calculation of apheresis platelet units transfused, though FWB has previously been shown to be as effective as 10 units of platelet concentrate.[33] The initial 24-hour amount of crystalloid and blood products transfused was also calculated as liters or units per hour. The rate of crystalloid and blood products per hour was calculated to adjust for the amount of crystalloid and blood products transfused to patients who died less than 24 hours from the initiation of the massive transfusion.

One investigator reviewed each patient's chart or autopsy results to record all injuries, from which the AIS score and ISS were calculated.[34] Primary outcome for all patients in this study was hospital discharge or overall mortality. For US military patients, this was tracked throughout all levels of care, including discharge from acute care hospitals in the United States. For non-US military patients, mortality was tracked until discharge from the CSH in Baghdad. Non-US military patients were not discharged or transferred until their surgical repair was stable, were not hemodynamically compromised, and did not require vasoactive agents or mechanical ventilation. The length of stay from admission to hospital discharge for both groups was measured. Time to death was defined as the time, in hours, from hospital admission to the time of death. For patients who had two mechanisms of death listed, a 0.5 was used for each in the calculation of the percentage of cause of death in each ratio group.

To analyze the effect of plasma to RBC ratios on mortality, patients were divided into groups based on the ratio of plasma to RBC units transfused. Three separate groups of patients were identified based on a "bootstrapping" technique that combined groups of patients that had similar mortality rates based upon the plasma to RBC ratios transfused to individual patients. With use of this method, the six groups of ratios that were initially constructed were combined to three groups. The plasma to RBC ratio was the number of plasma units divided by the RBC units transfused in the first 24 hours of care at the CSH.

Subpopulations were also analyzed to determine whether injury location affected the relationship between mortality and the ratio of plasma to RBCs transfused. To determine the effect of thoracic and head trauma in relationship to the plasma to RBC ratio and mortality, additional analyses were performed with and without patients who had thoracic or head and neck AIS scores of 4 or 5. The plasma to RBC ratio was also analyzed without the addition of FWB in the ratio, as well as without patients who were treated with rFVIIa.

All variables collected were analyzed to determine which were associated with overall mortality. Logistic regression was then used to determine independent associations between variables measured and overall mortality. The logistic regres-

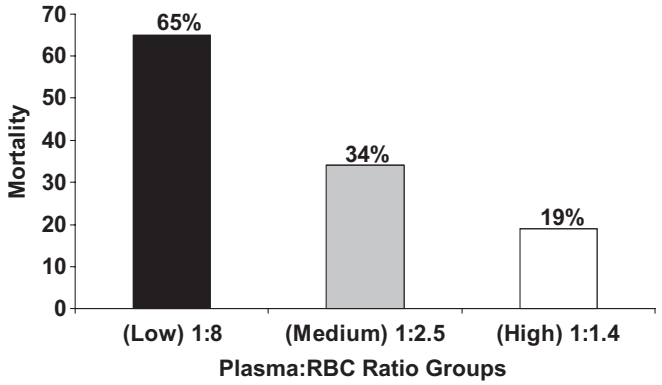


Fig. 1. *Percentage mortality associated with low, medium, and high plasma to RBC ratios transfused at admission. Ratios are median ratios per group and include units of fresh whole blood counted both as plasma and RBCs.*

sion model initially used all variables associated with mortality with a p value <0.2. Variables were removed if significant colinearity was measured by Pearson's correlation coefficient or variance inflation.

All continuous nonparametric data are described as median (interquartile range) or median (interquartile range) [mean] if the median value is zero. Mann-Whitney U test and Kruskal Wallis tests were used for comparisons of continuous data. All categorical data were compared with χ^2 or Fisher's exact test as appropriate. Statistical analysis was performed with SPSS 14.0 (Chicago, IL). Significant differences were determined at $p < 0.05$.

RESULTS

Between November 2003 and September 2005, 5,293 patients were admitted to the CSH in Baghdad. The JTTR identified 246 (4.6%) patients who received massive transfusion. Penetrating injuries occurred in 232 of 246 (94%) of these patients. Three patients were female. The median age of the patients studied was 24 years (interquartile range, 21–30). The median ISS was 18 (interquartile range, 16–25). The combat support hospital length of stay for patients was a median of 2 (1–6) days. The median time from admission to the CSH to evacuation to Germany for US patients was 1 day (1–2 days). The overall mortality was 28%. Median plasma to RBC transfusion ratios for survivors versus nonsurvivors were 1:1.6 (1:1.3–1:2.2) and 1:2.3 (1:1.4–1:5.1), respectively ($p < 0.001$). Median plasma to RBC ratios were 1:8, 1:2.5, and 1:1.4, and are defined as low, medium, and high ratios respectively, ($p < 0.001$). The low, medium, and high ratio groups had plasma to RBC ratio ranges of 0:22–1:4, 1:3.9–1:2.1, and 1:2–1:0.6, respectively. As the ratio of plasma to RBC increased, mortality significantly decreased (Fig. 1). The mortality of low, medium, and high groups were 65%, 34%, and 19%, respectively ($p < 0.001$).

Descriptive statistics for severity of injury, admission vital signs, and laboratory values for the three groups are in Table 1. Severe (AIS scores of 4 and 5) thoracic injuries were more common in the low ratio group compared with in the medium and high groups. All vital signs and laboratory results were comparable, except for hemoglobin, which was significantly lower in the low ratio group compared with in the medium and high groups.

In the first 24 hours of admission, the rate per hour of crystalloid and RBC units administered was less in the high ratio group compared with in the medium and low groups (Table 2). The total amount and rate per hour of plasma as well as the rate per hour of FWB was higher in the medium and high ratio groups ($p < 0.001$). The low ratio group did not receive aPLTs, which were only used in 27% of patients. Cryoprecipitate was used more in the high ratio group ($p < 0.01$), though given at a higher rate in the medium and low ratio groups ($p < 0.001$) and was only used in 51% of the patient population (Table 2).

Nonsurvivors in the low and medium ratio groups died significantly sooner than those in the high ratio group (Fig. 2). Median time of death measured in hours from admission to the hospital was 2 hours (interquartile range, 1–4) in the low group and 4 hours (interquartile range, 2–16) in the medium group, compared with 38 hours (interquartile range, 4–155) in the high ratio group ($p < 0.001$).

The relationship between plasma to RBC ratios transfused and overall mortality remained in the alternative analyses performed. Differences in mortality remained significant in the high, compared with in the low, ratio group when patients with thoracic and head trauma were individually removed from the analysis (Table 3). The relationship between plasma to RBC ratios transfused and overall mortality also remained when only stored FFP and RBCs (FWB units not included) were used to calculate the ratio, as well as when patients who were treated with rFVIIa were excluded (Table 3).

Table 4 indicates that many of the admission vital signs, laboratory values, and Injury Severity Scores, in addition to the ratio of plasma to RBCs, were associated with overall mortality. Table 5 reveals that the plasma to RBC ratio was independently associated with overall survival (odds ratio 8.6, 95% confidence interval 2.1–35.2) and that both base deficit and AIS for head and neck were independently associated with decreased overall survival upon logistic regression.

Figure 2 displays the primary causes of death in each ratio group. The percentage of deaths from hemorrhage was lower in the high ratio group (11.5 of 31; 37%), compared with in the low ratio group (18.5 of 20; 92.5%) ($p < 0.001$). This represents an absolute reduction of 55% and a relative reduction of 60%. There were fewer hemorrhagic deaths in the high ratio group compared with in the medium ratio group ($p < 0.05$). Likely reflecting the increased survival time, multiorgan failure deaths were more frequent in the high ratio group compared with in the low ratio group.

Table 1 Descriptive Statistics for Each Plasma to RBC Ratio Group

Variable Median (IQR)	Low Ratio Group,* n = 31 1:8 (0:12–1:5)	Medium Ratio Group, n = 53 1:2.5 (1:3.0–1:2.3)	High Ratio Group, n = 162 1:1.4 (1:1.7–1:1.2)
ISS†	18 (16–25)	17 (13–25)	18 (16–25)
ISS >25 (%)	23	21	22
AIS score (% 4 or 5)			
Head/neck	16	6	10
Face	0	0	0.6
Thorax§	26[a]	9[ab]	7[b]
Abdomen	26	23	27
Pelvis/extremity	19	23	28
% penetrating trauma	94	92	95
% blunt trauma	6	8	5
INR, n = 212	1.78 (1.00–2.86), n = 21	1.57 (1.31–2.10), n = 42	1.54 (1.30–2.20), n = 149
Hgb,‡ n = 234	9.4 (7.1–11.1), n = 27[a]	10.8 (8.5–12.7), n = 48[ab]	10.9 (9.1–13.1), n = 159[b]
Plt concentration, n = 174	225 (120–281), n = 14	177 (128–241), n = 33	218 (154–278), n = 127
Base deficit, n = 201	13 (4–14), n = 22	9 (3–14), n = 42	8 (4–13), n = 137
Temperature (°F), n = 195	97 (94.9–97.6), n = 18	96.2 (94.1–98.0), n = 45	95.9 (94.0–97.3), n = 132
Heart rate, n = 233	122 (97–149), n = 29	118 (104–133), n = 51	111 (90–128), n = 153
SBP, n = 231	90 (80–106), n = 29	98 (74–116), n = 49	97 (80–122), n = 153

Values with different superscripts ([a,b,c]) are significantly different ($p < 0.05$).

* Ratio calculated as (FFP + FWB):(RBC + FWB).

† Data presented as median (interquartile range).

‡ Mann-Witney *U* test.

§ Chi Square test.

ISS, Injury Severity Score; AIS, Abbreviated Injury Scale; INR, international normalized ratio; Hgb, hemoglobin (mg/dL); Plt concentration, platelet level ×1,000/μL; SBP, systolic blood pressure.

Table 2 Crystalloid and Blood Products for Each Plasma to RBC Ratio Group

Variable Median (IQR)	Low Ratio Group,* n = 31 1:8 (0:22–1:5)	Medium Ratio Group, n = 53 1:2.5 (1:3.0–1:2.3)	High Ratio Group, n = 162 1:1.4 (1:1.7–1:1.2)
Crystalloid (L)†§	7.0 (2.0–9.6)[a]	8.0 (4.4–11.5)[ab]	9.6 (6.0–12.9)[b]
Crystalloid (L/h)§	1.8 (0.36–4.2)[a]	0.6 (0.3–1.5)[ab]	0.5 (0.4–0.7)[b]
RBC	16 (12–18)	16 (12–26)	17 (12–24)
RBC/h§	4 (0.5–11.8)[a]	0.9 (0.6–4.0)[ab]	0.8 (0.6–1.3)[b]
FWB	0 (0–0) [0.1]	0 (0–2) [1.1]	0 (0–4) [3.1]
FWB/h§	0 (0–0) [0.01][a]	0 (0–0.1) [0.15][b]	0 (0–0.2) [0.23][c]
Plasma§	2 (0–3)[a]	6 (4–10)[b]	12 (9–18)[c]
Plasma/h§	0.1 (0–0.4) [0.57][a]	0.3 (0.2–1.4) [1.1][b]	0.6 (0.4–1.0) [1.1][c]
aPLT§	None received[a]	0 (0–0) [0.4][b]	0 (0–1) [0.8][c]
aPLT/h§	None received[a]	0 (0–0) [0.02][ab]	0 (0–0) [.05][b]
Cryoprecipitate§	0 (0–0) [1.6][a]	0 (0–10) [6.6][b]	9 (0–10) [9.1][b]
Cryoprecipitate/h§	0 (0–0) [0.7][a]	0 (0–1.3) [0.9][b]	0.4 (0–0.8) [0.6][b]
rFVIIa use‡	16%[a]	26%[ab]	38%[b]

* Ratio calculated as (FFP + FWB):(RBC + FWB).

† Data presented as median (interquartile range) with or without [mean].

‡ Data presented as percentage used in each cohort (ie rFVIIa use/total number in cohort).

§ Mann-Whitney *U* test.

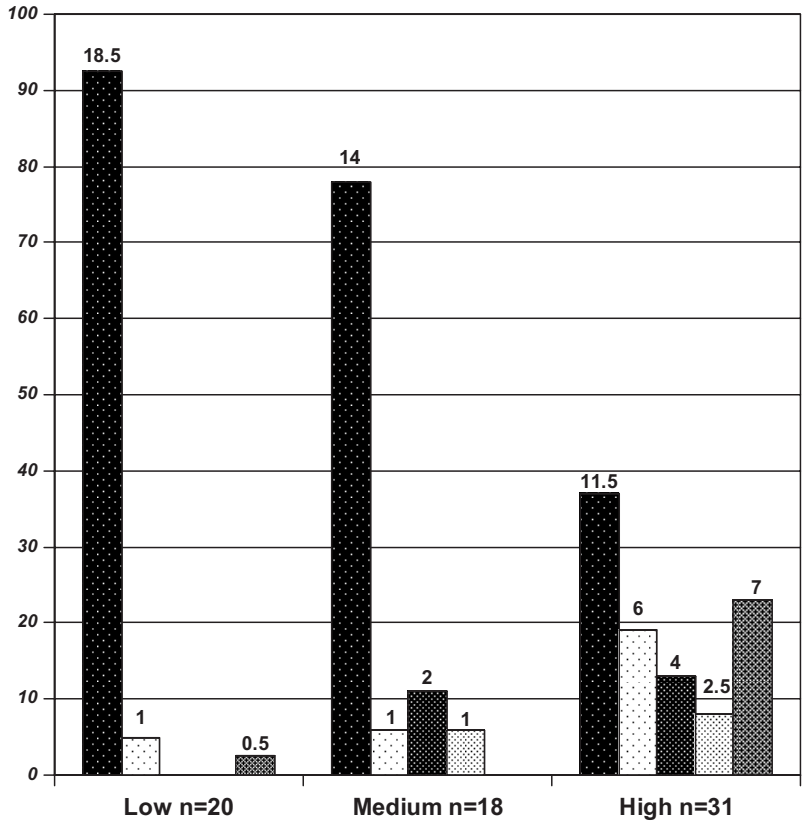
Values with different superscripts ([a, b, c]) are significantly different ($p < 0.05$).

Crystalloid, liters normal saline and Lactated Ringers; RBC, units packed red blood cells and fresh whole blood; FWB, units fresh whole blood; Plasma, units fresh frozen plasma and fresh whole blood; aPLT, apheresis platelet units; rFVIIa, recombinant Factor VIIa.

DISCUSSION

Our results indicate that for patients with significant traumatic injuries requiring massive transfusion, a higher plasma to RBC ratio is independently associated with improved survival, primarily decreasing early (<4 hours from admission) death from hemorrhage. The patients with the lowest mortality rate in our study were transfused a median plasma to RBC ratio of 1:1.4. This study supports recent reports in the literature that have called for the increased transfusion of coagulation factors for patients requiring massive transfusion[1,15,25,26,35,36] and that have raised concerns about the increased use of RBCs and crystalloids in critically ill patients.[26,35,37–50]

Earlier massive transfusion protocols developed for patients bleeding a large amount of whole blood, did not replace



	Low n=20	Medium n=18	High n=31
Hemorrhage %†	**92.5 [a]**	**78 [a]**	**37 [b]**
Sepsis %	5	6	19
MOF %	0	11	13
Airway/Breathing %	0	6	8
CNS %	2.5	0	23
Time to death (hrs)[2]*	**2 (1 – 4) [a]**	**4 (2-16) [b]**	**38 (4 – 155) [c]**

Fig. 2. *Comparison of the number and percentage of the primary cause of death for all of the deaths in each plasma to RBC ratio group. Number on column represents absolute number that died from each cause listed. When two causes were listed for a patient, they were counted as 0.5. [2]Data presented in hours as median (interquartile range); *Mann-Whitney U* test; †Chi Square test. Values with different superscripts ([a, b, c]) are significantly different ($p < 0.05$).

Table 3 Comparison of Mortality Rates of Alternative Patient Cohorts and Plasma to RBC Ratios

Plasma to RBC Ratio (Range)	Low Ratio (0:22–1:4)	Medium Ratio (1:3.9–1:2.1)	High Ratio (1:2–1:0.59)
Primary analysis*	65%[a] n = 31	34%[b] n = 53	19%[c] n = 162
Excluding thoracic trauma	57%[a] n = 23	29%[b] n = 48	19%[b] n = 152
Excluding neurotrauma	62%[a] n = 26	36%[b] n = 50	15%[c] n = 145
Excluding whole blood†	66%[a] n = 38	27%[b] n = 59	19%[b] n = 149
Excluding rFVIIa	69%[a] n = 26	38%[b] n = 39	15%[c] n = 100

Values with different superscripts ([a, b, c]) are significantly different ($p < 0.05$) (Chi Square Test).
* See Methods Section.
† Ratio calculated as FFP:RBC units.

whole blood, but rather called for a much greater percentage of RBC units.[35] Such protocols recommended that FFP only be transfused if prothrombin time (PT) or partial thromboplastin time (PTT) was 1.5 times normal, or after 10 RBC units were transfused. Additionally, these massive transfusion protocols called for 1 unit of FFP to be given for every 4 to

Table 4 Analysis of Data Associated With Mortality

Variable	Survivors	Nonsurvivors	*p* Value
AIS head/neck score, % 4 or 5 (n = 245)	7	19	0.005†
AIS face score, % 4 or 5 (n = 245)	0	1.4	0.11†
AIS external score, % 4 or 5 (n = 245)	0.5	0	0.53†
AIS pelvis/extremity score, % 4 or 5 (n = 246)	28	19	0.13†
AIS abdomen score, % 4 or 5 (n = 245)	22	36	0.024†
AIS thorax score, % 4 or 5 (n = 245)	6	20	0.011†
ISS (n = 246)	17 (13–25)	25 (17–29)	<0.001*
Systolic blood pressure (n = 231)	98 (80–120)	90 (70–109)	0.024*
Heart rate (n = 233)	112 (91–132)	121 (100–140)	0.052*
Temperature (n = 195)	96.1 (94.4–97.7)	94.9 (93.2–97.3)	0.049*
Base deficit (n = 201)	7 (3–12)	13 (8–18)	<0.001*
INR (n = 212)	1.5 (1.2–1.8)	2.1 (1.6–3.4)	<0.001*
Platelet level (n = 174)	222 (152–278)	175 (118–234)	0.015*
Hemoglobin (n = 234)	11.1 (9.0–13)	9.9 (7.2–11.5)	0.003*
% rFVIIa use (n = 246)	34	30	0.44†
Plasma:RBC ratio (n = 246)	1:1.6 (1:1.3–1:2.2)	1:2.3 (1:1.4–1:5.1)	<0.001*

n = number of patients with data available.
* Mann-Whitney *U* test.
† Chi Square test.
AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; rFVIIa, recombinant Factor VIIa.

10 RBC units and platelets to be infused at less than 50,000 to 100,000.[35,52,53]

The standard clinical practice guidelines for optimally diagnosing and treating seriously injured casualties are based on expert opinion and theoretical assumptions rather than robust laboratory or clinical data.[35,52,54] Furthermore, they have frequently been extrapolated from elective operative settings, and may not be applicable to the patient with severe trauma who is in a hypocoagulable state and in hemorrhagic shock. Given these concerns, there has been recent controversy in the approach to patients requiring massive transfusions after injury.

Several current clinical practice guidelines have called for a strategy of aggressive early correction of coagulation factors in a 1:1:1 ratio (i.e., plasma:RBC:platelets) in patients with severe trauma or requiring massive transfusions.[1,25] These recommendations are echoed in a clinical practice guideline instituted in September 2004 at US combat hospitals, which support the early use of a 1:1:1 ratio of plasma to RBC to platelets for patients at high risk of requiring a massive transfusion based upon clinical or laboratory data. The majority of these recommendations are based upon expert opinion or computer modeling. This study is the first to support, with comparative ratio data in three equally injured groups of patients and regression analysis, the concept that early and aggressive replacement of coagulation factors may improve survival by decreasing death from hemorrhage for patients requiring massive transfusions based on data from a large population with traumatic injuries. Interestingly, our results support a report by Hirshberg et al. that used a computer simulation model and found that a plasma to RBC ratio of 2:3 was necessary to effectively minimize coagulopathy in exsanguinating hemorrhage.[55]

Table 5 Odds Ratio Predicting Survival Using Multivariate Logistic Regression

Variable	Odds Ratio (95% CI)	*p* Value
Plasma:RBC ratio	8.6 (2.1–35)	0.003
AIS head/neck score	0.76 (0.61–0.94)	0.013
AIS thorax score	0.73 (0.57–0.92)	0.009
Systolic blood pressure	1.0 (0.98–1.01)	0.457
Hemoglobin	1.1 (0.91–1.2)	0.501
Base deficit	0.89 (0.84–0.95)	<0.001

AIS, Abbreviated Injury Scale.

Previous reports of the outcomes of patients requiring massive transfusion have documented similar results in smaller populations. Lucas and Ledgerwood found that coagulopathy was exacerbated in several studies in which trauma patients were transfused less plasma relative to RBCs.[53,54] Cinat et al., in a study of 45 massively transfused patients reported the plasma to RBC ratio for survivors was 1:1.8 compared with 1:2.5 in nonsurvivors ($p = 0.06$).[57] Cosgriff et al. in a prospective cohort of 56 massive transfusion patients found significant coagulopathy in 47% of patients, predicted by persistent hypothermia and progressive metabolic acidosis.[10] Several other retrospective studies have confirmed the presence of coagulopathy in patients requiring massive transfusion[31] and have called for increased use of coagulation factors.[2,14,17,44,58,59]

There was an absolute and relative reduction in mortality of 55% and 60%, respectively, in the high (1:1.4) plasma to RBC ratio group compared with in the low (1:8) plasma to RBC ratio group. The correction of the coagulopathy of trauma must begin early, before the patient enters the "bloody vicious cycle". Our results reinforced this approach, as those in the low plasma to RBC ratio group died from uncontrolled

hemorrhage within a median of 2 hours. Other studies have demonstrated that the coagulopathy of trauma occurs early in patients with severe trauma and that the severity of coagulopathy is associated with mortality.[10,11,14,58,60,61] Early and appropriate use of plasma in the high ratio group likely prevented the start of this cycle. Gonzalez et al. have recently elegantly demonstrated that trauma patients who arrive in the intensive care unit with a persistent coagulopathy have increased mortality rates and they recommend earlier and more aggressive use of plasma.[36]

Our population of patients also received an increased amount of aPLT and cryoprecipitate. One apheresis platelet unit usually also contains 250 to 350 mL of plasma. This increased use of plasma, in addition to platelets and cryoprecipitate, supports the concept of damage control or hemostatic resuscitation.[15,26,28] This approach emphasizes the aggressive diagnosis and treatment of coagulopathy in patients at high risk of requiring massive transfusion before it occurs or early in the resuscitation. If successful it will prevent and treat the lethal triad of trauma, which includes the early coagulopathy of trauma, from occurring.[15,18,28,62] Similar in philosophical approach to damage control surgery the concept is to "stay out of trouble rather than get out of trouble".

Our results indicate that the rate per hour of crystalloid and blood products was decreased with higher plasma to RBC ratios. We hypothesize that the early, increased use of plasma in these severely injured patients helped control the coagulopathy of trauma more efficiently, and, as a result required less crystalloid and RBCs per hour during the first 24 hours of resuscitation. Additionally, the use of plasma instead of crystalloids and RBCs helped prevent or limit the development of dilutional coagulopathy.[15] Conversely, we believe that patients who received less plasma and more crystalloid and RBCs in the low and medium plasma to RBC ratio groups entered the "bloody vicious cycle", and died significantly sooner from uncontrolled hemorrhagic shock. The rate of blood products and crystalloid may have also been reduced for the survivors in the high plasma to RBC ratio group as a result of not requiring active resuscitation during the entire 24 hours after initiating a massive transfusion. We suspect that both improved hemostasis and survival, and the lack of need to be actively resuscitated contributed to the decreased rate of products and crystalloid transfused in the high plasma to RBC ratio group.

Patients who received low or medium plasma to RBC ratios died predominantly of hemorrhage at a median of 2 to 4 hours. This supports the concept that patients who require massive transfusion are at risk of early (<6 hours from admission) death from hemorrhage,[30] and indicates rapid treatment of coagulopathy with a higher ratio of plasma to RBC prevents early death from hemorrhage. This was evidenced by the median time to death of 38 hours in the high ratio group. Patients who received high plasma to RBC ratios had a higher incidence of death from sepsis and multiorgan failure versus hemorrhage as a result of surviving long enough to develop these complications. This is supported by the median time to death in the low and medium ratio groups compared with in the high ratio group. This relationship was noted in another similar study evaluating the effect of blood products on mortality.[63] Because of the retrospective nature of this study, we cannot rule out the possibility that the increased use of plasma, apheresis platelets, and cryoprecipitate may have contributed to these results, as has been previously reported.[64]

Our results are subject to limitations inherent in retrospective studies, including incomplete data collection, lack of standard timing for measuring variables, and lack of a massive transfusion protocol that was consistently applied to patients. The variable with the highest percentage of missing data was the admission platelet concentration at 30%. It is possible that the exclusion of these missing values may have affected our results, but because ISS and mechanism of injury were equal in all three groups, it is likely that there was a comparable degree of coagulopathy, as has been shown previously.[14] Another potential confounder is the possibility that the patients who did not receive plasma did not primarily as a function of dying before they had a chance to receive plasma. These patients may have been more critically ill than the others who were able to wait for plasma to be thawed. Although this is possible, all available indicators of severity of injury including ISS, systolic blood pressure, base deficit, and INR were equal between the three groups of patients which makes this potential confounder less likely.

Despite these limitations, this study is currently one of the largest reviews of patients with massive transfusion in trauma to analyze the effects of blood product transfusion and mortality. Additionally, we were able to adjust for many confounding variables in our regression analysis to include thoracic AIS values, admission hemoglobin concentrations, and rFVIIa use, which were each different in the low, medium, and high ratio groups that were compared. In addition to adjusting for thoracic AIS score in the regression model, we also analyzed the relationship between ratio of plasma to RBCs transfused with the exclusion of patients with severe thoracic injuries. In this analysis, the relationship of increased plasma to RBC ratio and decreased mortality remained between the low and high ratio groups (Table 3).

We believe that our results support the development of randomized controlled trials in animal and human subjects that will evaluate the effect of plasma to RBC ratios transfused to patients at risk of requiring massive transfusions. Ratios tested should also include plasma to RBC ratios of greater than 1:1 to evaluate if more plasma than RBCs would improve survival in coagulopathic patients with severe traumatic injury. Strategies that aggressively treat the coagulopathy of trauma and decrease the use of stored RBCs in patients with severe traumatic injuries including early and increased use of plasma, platelets, cryoprecipitate, or fresh whole blood if available, and the aggressive treatment of hypothermia,

metabolic acidosis, and hypocalcemia need continued study to determine whether they can improve outcomes.

One method that combat support hospitals and some large civilian trauma centers are currently using to facilitate early transfusion of increased plasma to RBC ratios is the use of thawed plasma. Thawed plasma is simply FFP, which after thawing, is kept refrigerated at 4°C for up to 5 days. This product is an American Association of Blood Banks (AABB) approved concept. Thawed AB plasma is stored at amounts equal to that of emergency release type O RBCs in emergency department refrigerators. This allows both blood products to be used immediately and concurrently upon presentation of a patient at risk for massive transfusion. Once thawed plasma is transfused it is immediately replaced by the blood bank to maintain availability for the next patient. Although thawed plasma was not used in the patients analyzed in this study, the results presented here have helped change our practice in the theater of operations and today thawed plasma is widely available at the busiest combat support hospitals, resulting in a decrease in plasma waste. Large civilian trauma centers should consider the use of thawed plasma to permit the transfusion of plasma to RBCs in a 1:1 ratio or at least in a 1:2 ratio at admission for patients with severe traumatic injuries who present with the coagulopathy of trauma.

Based upon these data the US Army Surgeon General has recently distributed a policy recommending that a 1:1 plasma to RBC ratio be transfused to all patients with significant trauma and who are at risk for requiring a massive transfusion.

CONCLUSIONS

Recent literature demonstrates that the risk of requiring a massive transfusion can be rapidly identified and death from hemorrhage occurs quickly for patients with severe traumatic injuries requiring massive transfusion. The transfusion of plasma to RBCs in a 1:1 ratio is a rapid treatment that improves survival for patients at risk of hemorrhagic shock. We suggest that the empiric ratio of plasma to RBC should approximate 1:1 for patients with traumatic injuries requiring massive transfusions. Future prospective randomized controlled trials are needed to compare empiric plasma to RBC ratios for patients with severe traumatic injuries.

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