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A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study

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Abstract

BACKGROUND: In trauma, most hemorrhagic deaths occur within the first 6 hours. This study examined the effect on survival of high ratios of fresh frozen plasma (FFP) and platelets (PLTs) to packed red blood cells (PRBCs) in the first 6 hours.

METHODS: Records of 466 massive transfusion trauma patients (≥10 U of PRBCs in 24 hours) at 16 level 1 trauma centers were reviewed. Transfusion ratios in the first 6 hours were correlated with outcome.

RESULTS: All groups had similar baseline characteristics. Higher 6-hour ratios of FFP:PRBCs and PLTs:PRBCs lead to improved 6-hour mortality (from 37.3 [in the lowest ratio group] to 15.7 [in the middle ratio group] to 2.0% [in the highest ratio group] and 22.8% to 19.0% to 3.2%, respectively) and in-hospital mortality (from 54.9 to 41.1 to 25.5% and 43.7% to 46.8% to 27.4%, respectively). Initial higher ratios of FFP:PRBCs and PLTs:PRBCs decreased overall PRBC transfusion.

CONCLUSIONS: The early administration of high ratios of FFP and platelets improves survival and decreases overall PRBC need in massively transfused patients. The largest difference in mortality occurs during the first 6 hours after admission, suggesting that the early administration of FFP and platelets is critical.

Hemorrhage is the leading cause of potentially preventable death in severely injured military and civilian trauma patients.[1,2] The current dogma regarding resuscitation practice is being critically evaluated for evidence-based improvements in care. Traditional resuscitation strategies are based on Advanced Trauma Life Support guidelines, which dictate starting resuscitation with crystalloid followed by packed red blood cells (PRBCs).[3] The use of other blood products is then based on laboratory tests. In massively bleeding patients, there often is not time to await laboratory tests, and, thus, the use of other blood products must be done empirically. When component therapy largely replaced the use of whole blood in the 1980s, there were no evidence-based guidelines dictating how much of each product to use in massively bleeding patients. Coagulopathy was believed to be mostly dilutional, occurring after enough fluids and PRBCs had been administered to reduce the concentration of coagulation factors. Massive transfusion protocols at many centers have not recommended the infusion of fresh frozen plasma (FFP) until after anywhere from

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6 units (U) to 10 U of PRBCs have been given. The recommended ratio of FFP to PRBCS ranges from 1:4 to 1:10. Many guidelines do not include specific recommendations for platelets (PLTs) until laboratory data show low platelet levels.[4,5] Recent literature from military and civilian sources questions these guidelines, and numerous studies are showing benefits of higher ratios of FFP to PRBCs.[4–11]

The purpose of this study was to determine the effect of early ratios of plasma and platelets compared with PRBCs on outcomes in bleeding trauma patients. Our hypothesis was that early high ratios of FFP and PLTs improve outcomes. Most hemorrhagic deaths occur in the first 6 hours after trauma so we hypothesized that this was the critical time to achieve high ratios.

Methods

A multicenter, retrospective analysis was performed at 16 level 1 trauma centers in the United States.[10] The protocol was approved by the institutional review boards at all participating centers. Data were collected from trauma patients injured between July 2005 and June 2006 who received any PRBCs within 24 hours of admission. Patients who were transferred from other hospitals, prisoners, children less than age 16, pregnant patients, burn-injured patients, patients who had greater than or equal to 5 minutes of cardiopulmonary resuscitation before admission, and patients undergoing an emergency room thoracotomy for blunt injury were excluded from analysis. To remove the bias of the delay in availability of plasma and platelets, all patients who died within 30 minutes of arrival to the emergency room were excluded (n = 1).

Each center queried its own trauma registry or American Association of Blood Banks–required data to locate all patients who received blood transfusions for trauma during the study period. A database was created, including blood products and fluids received and the timing of those blood products from admission to the emergency room (0–6 hours and 6–24 hours). Also collected were the time and date of injury and admission, mechanism of injury, age, sex, Injury Severity Score (ISS), initial Glasgow Coma Score (GCS), initial vitals, initial laboratory tests, mortality by time from emergency room admission (0–6 hours, 6–24 hours, and >24 hours), and ventilator days. Early transfusion was defined as transfusion given within the first 6 hours after admission. Massive transfusion was defined as the receipt of greater than or equal to 10 U of PRBCs in the first 24 hours after injury.

The study data were assessed for differences in outcome based on the ratios of blood products transfused in the first 6 hours after admission. We compared low, medium, and high ratios of FFP:PRBCs and PLTs:PRBCs, specifically at ratios of <1:4, ≥1:4 to 1:1, and ≥1:1. Our primary outcome was in-hospital mortality. Secondary outcomes were mortality in the first 6 hours, overall PRBCs transfused in the first 24 hours, and ventilator-free days. All statistical analyses were performed with SAS version 9.1.3 for Windows (SAS Institute, Cary, NC) using 2-sided tests with a significance level of 5%.

Results

Data were obtained from 1,489 patients who received at least 1 U of PRBCs, including 466 massive transfusion patients. There were 14 patients for whom complete data was not available and they were excluded from analysis.

Demographics

The number of massively transfused patients receiving the various ratios of FFP and PLTs and their demographics are shown in Tables 1 and 2. Most patients received FFP:PRBCs in a ratio between 1:4 and 1:1 and PLTs:PRBCs in a ratio of <1:4. All groups had similar ISS, GCS, mechanism of injury, gender and age (Tables 1 and 2). The initial systolic blood pressure (SBP) and initial laboratory tests were similar among all groups, with the exception that those who received a ≥1:1 ratio of FFP:PRBCs had a higher international normalized ratio at baseline.

Outcomes

The overall mortality was 41%. Mortality decreased significantly when patients received higher early ratios of FFP:PRBCs, with most of the differences occurring in the first 6 hours from admission and persisting though hospital dis-

Table 1 Demographics based on FFP:PRBC ratio in first 6 hours

	<1:4	1:4-1:1	≥1:1	*P*
Number of patients	102	299	51	
Age*	36	36	28.3	.33
Male sex (%)†	72.5	76.3	88.2	.08
ISS*	29	32	33.5	.76
GCS*	12	10	4	.39
Mechanism (% blunt)†	66.7	63.8	62.7	.85
Initial systolic blood pressure*	101.5	100	102	.41
Initial hemoglobin*	11	10.8	10.9	.99
Initial PTT*	28.9	30.5	32.7	.30
Initial fibrinogen*	166.5	142	138	.64
Initial INR*	1.3	1.3	1.5	.03
Initial platelet count*	220	196	200	.19

All values are medians.

PTT = partial thromboplastin time; INR = international normalized ratio.

*Kruskall-Wallis test.

†Fisher exact test.

Table 2 Demographics based on PLT:PRBC ratio in first 6 hours

	<1:4	1:4-1:1	≥1:1	*P*
Number of patients	219	171	62	
Age*	36	35	34	.76
Male sex (%)†	76.7	78.9	71	.44
ISS*	30	32	29	.9
GCS*	10	10.5	14	.17
Mechanism (% blunt)†	67.0	62.6	59.7	.85
Initial systolic blood pressure*	101	102	99.5	.57
Initial hemoglobin*	10.7	10.7	11.3	.33
Initial PTT*	31.5	30.4	27.5	.19
Initial fibrinogen*	157	138	133	.63
Initial INR*	1.4	1.4	1.3	.37
Initial platelet count*	210.0	199.5	199.0	.29

All values are medians.
PTT = partial thromboplastin time; INR = international normalized ratio.
*Kruskall-Wallis test.
†Fisher exact test.

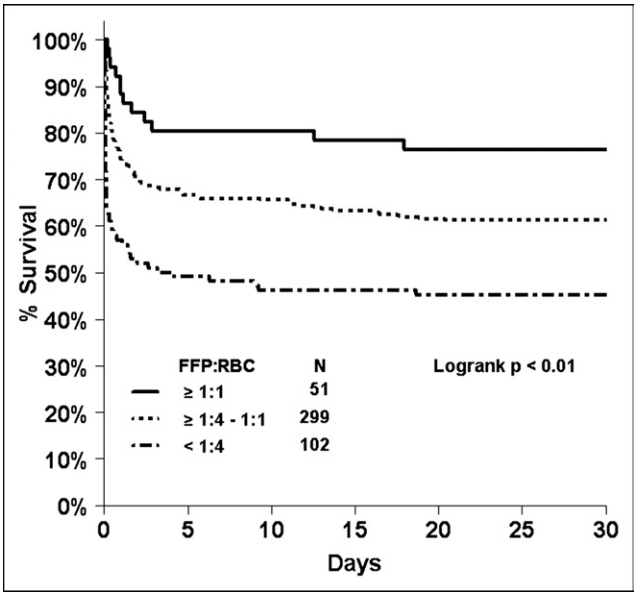

Figure 1 Survival by FFP:red blood cell ratio.

charge (Table 3 and Fig. 1). Similar to the FFP:PRBC ratios, mortality decreased significantly when patients received higher early ratios of PLTs:PRBCs. Again, most of the differences occurred in the first 6 hours from admission (Table 3 and Fig. 2).

With higher early ratios of both FFP:PRBCs and PLTs:PRBCs, fewer total PRBCs were needed in the first 24 hours. Patients who received a <1:1 ratio of FFP:PRBCs in the first 6 hours needed a median of 18 U of PRBCs over the first 24 hours, whereas those with a ratio ≥1:1 only needed a median of 13 U of PRBCs ($P < .001$). Patients who received <1:1 ratio of PLT:PRBCs needed a median of 17.5 U of PRBCs compared with 13 U in those with a ratio ≥1:1 ($P = .008$).

Due to the concern that higher amounts of platelets and plasma lead to more transfusion related acute lung injury and acute respiratory distress syndrome from inflammatory mediators, we evaluated respiratory outcomes. In order to eliminate confounding due to early mortality, patients who survived to 30 days were examined. There was no difference seen in respiratory outcomes based on ratio of FFP:PRBC. For ratios of PLT:PRBC, respiratory outcomes improved with higher ratios. The patients in the two higher ratio groups of PLT:PRBC had more ventilator free days than the low ratios (<1:4), but were not different from each other (Table 3).

Table 3 Mortality differences and respiratory outcome based on the ratio of blood products

Product ratio	Measure	Transfusion ratio in first 6 hours <1:4	1:4-1:1	≥1:1	*P*
FFP:PRBC	6 hour mortality %	37.3*	15.2*	2.0*	<0.001
	In-hospital mortality %	54.9*	41.1*	25.5*	<0.04
	Ventilator free days†	9	7.9	6.3	0.35
PLT:PRBC	6 hour mortality %	22.8	19.0	3.2*	<0.002
	In-hospital mortality %	43.7	46.8	27.4*	<0.03
	Ventilator-free days†	6*	9.9**	9.1**	<0.004

*Significant difference from other two ratios.
**P = non-significant (0.79).
†Massive transfusion patients who survived >30 days (n = 277). Fisher exact test.

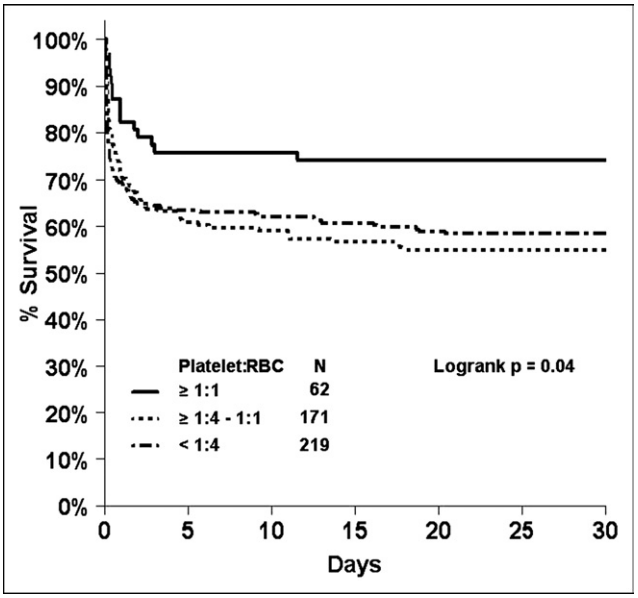

Figure 2 Survival by PLT:red blood cell ratio.

Comments

Hemorrhage remains the leading cause of preventable death in trauma patients. Most trauma deaths are not preventable, about 80% in combat operations and >90% in civilian traumas. Of the remaining potentially preventable deaths, 45% to 85% are potentially salvageable hemorrhagic deaths, most of which occur in the first 6 hours after injury.[1,2,10,12–14] It is this group of patients that this study is directed toward. Optimal treatment of these severely injured patients is required. Rapid identification of those at risk followed by effective surgical intervention and transfusion practices tailored to trauma requirements are necessary to save the lives of the most severely injured patients. Determining the optimal ratios of plasma, cryoprecipitate, and PLTs is a major step in delivering optimal care.

This study examined the effect of early transfusion ratios on patient outcomes in trauma patients requiring massive transfusion (>10 U of PRBCs in 24 hours) at 16 US level 1 trauma centers looking primarily at in-hospital mortality and secondarily at 6-hour mortality, need for total blood product, and respiratory outcomes. Six-hour and in-hospital mortality were found to be significantly decreased with the use of higher transfusion ratios of FFP:PRBCs and PLTs:PRBCs. Additionally, patients who received a higher ratio at FFP:PRBCs and platelet:PRBCs in the first 6 hours needed less PRBCs over the first 24 hours.

When developing this study, there was concern that higher amounts of plasma and PLTs would lead to a greater release of inflammatory mediators leading to worse respiratory outcomes. As discussed by Holcomb et al,[10] true transfusion-related acute lung injury only occurs in 1 to 5 of every 10,000 transfusions. However, it was possible that lung inflammation and injury to a lesser degree could lead to multiorgan dysfunction and worsened respiratory outcomes. This was found to not be the case. Patients who received higher ratios of FFP:PRBCs had a similar number of ventilator-free days as those with low ratios. Patients who received higher ratios of PLT:PRBCs actually had more ventilator-free days and thus better respiratory outcomes.

In the past, transfusions were completed with whole blood until the development of component therapy in the 1980s.[6] Dividing whole blood into components allowed for longer storage of each component and led to improved resource utilization by only giving each patient the portion of blood that was required. Corresponding to this change in delivery, transfusions were based on laboratory analysis, which proved to work well in nonurgent situations.

In massively bleeding patients, there often is not time to await laboratory analysis to decide on product administration. Thus, massive transfusion protocols were developed to treat severely bleeding patients empirically. The foundations of most massive transfusion protocols were based on elective surgery data. Otherwise, they were based on theory because studies looking at optimal ratios had not been performed. The predominant theory behind these protocols was that the observed traumatic coagulopathy in patients was primarily dilutional. It was believed to develop late in the patient's course as part of the lethal triad of hypothermia, acidosis, and coagulopathy. Recommendations were to administer FFP in addition to PRBCs only when prothrombin time (PT) or partial thromboplastin time (PTT) values exceeded 1.5 times normal, after 6 U to 10 U of PRBC, or in a ratio of 1 U of FFP to every 4 U to 10 U of PRBC.[6]

Recent data have shown that severe trauma results in early coagulopathy prior to resuscitation. This phenomenon has been called the acute coagulopathy of trauma. It was described separately by Brohi and MacLeod in 2003, is present on admission, and is directly related to severity of injury and mortality.[1,15] Anywhere from 24-30% of trauma patients are coagulopathic on admission, and hemorrhage remains an important cause of early death in trauma patients.[1,6,7,15,16]

This problem can be made worse by standard resuscitation practices, which likely serve to exacerbate the coagulopathy of trauma present on admission in the most critically injured patients. Hirschberg et al[17] created a computer simulation of the exsanguinating patient that showed that the dilution of clotting factors in severely bleeding patients is underestimated. There is a narrow timeframe early in the patient's course during which aggressive plasma component replacement can prove effective in preventing dilutional coagulopathy. Patients who require massive transfusion are at risk of early death from hemorrhage (<6 hours from admission) and are in need of aggressive rapid resuscitation with sufficient ratios of plasma, PLTs, and clotting factors to perform the vital role of hemostasis.[6] In our study, the biggest difference in mortality occurred during the first 6 hours after admission, supporting a role for early administration of plasma and platelets. The fact that patients who had higher ratios of plasma and platelets needed fewer PRBCs overall suggests that correcting coagulopathy early leads to less hemorrhage.

Several studies have found that patients who develop an early coagulopathy after severe trauma have a higher mortality.[1,7,15,16] It is thus advisable to administer component therapy in a high ratio to expeditiously correct this coagulopathy, promoting improved survival and decreased hemorrhagic death, in accordance with the tenets of damage control resuscitation.[4–6,9,18] Newer transfusion protocols, based on research from the War on Terror, treat coagulopathy in those requiring massive transfusion aggressively with early use of plasma, platelets, cryoprecipitate, and recombinant factor VIIa. The concept of damage control resuscitation (DCR), according to Spinella et al, encompasses rapid surgical correction of large vessel bleeding, prevention and treatment of acidosis and hypothermia, transfusion of plasma, PRBC, and platelets in a 1:1:1 ratio, early use of fibrinogen, potential use of recombinant activated factor VII, and decreased emphasis on excessive crystalloid and RBC use.[5,11] This has been anecdotally shown to decrease intraoperative coagulopathic bleeding, improve/resolve the abnormalities of the lethal triad, and decrease ventilator

time.[9] This difference in ventilator-free days is supported in our study as well with the use of high PLT:PRBC ratios.

There are several limitations to this study. It is a retrospective study which only allows us to show associations, rather than direct cause and effect. There was a large variability in transfusion practices across trauma centers and differing mortality outcomes between centers. Thus, it is unclear if mortality differences were purely due to differences in transfusion ratios, or if they were more reflective of overall differences in practices between different centers. The exact timing of component delivery was unknown, other than in the large grouping of 0–6 hours and 6–24 hours, so there may have been important differences in the exact time frame of various transfusions.

Another potential confounder is the possibility that some patients in the group receiving low ratios expired prior to being able to receive FFP or PLT. Many centers have PRBC available in their emergency rooms, but need to obtain plasma and platelets from the blood bank. Unless a center has thawed plasma available, there is a delay while FFP thaws. Patients who are more likely to die quickly regardless of transfusion practices may not have had time to receive plasma, as opposed to reduced plasma ratios leading to their death. However, patients who expired within the first 30 minutes of arrival were excluded from the study to decrease this effect (n = 1). Also, no notable differences were seen in ISS, GCS, initial vital signs, or labs between ratio groups to indicate disparity in severity of injury, making this a less likely confounding factor.

Despite these limitations, this study showed significant findings in a large review of U.S. Level 1 trauma centers. In massively transfused trauma patients, early administration of high ratios of FFP and platelets improves survival. This difference in mortality is largest during the first 6 hours after admission, reaffirming the importance of rapid assessment and treatment of presenting coagulopathy in severe trauma. The results highlight the potential importance of having thawed plasma available for immediate infusion in patients with the acute coagulopathy of trauma who are at risk for needing a massive transfusion. In addition, a decrease in overall PRBC need and ventilator time was seen, revealing the possibility of other beneficial effects of high ratio plasma and platelet administration. This study emphasizes the need for prospective randomized controlled trials to more closely examine the effect of FFP and PLT to PRBC ratios in patients requiring massive transfusions. In the meantime, our study supports recent literature associating decreased mortality with higher plasma and platelet to PRBC transfusion ratios.

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Discussion

Robert M. Rush, M.D. (Tacoma, WA): The resuscitation of the trauma patient has undergone a revolutionary change in the last 5 years. New ideas about the treatment of hemorrhagic shock started in the battlefield support setting in which 7% to 10% of the trauma patients seen required massive transfusion. There they found that the use of resuscitation strategies that involved whole blood and high ratios of plasma to packed red blood cells led to better overall survival of combat casualties with injuries requiring massive transfusion. Combine this strategy with that of hypotensive resuscitation, limiting crystalloid infusion, the early correction of surgical bleeding, factor VII administration (when indicated), and the further refinement of adding early and high ratios of platelet transfusions brought out by this study and we indeed have a new paradigm for the successful resuscitation of severely injured trauma patients who are bleeding to death, one that should be propagated everywhere at the most and tested prospectively at the very least.

The applications of lessons learned after military campaigns in the civilian setting have led to marked strides in the care of both the civilian and military trauma patient and surgical patients in general. This time, however, with the efforts of research groups like the one at the 31st Combat Support Hospital (CSH) and the Army's Institute of Surgical Research, near real-time changes in both military and civilian trauma protocols have taken place. We did not have to wait until after the conflict to advance our discovery, refinement, and application of one of the top 10 "inventions" of 2007 (as officially designated by the United States Army), simply coined, damage control resuscitation of the severely injured soldier.

At our level II trauma center, we are able to, or are now at least evaluating, having thawed plasma available for immediate massive transfusion needs. Platelets, however, at least at our institution, are a very limited resource. The 31st CSH is able to maintain and use a walking donor pool because of the strict adherence to pre and post deployment screening of communicable blood-borne infections such as hepatitis and HIV.