ORIGINAL ARTICLE

Effect of Blood Products Transfusion on the Development of Postinjury Multiple Organ Failure

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Hypothesis: Transfusion of fresh frozen plasma (FFP) and platelets is independently associated with the development of multiple organ failure (MOF) in critically injured patients.

Design: Prospective cohort study.

Setting: Academic regional level I trauma center.

Patients: From 1992 to 2004, a total of 1440 critically injured patients were admitted to our surgical intensive care unit and survived at least 48 hours. Of these, 1415 had complete data on age, Injury Severity Score (ISS), and units of FFP, platelets, and packed red blood cells (PRBCs) transfused. Multiple organ failure was defined using the Denver MOF score. Multiple logistic regression analysis was used to adjust transfusion of FFP, platelets, and PRBCs for known MOF risk factors.

Main Outcome Measure: Multiple organ failure.

Results: The mean (SD) ISS was 29.3 (11.3), and the mean (SD) patient age was 37.4 (16.6) years. Among 1440 patients, 346 (24.0%) developed MOF, and 118 (8.2%) died. Multiple logistic regression analysis detected a significant interaction between units of FFP and PRBCs transfused ($P < .001$). Regardless of the units of PRBCs transfused, FFP transfusion was independently associated with the development of MOF. However, the deleterious effect associated with FFP transfusion was more prominent among patients receiving fewer than 6 U of PRBCs. Platelet transfusion was unassociated with MOF after adjustment for age, ISS, and FFP and PRBC transfusion.

Conclusions: Early transfusion of FFP is associated with an increased risk of postinjury MOF, even after adjusting for age, ISS, and PRBC transfusion. Caution is warranted in developing protocols for empirical FFP transfusion. Specifically, transfusion triggers for FFP should be reexamined, as well as the practice of delivering FFP in fixed ratios to the units of PRBCs transfused.

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COAGULOPATHY COMPLICATES the care of approximately 35% of patients who are critically injured.[1] For the patient, a combination of coagulopathy, hypothermia, and acidosis is too often a terminal event. For the surgeon, persistent bleeding after surgical control remains a frustrating challenge. This "bloody vicious cycle" is mediated by early events related to the nature of the injury and to the depth and duration of hemorrhagic shock.

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Despite the description of the bloody vicious cycle more than 25 years ago,[2] the optimal way to preempt the development of coagulopathy remains ill defined. Furthermore, although blood component therapy is readily available for treatment, guidelines are lacking for administration, including timing, amount, and ratio of products.[3] An evidence-based approach is needed that systematically assesses the safety and efficacy of component therapy in the injured patient. Damage control approaches to surgery provide an opportunity to improve the metabolic and coagulation variables of the patient, but the treatments best suited to achieve this remain unclear. Massive transfusion protocols seem to improve the delivery of products to the patient and may improve outcome, but do we know what should be delivered and how the effect should be monitored?

There has been a shift in the enthusiasm for administration of banked packed red blood cells (PRBCs) in restoring oxygen delivery after hemorrhagic shock. Red blood cell transfusion is life saving in the

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exsanguinating patient, yet there are substantial associated risks, and the efficacy of stored red blood cells has been questioned in critically ill patients.[4-6] The risk of disease transmission seems to be low at present, but an increased risk of nosocomial infection, multiple organ failure (MOF), and death has been associated with liberal transfusion triggers.[7-9] Although PRBCs may restore oxygen delivery, they are in fact a complex immunomodulatory therapy.[10] Other blood components, such as fresh frozen plasma (FFP) and platelets (PLTs), are known to contain biologically active mediators.[11,12] Changes in cell-mediated and humoral immunity are well established after transfusion and likely contribute to the increased risk of infection and MOF. Indeed, a shift toward more conservative PRBC transfusion strategies is associated with decreased rates of progression to MOF in critically injured patients.[13]

A 2007 article[14] based on a retrospective review of the military experience in Iraq recommended that FFP should be transfused 1:1 with PRBCs after hemorrhagic shock. However, whether FFP also perturbs immunity and organ function remains an unanswered question. Additionally, a recent analysis of a 2008 study[15] by 2 of us (E.E.M. and A.S.) in a civilian population suggests that better outcomes are achieved with substantially less FFP (ratio of FFP to PRBCs of 1:2-1:3). The risk-adjusted survival in this study was a U-shaped curve, suggesting harm at too little or too much plasma. In that light, it would seem prudent to specifically address any risk to the patient from FFP transfusion. Furthermore, although transfusion triggers for PLTs are generally based on physiologic arguments, the potential risk of PLT transfusion in the injured patient is poorly described.

Our transfusion protocols acknowledge the need for prompt factor and PLT transfusion; however, component therapy may also confer risk. We hypothesized that transfusion of FFP and PLTs is independently associated with the development of MOF in critically injured patients, even after adjusting for known risk factors, such as age, Injury Severity Score (ISS), depth of shock, and PRBC transfusion.

METHODS

Data were obtained from the Denver MOF database, which contains prospective information on critically injured patients admitted since 1992 to the surgical intensive care unit of Denver Health Medical Center, a state-designated regional level I trauma center verified by the American College of Surgeons Committee on Trauma. Study inclusion criteria were ISS exceeding 15, admission to the intensive care unit, survival of at least 48 hours, and admission to our facility within 12 hours of injury. Patients with isolated head injuries or spinal cord injuries (external or extremity abbreviated injury score <2) were excluded.

Demographic, clinical, laboratory, and outcome data were abstracted from our electronic medical record and were entered into a secure relational database (SQL server; Microsoft, Redmond, Washington). Daily physiologic and laboratory data were collected through surgical intensive care unit day 28, and clinical events were recorded thereafter until death or hospital discharge. The primary independent variables of interest were units of FFP, PLTs, and PRBCs transfused in the first 12 hours after injury. The primary dependent variable was MOF after day 2. Data collection and storage processes are in compliance with Health Insurance Portability and Accountability Act of 1996 regulations and were approved by our institutional review board.

Organ dysfunction was defined using the Denver MOF score.[16-18] In brief, 4 organ systems (pulmonary, hepatic, renal, and cardiac) are evaluated daily throughout the patient's intensive care unit stay, and organ dysfunction is graded on a scale from 0 to 3. The values that determine the division points have been adjusted for altitude by multiplication of the value by the ratio of atmospheric pressure in Denver to that at sea level (630:760 mm Hg). The MOF score is calculated as the sum of the simultaneously obtained individual organ scores on each hospital day. Single organ dysfunction is defined as an organ failure grade exceeding 0; MOF is defined as a total score of 4 or higher occurring 48 hours after injury. The day of MOF onset was defined as the first postinjury day on which the calculated MOF score exceeded 3.

Statistical analyses were performed using commercially available software (SAS for Windows, version 9.0; SAS Institute, Cary, North Carolina). Continuous data are given as the mean (SD) or, when not normally distributed, as the median (range). For crude associations between risk factors and MOF, the *t* test was used for normally distributed variables, while Wilcoxon nonparametric test was used when the distribution was unlikely to be normal. Multiple logistic regression analysis was used to determine the independent effect of blood products transfusion, adjusting for known MOF risk factors (age, ISS, and units of PRBCs transfused in the first 12 hours). Effect modification between variables was tested by including interaction terms between pertinent variables in the model. $P<.05$ was considered statistically significant. Power analysis for negative results (lack of statistically significant association) was performed using commercially available software (Pass 6.0; NCSS, Kaysville, Utah). An additional analysis was performed among the subgroup of patients who received at least 1 U of PRBCs within 12 hours after injury, for whom it was possible to include a variable representing the ratio of FFP to PRBCs at 12 hours.

RESULTS

Data among 1440 critically injured patients from 1992 to 2004 were analyzed. The mean ISS for the cohort was 29.3 (11.3), the mean patient age was 37.4 (16.6) years, and 72.3% were male. Overall, blunt force was the most common injury mechanism (76.1%), most often due to motor vehicle crashes. Three hundred forty-six patients (24.0%) developed MOF, and 118 (8.2%) died. Among 1440 patients, 660 (45.8%) received PRBC transfusion ($\leq$23 U in about 90.0%), 410 (28.5%) received FFP transfusion ($\leq$16 U in about 90%), and 147 (10.2%) received PLT transfusion ($\leq$20 U in about 90%). Simple, nonadjusted statistically significant associations with MOF were detected for older age and higher ISS, as well as for more transfused units of FFP, PLTs, and PRBCs, as summarized in **Table 1**. Among 1440 patients, 388 (26.9%) had a previous chronic medical condition (of these, 35% had chronic substance abuse, 18.0% cardiovascular disease, 12.9% pulmonary disease, and 9.0% diabetes mellitus). If substance abuse was excluded, only 17.5% had significant previous comorbidities. The comorbid condition frequency was similar among patients who developed MOF (25.8%) and those who did not (23.9%), and this difference was not significant ($P=.48$, χ^2 test). Prothrombin time (PT)

Table 1. Bivariate Analysis of the Association Between Potential Risk Factors and Multiple Organ Failure (MOF)

MOF	Mean (SD)	Median (Range)	*P* Value
Injury Severity Score			
Yes	27.7 (10.0)	25 (20-34)	<.001[a]
No	34.1 (13.5)	32 (25-41)	
Age			
Yes	35.8 (15.7)	32 (23-44)	<.001[b]
No	42.4 (18.2)	39 (28-53)	
PRBCs, U per 12 h			
Yes	3.0 (6.5)	0 (0-4)	<.001[a]
No	8.7 (12.8)	4 (0-12)	
Platelets, U per 12 h			
Yes	1.5 (16.0)	0	<.001[a]
No	1.6 (10.5)	0	
FFP, U per 12 h			
Yes	1.5 (4.0)	0	<.001[a]
No	4.6 (7.4)	0	
Blood Substitute, U per 12 h[a]			
Yes	0.1 (1.1)	0	.38[a]
No	0.1 (1.1)	0	
Ratio of FFP to PRBCs			
Yes	0.4 (0.5)	0 (0-1)	<.001[a]
No	0.5 (0.7)	0 (0-1)	
Worst Prothrombin Time in the First 12 h			
Yes	17.4 (5.5)	15.8 (13.7-18.8)	<.001[a]
No	15.2 (5.2)	13.8 (12.5-16.1)	
Worst Partial Prothromboplastin Time in the First 12 h			
Yes	57.1 (46.2)	37.7 (29.3-62.6)	<.001[a]
No	42.5 (34.5)	30.8 (26.8-40.7)	

Abbreviations: FFP, fresh frozen plasma; PRBCs, packed red blood cells.
[a] Wilcoxon nonparametric test.
[b] *t* Test.

Table 2. Multiple Logistic Regression Analysis of the Independent Effect of Blood Products Transfusion on the Development of Postinjury Multiple Organ Failure

Variable	Estimate (SE)	*P* Value
Intercept	–4.1190 (0.4019)	<.001
Injury Severity Score	0.0476 (0.0067)	<.001
Age	0.0300 (0.0047)	<.001
Worst prothrombin time in the first 12 h	–0.0155 (0.0202)	.44
Worst partial prothromboplastin time in the first 12 h	–0.0014 (0.0030)	.63
PRBCs, U per 12 h	0.0903 (0.0184)	<.001
Platelets, U per 12 h	–0.0161 (0.0179)	.37
FFP, U per 12 h	0.0782 (0.0306)	.01
Blood substitute, U per 12 h[a]	–0.0204 (0.0594)	.73
PRBC U × FFP U	–0.0024 (0.0007)	<.001

Abbreviations: FFP, fresh frozen plasma; PRBCs, packed red blood cells.
[a] Polyheme (Northfield Laboratories Inc, Evanston, Illinois).

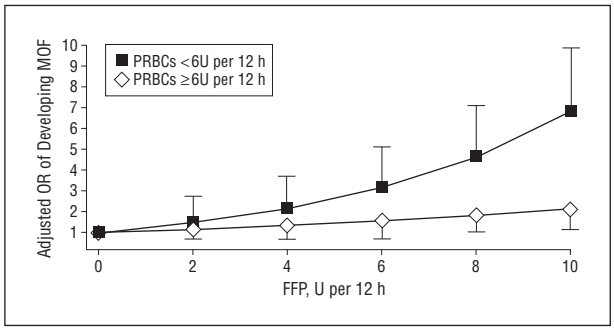

Figure. Odds ratio (OR) of developing postinjury multiple organ failure (MOF) associated with fresh frozen plasma (FFP) and packed red blood cell (PRBC) transfusion, adjusted for age, Injury Severity Score, and transfusion of platelets.

and partial thromboplastin time (PTT) within 12 hours were significantly associated with MOF. When 12-hour PT and PTT were categorized as longer than 15 seconds and longer than 35 seconds, respectively, patients with MOF were significantly more likely to have abnormal PTs and PTTs (45.7% had PTs >15 seconds and 43.6% had PTTs >35 seconds) than patients without MOF (25.2% had PTs >15 seconds and 25.6% had PTTs >35 seconds) ($P<.001$, χ^2 test for both).

Of 1440 patients, 1081 (75%) had complete data on age, ISS, coagulation tests, and blood products transfused and were included in the multivariate analysis. To evaluate the effect of coagulopathy, we kept PTs and PTTs during the first 12 hours in the model. Neither of these 2 coagulation tests showed independent effects on increasing the likelihood of MOF, regardless of the format (continuous or categorical). Interactions of PT and PTT with the other variables were tested, but none were significant. Multiple logistic regression analysis detected a significant interaction between units of FFP and PRBCs ($P<.001$), as summarized in **Table 2**. Regardless of the units of PRBCs transfused, FFP transfusion was independently associated with the development of MOF. However, the deleterious effect associated with FFP transfusion was more prominent among patients receiving fewer than 6 U of PRBCs within 12 hours after injury (**Figure**).

As shown in previous work by 2 of us,[16] age, ISS, and units of PRBCs within 12 hours were independently associated with postinjury MOF. After adjustment for age, ISS, and units of FFP and PRBCs transfused, PLT transfusion was unassociated with MOF. No other interactions were detected. The power analysis of the lack of association between MOF and PLT transfusion (with 80% power required to detect a 3% increase in adjusted MOF risk) suggested that the lack of association was not due to insufficient sample size or type II error.

A second multiple logistic regression analysis was conducted among the subgroup of 615 patients who required transfusion of at least 1 U of PRBCs and had complete information for the logistic regression models. The results were remarkably similar, as summarized in **Table 3**. As anticipated, the incidence of MOF among this subgroup of patients requiring blood products was higher (33.1%) than that in the study population as a whole.

COMMENT

Trauma patients manifest early abnormalities in coagulation profiles, even before vigorous crystalloid or blood product administration, and such findings are independent pre-

Table 3. Multiple Logistic Regression Analysis of the Independent Effect of Blood Products Transfusion on the Development of Postinjury Multiple Organ Failure in the Subgroup of 615 Patients Who Required Blood Products in the First 12 Hours

Variable	Estimate (SE)	*P* Value
Intercept	–3.5363 (0.4871)	<.001
Injury Severity Score	0.0409 (0.0079)	<.001
Age	0.0292 (0.0057)	<.001
Worst prothrombin time in the first 12 h	–0.0344 (0.0224)	.12
Worst partial prothromboplastin time in the first 12 h	–0.0003 (0.0029)	.93
PRBCs, U per 12 h	0.0878 (0.0199)	<.001
Platelets, U per 12 h	0.00005 (0.02950)	>.99
FFP, U per 12 h	0.0726 (0.0308)	.02
Blood substitute, U per 12 h[a]	–0.0310 (0.0635)	.63
PRBC U × FFP U	–0.0023 (0.0007)	.002

Abbreviations: FFP, fresh frozen plasma; PRBCs, packed red blood cells.
[a] Polyheme (Northfield Laboratories Inc, Evanston, Illinois).

dictors of mortality.[16,19,20] The mortality associated with the bloody vicious cycle is so high that it seems prudent to preempt all possible components in the early postinjury period. This has been the argument for early administration of FFP to perform a 1:1 match with PRBC transfusion. Nevertheless, the scientific rationale for early FFP administration remains a matter of debate; neither the efficacy nor the safety of this approach is well described. In fact, the clinical efficacy of FFP transfusion remains largely unproven, and most evidence for FFP administration is from observational data alone.[21,22] The importance of guidelines for FFP administration was recently emphasized by Lauzier et al,[23] who found that FFP transfusion in critically ill patients is often inappropriate.

At a recent consensus conference on massive transfusion, some investigators called for a common massive transfusion protocol based on a 1:1 ratio of FFP to PRBCs, emphasizing the need for additional FFP in an attempt to approximate concentrations found in whole blood.[24-27] Other evidence often cited to support a 1:1 ratio for massive transfusions includes a computer model[28] that suggests an optimal ratio of FFP to PRBCs of 2:3 using a mathematical model of normovolemic hemodilution.

However, these approaches to FFP transfusion are predicated on the concept that early postinjury coagulopathy represents primarily a lack of clotting factors.[29,30] In contradistinction, recent strong evidence indicates that synergistic effects of tissue injury and shock (rather than a depletion of coagulation factors) are the trigger of early postinjury coagulopathy. Specifically, excess activation of protein C concurrent with an increase in tissue plasminogen activator has been implicated, with the net result being a hypocoagulable and fibrinolytic state.[31,32] This suggests that administration of additional clotting factors in FFP may be of little benefit. Furthermore, because anticoagulant (eg, antithrombin III) and fibrinolytic (eg, plasminogen) factors are present in FFP, it is unclear a priori that plasma transfusion during the phase of "acute endogenous coagulopathy" tips the balance in the correct direction after early postinjury coagulopathy. It is conceivable that the untimely infusion of FFP may augment the early coagulopathy of trauma.

Herein, we highlight another potential adverse effect of FFP administration. It has long been known that blood components contain an array of biologically active mediators. These include cytokines and biologically active lipids. These transfused mediators are likely to contribute to the profound immunomodulation that results from delivery of blood components.

The risks associated with FFP transfusion are significant, including transmission of infectious diseases and triggering of transfusion-associated lung injury, which has become the most important cause of transfusion-related morbidity and mortality in the United States.[22,33-35] Infusion of FFP has been suggested to triple the risk of transfusion-associated lung injury among patients who are mechanically ventilated.

We found herein that early FFP transfusion is an independent risk factor for the development of MOF, in addition to the previous observation that PRBC transfusion confers this risk.[8] In the present study, the absolute amount of FFP delivered and increased ratios of FFP to PRBCs were associated with subsequent development of MOF, which remains the leading cause of late postinjury death. Notably, the attributable risk was more apparent among patients receiving fewer units of blood.

Our results must be interpreted with some caution because the Denver MOF database specifically excludes patients who die within the first 48 hours after injury. Because our focus was late MOF, we chose not to observe and categorize the process of early death. It is conceivable that patients administered more FFP in the early period are more likely to survive the initial postinjury period, even if it confers some increased risk of late MOF. However, ratios of FFP to PRBCs of 1:2-3 vs 1:1 were associated with lower risk-adjusted mortality in a 2008 study[15] of massive transfusion, again suggesting some harm associated with aggressive use of early FFP. That study group included all patients undergoing massive transfusion, regardless of survival in the first 48 hours. Therefore, our early survival data among the civilian population, as well as our data for late postinjury MOF, do not suggest that a 1:1 ratio of FFP to PRBCs represents optimal therapy.

Our data highlight the importance of delivering FFP when it is physiologically necessary and not simply when there is laboratory evidence of coagulopathy. This fits well with the concept that correction of the underlying disorder may be more pivotal than administration of FFP.[26,36] Until we have functional clotting assays that allow differentiation between impaired PLT function, disordered fibrin production, and excess fibrinolysis, it is likely that targeted therapy for postinjury coagulopathy is untenable. Tools such as thromboelastography may remain the best option in this regard.[20,37] Further delineation of the precise postinjury changes in the clotting and fibrinolysis cascades is required before a scientific basis for FFP transfusion can be established. In the interim, although FFP remains a tool in the bloody vicious cycle, it would seem wise to proceed with caution.[38]

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