Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy*

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Objective: **Although restrictive red cell transfusion practice has become a standard of care in the critically ill, data on the use of fresh frozen plasma (FFP) are limited. We hypothesized that the practice of FFP transfusion in the medical intensive care unit is variable and that liberal use may not be associated with improved outcome.**

Design: **Retrospective cohort study.**

Setting: **A 24-bed medical intensive care unit in a tertiary referral center.**

Patients: **All patients admitted to a medical intensive care unit during a 5-month period who had abnormal coagulation defined as international normalized ratio (INR) of ≥1.5-times normal.**

Interventions: **None.**

Measurements and Main Results: **We collected data on demographics, severity of illness as measured by Acute Physiology and Chronic Health Evaluation (APACHE) III scores, INR, bleeding episodes, and transfusion complications. We identified 115 patients with coagulopathy (INR of ≥1.5) but without active bleeding. A total of 44 patients (38.3%) received FFP transfusion. INR was corrected in 16 of 44 patients (36%) who received transfusion. Median dose of FFP was 17 mL/kg in patients who had INR corrected vs. 10 mL/kg in those who did not ($p = .018$). There was no difference in age, sex, APACHE III scores, liver disease, Coumadin treatment, or INR level between those who did and did not receive FFP. Invasive procedures (68.2% vs. 40.8%, $p = .004$) and history of recent gastrointestinal bleeding (41% vs. 7%, $p < .001$) were more frequent in the group with transfusion. Although there was no difference in new bleeding episodes (6.8% in transfused vs. 2.8% in nontransfused group, $p = .369$), new onset acute lung injury was more frequent in the transfused group (18% vs. 4%, $p = .021$). Adjusted for severity of illness, hospital mortality and intensive care unit length of stay among survivors were not different between the two groups.**

Conclusion: **The risk–benefit ratio of FFP transfusion in critically ill medical patients with coagulopathy may not be favorable. Randomized controlled trials evaluating restrictive vs. liberal FFP transfusion strategies are warranted. (Crit Care Med 2005; 33:2667–2671)**

Key Words: fresh-frozen plasma; transfusion; outcome study; pulmonary edema; clinical use

Although restrictive strategy for transfusion of red blood cells has been shown to be associated with equal or superior outcome to liberal strategy (1), data are scarce regarding the use of fresh frozen plasma (FFP) in clinical practice (2). Most clinical uses of FFP, even those currently recommended by practice guidelines (3, 4), are not supported by evidence from randomized trials (5). In addition to very little medical evidence documenting the effectiveness of its use (5, 6), FFP transfusion is associated with significant adverse affects. These include transfusion-related acute lung injury, transfusion-related circulatory overload, and rarely, allergic reactions.

Although active bleeding is usually considered an absolute indication for the use of FFP for correction of coagulopathy, prophylactic use of FFP (such as before an invasive procedure) has been controversial (5). The risk–benefit ratio of prophylactic FFP use for correction of coagulopathy in the absence of active bleeding has not been studied. The aims of the present study were: 1) to assess the variability in practice regarding the use of FFP in patients admitted to a medical intensive care unit (ICU) with coagulopathy but no active bleeding, 2) to assess the compliance with published practice guidelines for the use of FFP, and 3) to compare the prevalence of new bleeding, transfusion complications, and overall outcome in critically ill patients without active bleeding who did or did not receive FFP for the correction of coagulopathy.

MATERIALS AND METHODS

This retrospective cohort study was conducted at a 24-bed medical ICU at a tertiary care medical center in Rochester, MN. The institutional review board of our institution approved this study.

From a cohort of patients admitted to the medical ICU who had a prothrombin time measured between March 1 and July 31, 2004, we identified those who had international normalized ratio (INR) of >1.5 at any time during their ICU stay (Fig. 1). Each patient's electronic medical record was searched for the details of predictor and outcome variables.

Predictor variables measured included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) III Score (7), INR level, FFP transfusion, and indication. For patients who received FFP transfusion, the level of INR prompting FFP transfusion was recorded. For patients not transfused FFP, the highest level of INR during their ICU stay was recorded. FFP transfusion was considered to be outside published guidelines (3–5) if it was given in the absence of active bleeding (absolute indication) or invasive procedure (relative indication).

***See also p. 2714.**

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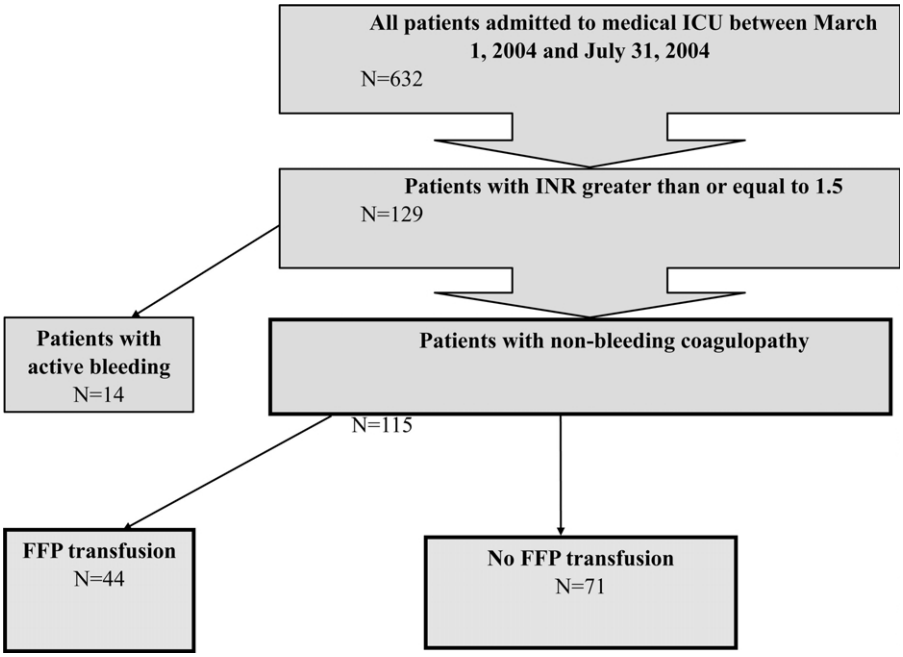

Figure 1. Flow diagram of the study. Cohort of patients admitted to the medical intensive care unit (*ICU*) between March 1, 2004, and July 31, 2004. *INR*, international normalized ratio; *FFP*, fresh frozen plasma.

Outcome variables included new bleeding episodes and FFP complications: acute lung injury, circulatory overload, and allergic reactions. New bleeding was defined as a bleeding episode requiring at least one unit of RBC transfusion that developed within 24 hrs of FFP administration or, in patients who did not receive FFP, within 24 hrs of the highest recorded INR value. Transfusion reactions associated with skin manifestations were generally classified as allergic (8). Acute lung injury was defined according to American European Consensus Conference Definition as acute hypoxemia ($Pao_2/Fio_2 < 300$) and development of bilateral pulmonary infiltrates on chest radiographs in the absence of clinical evidence of left atrial hypertension (9). Acute lung injury was considered a new onset if it developed within 48 hrs after FFP administration or within 48 hrs after the highest recorded INR value in patients who did not receive FFP. Clinical outcomes including hospital mortality and ICU length of stay among survivors were also recorded.

Categorical outcome variables were compared between two groups based on the chi-square test or Fisher's exact test. Continuous outcome variables were compared using Student's *t*-test or rank-sum tests as appropriate. To determine the clinical characteristics associated with FFP transfusion, logistic regression analysis was performed with FFP transfusion as the dependent variable. The potentially significant variables identified in univariate analysis ($p < .1$) and nonsignificant biologically plausible variables were entered in the analysis. The final model was chosen by stepwise forward selection method to achieve the best goodness of fit for the whole model. INR level, recent bleeding, Coumadin anticoagulation, liver insufficiency, RBC transfusion, and invasive procedure were used as independent variables in the final model.

RESULTS

A total of 632 patients were admitted to the medical ICU during the study time period (Fig. 1). Of these, 129 patients (20.4%) met our criteria. A total of 14 patients with active bleeding (of whom 13 received FFP) were excluded from subsequent analysis. Of 115 patients with elevated INR and no active bleeding, 44 (38.3%) received FFP (Table 1), the majority (87%) on the first ICU day. FFP was transfused at a wide range of INR levels (median, 2.7; range, 1–22), and 14 of 44 patients (32%) received FFP outside published guidelines (3, 4). INR was corrected (to <1.5) in only 16 of 44 transfused patients (36%). Median dose of FFP was 17 mL/kg in patients who had INR corrected vs. 10 mL/kg in those who did not ($p = .018$).

There was no difference in age, sex, median APACHE III scores, underlying reason for coagulopathy, presence of acute lung injury risk factors, or INR level between the FFP and non-FFP groups (Table 1). Invasive procedure use was more frequent in the FFP group (68.2% vs. 40.8%, $p = .004$). Of 59 patients who had to undergo an invasive procedure, 30 (51%; 95% confidence interval, 38% to 64%) received FFP and 29 (49%; 95% confidence interval, 36% to 62%) did not.

Although there was no difference in new bleeding episodes (6.8% in FFP vs. 2.8% in the non-FFP group $p = .369$), new onset acute lung injury was more frequent in the FFP group: 18% vs. 4% ($p = .021$) (Table 2). The characteristics of patients who developed acute lung injury are listed in Table 3. There was no significant difference in number of FFP units given to patients who did and did not develop acute lung injury (median [range]): 5 (3–8) vs. 4 (1–8), $p = .319$. No allergic transfusion complications were observed.

Hospital mortality in the transfused group was 25.6% in the FFP group vs. 28.2% in the non-FFP group ($p = .763$). In survivors, median ICU length of stay was 2.4 days (interquartile range, 1.7–6.8) in the FFP group vs. 2 days (interquartile range, 0.9–3.0) in the non-FFP group ($p = .184$). When adjusted for the severity of illness (APACHE III predicted mortality), FFP transfusion was not independently associated with hospital mortality (odds ratio, 0.94; 95% confidence interval, 0.36 to 2.39).

In the multivariate logistic regression analysis, invasive procedure (odds ratio, 4.15; 95% confidence interval, 1.62 to 11.71) and recent gastrointestinal bleeding (odds ratio, 8.05; 95% confidence interval, 2.51 to 29.14) were independently associated with FFP transfusion (Table 4).

DISCUSSION

The main findings of this study are: 1) significant variation exists in the use of FFP in nonsurgical critically ill patients with coagulopathy but without evidence of active bleeding; 2) in this sample, the rate of new bleeding episodes was uncommon and did not differ between the groups that did and did not receive prophylactic FFP transfusions; 3) the use of FFP was associated with the development of acute lung injury; and 4) FFP was commonly transfused outside published guidelines.

We found a considerable variation in the FFP transfusion practice. This is evidenced by the wide range of INR levels over which FFP was transfused and the

Table 1. Baseline differences between fresh frozen plasma (FFP) and non-FFP groups

	FFP (n = 44)	No FFP (n = 71)	*p* Value
Demographic			
Median age, yrs (IQR)	72 (57 to 81)	68 (59–78)	.468
Female Sex, n (%)	25 (56.8)	34 (47.8)	.352
Baseline clinical characteristics			
Median admission APACHE III score (IQR)	63 (54 to 85)	65 (48 to 82)	.924
Median day of interest APACHE III score (IQR)[a]	62 (54 to 83)	64 (51 to 77)	.940
Median INR level (IQR)[a]	2.7 (1.7 to 4.1)	2.5 (1.7 to 3.9)	.532
Coumadin anticoagulation, n (%)	32 (73)	49 (69)	.672
Liver disease, n (%)	9 (20.5)	7 (9.9)	.111
DIC, n (%)	2 (4.6)	4 (5.6)	.799
Sepsis, n (%)	11 (25)	16 (22.5)	.762
Pneumonia, n (%)	3 (6.8)	9 (12.7)	.367
Aspiration, n (%)	1 (2.3)	1 (1.4)	.855
Other clinical characteristics			
Recent GI bleeding, n (%)	18 (40.9)	5 (7)	<.001
Invasive procedure, n (%)	30 (68.2)	29 (40.8)	.004
Mechanical ventilation, n (%)	17 (39%)	38 (54%)	.130
Platelet count (IQR)	194 (131 to 287)	198 (116 to 198)	.701
APTT, secs (IQR), n = 33 vs. 47	42 (33 to 59)	37 (32 to 53)	.899
Vitamin K, n (%)	20 (45%)	14 (20%)	.005
RBC transfusions, n (%)	27 (61.4)	19 (26.8)	<.001
Median fluid balance, L (IQR)[a]	3.0 (1.4 to 4.2)	1.5 (0.1 to 4.0)	.057

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; INR, international normalized ratio; DIC, disseminated intravascular coagulation; GI, gastrointestinal; APTT, activated partial thromboplastin time; RBC, red blood cells.

[a]Day of highest INR/FFP transfusion; in 100 of 115 patients, day 1 was the day of interest. Complete data sets were available for all the variables of interest except for pneumonia (14 missing), aspiration (14 missing), sepsis (15 missing), and DIC (14 missing).

Table 2. Outcome of patients who did and did not receive fresh frozen plasma (FFP) transfusion

Outcome	FFP (n = 44)	No FFP (n = 71)	*p* Value
New bleeding episodes, n (%)	3 (6.8)	2 (2.8)	.369
New onset acute lung injury, n (%)	8 (18.2)	3 (4.2)	.021
Hospital mortality, n (%)	11 (25.6)	20 (28.2)	.763
Median (IQR) ICU length of stay, days[a]	2.4 (1.7–6.8)	2 (0.9–3)	.184

IQR, interquartile range; ICU, intensive care unit.

[a]In survivors.

Table 3. Characteristics of patients who developed acute lung injury (ALI; n = 11)

General	
Median (IQR) age, yrs	73 (51–79)
Female sex, n (%)	5 (46)
Median (IQR) APACHE III score	97 (65–127)
ALI risk factors	
FFP transfusion, n (%)	8 (73)
Median (IQR) number of FFP units	5 (4–7)
Sepsis, n (%)	5 (45)
Aspiration, n (%)	0 (0)
Pneumonia, n (%)	1 (9)
DIC, n (%)	2 (18)
Outcome	
Hospital mortality, n (%)	4 (36)
Ventilator days, median (IQR)[a]	7.0 (2.0–9)
Median (IQR) ICU length of stay, days[b]	5.4 (2.0–12.7)

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; FFP, fresh frozen plasma; DIC, disseminated intravascular coagulation; ICU, intensive care unit.

[a]Nine of 11 patients required mechanical ventilation; [b] in survivors.

overlap with INR levels of patients not transfused with FFP (Table 1). Of 59 patients who underwent an invasive procedure, half received FFP and half did not. This is in line with the previous data regarding practice variability of other blood component therapy among critically ill patients (10). Based on the multivariate analysis (Table 3), we speculate that 1) the fear of procedural complications or recurrent bleeding (justified or unjustified) and 2) the absence of evidence from the randomized trials are the main sources of variability.

A significant number of patients with coagulopathy receive FFP transfusion without demonstrated efficacy (2, 6). INR level is known to be a poor predictor of subsequent bleeding in the critically ill patient, and in many patients, specific factor concentrations remain adequate to prevent microvascular bleeding (2). On the other hand, our findings confirm previous observations (2) that the standard recommended dose of FFP fails to correct coagulation deficit in a majority of critically ill patients (in only 16 of our 44 transfused patients was INR corrected after the FFP transfusion). Therefore, the current practice of FFP transfusion is likely to expose the patients to transfusion risks with little or no documented benefit. Due to recognition of this problem over the last two decades, new guidelines have been promoted to educate the involved personnel (5). The present study expands on this literature by demonstrating that 32% of critically ill medical patients with elevated INR are transfused FFP outside of guidelines. It is important to emphasize that recommendations in the current guidelines are based on expert opinion, as no randomized studies are available.

In the current study, FFP was commonly used before an invasive procedure. Although there is a little evidence for the effectiveness of the prophylactic use of FFP (6), previous studies have shown that invasive procedures can be done safely in patients with disorders of hemostasis by skilled physicians who frequently perform these procedures (11). This has been shown repeatedly for central venous catheterization in multiple settings, including general medical, and in liver transplant recipients (12, 13). It has also been shown for other procedures, including thoracocentesis and paracentesis (14). Although some published guidelines currently define invasive procedure as one of the indications for FFP transfusion

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(3), our data do not support this practice for the common critical care procedures.

We also found considerable use of FFP in patients who had recent bleeding but no active ongoing bleeding. Of the 18 patients with recent bleeding, 15 (83%) had been receiving chronic oral anticoagulant therapy. FFP transfusion was primarily aimed for reversal of warfarin effect. However, the latest British Society for Hematology guidelines clearly state that FFP should not be transfused for the reversal of warfarin anticoagulation when there is no evidence of severe active bleeding (5). This is particularly noteworthy in the context of our data (see above) and previous studies suggesting that FFP may not be particularly effective in replacing coagulation factors (2).

Although the association between FFP transfusion and pulmonary edema caused by transfusion-related acute lung injury and transfusion-related circulatory overload is well known (7), the effect of liberal FFP transfusion in clinical practice on the prevalence of acute lung injury has not been studied. Similar to our previous report in the cohort of patients receiving mechanical ventilation, in the current study, FFP transfusion was associated with a higher rate of acute lung injury (15, 16). It is possible that the observed difference in acute lung injury was due simply to the fact that the patients were different. Similar APACHE scores and demographics do not rule out all differences in case-mix or unmeasured severity of illness. Although non–transfusion-related risk factors for acute lung injury (including shock, sepsis, aspiration, and pneumonia) were not different among the two groups (Table 1), the small sample size precluded adequate adjusted analysis. When adjusted for either APACHE III scores, sepsis, pneumonia, invasive procedures, or recent bleeding in a bivariate analysis, FFP transfusion remained significantly associated with the development of acute lung injury ($p < .05$). Small sample size, however, does not allow us to speculate on a possible cause-and-effect relationship.

This study has several additional limitations. It was conducted at a single tertiary medical center. As such, the results may lack wider applicability. Due to the nature of the study, outcome assessors were not blinded to the transfusion data charted in the electronic medical record. Because of the observational design of the study, we cannot exclude the effect of unmeasured confounding variables. As a result of our choice of threshold for definition of new bleeding episode and of the retrospective design, episodes of bleeding not requiring transfusion may have been missed. Another limitation is related to the time points chosen for the comparison between the two groups. Although we chose a time point and INR level prompting the transfusion in the FFP group, the control group had a time point in the care identified by a peak INR result, which was not necessarily associated with any clinical event. However, the first day of the ICU stay was the day of interest (highest INR with or without FFP transfusion) in 100 of 115 patients, minimizing the selection bias. Finally, the small sample size may have contributed to a lack of effect of FFP transfusion on hospital mortality and ICU length of stay.

In conclusion we observed variability in practice of FFP transfusion in critically ill medical patients with coagulopathy but without active bleeding. As the risk–benefit ratio of liberal FFP transfusion strategy may not be favorable, randomized controlled trials evaluating restrictive vs. liberal FFP transfusion strategy are warranted.

Table 4. Factors associated with fresh frozen plasma (FFP) transfusion: multivariate analysis

	Odds Ratio	95% Confidence Interval	*p* Value
Liver insufficiency	3.04	0.87–11.14	.084
Invasive procedure	4.15	1.62–11.71	.004
Recent GI bleeding	8.05	2.51–29.14	.001
RBC transfusion	2.00	0.74–5.38	.167
INR	1.17	0.99–1.45	.104

GI, gastrointestinal; RBC, red blood cells; INR, international normalized ratio.
Whole model $R^2 = .24$, $p < .001$.

REFERENCES

1. Hebert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care: Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340: 409–417
2. Chowdhury P, Saayman AG, Paulus U, et al: Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *Br J Haematol* 2004; 125: 69–73
3. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets: Fresh-Frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. *JAMA* 1994; 271: 777–781
4. Consensus conference: Fresh-frozen plasma. Indications and risks. *JAMA* 1985; 253: 551–553
5. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al: Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004; 126: 11–28
6. Stanworth SJ, Brunskill SJ, Hyde CJ, et al: Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; 126: 139–152
7. Knaus WA, Wagner DP, Draper EA, et al: The APACHE III prognostic system: Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; 100: 1619–1636
8. Domen RE, Hoeltge GA: Allergic transfusion reactions: an evaluation of 273 consecutive reactions. *Arch Pathol Lab Med* 2003; 127: 316–320
9. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818–824
10. Corwin HL, Gettinger A, Pearl RG, et al: The CRIT Study: Anemia and blood transfusion in the critically ill. Current clinical practice in the United States. *Crit Care Med* 1999; 32: 39–52
11. Doerfler ME, Kaufman B, Goldenberg AS:

Central venous catheter placement in patients with disorders of hemostasis. *Chest* 1996; 110:185–188
12. Mumtaz H, Williams V, Hauer-Jensen M, et al: Central venous catheter placement in patients with disorders of hemostasis. *Am J Surg* 2000; 180:503–505; discussion, 506
13. Foster PF, Moore LR, Sankary HN, et al: Central venous catheterization in patients with coagulopathy. *Arch Surg* 1992; 127: 273–275
14. McVay PA, Toy PT: Lack of increased bleeding after paracentesis and thoracentesis in patients with mild coagulation abnormalities. *Transfusion* 1991; 31:164–171
15. Gajic O, Rana R, Mendez JL, et al: Acute lung injury after blood transfusion in mechanically ventilated patients. *Transfusion* 2004; 44:1468–1474
16. Gajic O, Dara S, Mendez JL, et al: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; 32: 1817–1824