Toward Rational Fresh Frozen Plasma Transfusion

The Effect of Plasma Transfusion on Coagulation Test Results

Lorne L. Holland, MD,[1] and Jay P. Brooks, MD, MBA[2]

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Abstract

Numerous published guidelines encourage appropriate use of fresh frozen plasma (FFP). However, adherence is documented as poor. Therefore, we sought to determine the laboratory effect of FFP administration to patients with an international normalized ratio (INR) less than 1.6 (prothrombin time <1.6 times normal).

We found minimally prolonged INRs decreased with treatment of the underlying disease alone. Adding FFP to the treatment failed to change the decrease in INR over time. In addition, we observed that the change in the INR per unit of FFP transfused can be predicted by the pretransfusion INR (INR change = 0.37 [pretransfusion INR] – 0.47; $r^2 = 0.82$).

With an observed analytic variation of 3.2%, a significant amount of change in the INR following FFP transfusion is expected at an INR of more than 1.7. Indeed, only 50% of patients with an INR of 1.7 showed a significant change in INR with FFP transfusion. Therefore, transfusion for patients not meeting current FFP guidelines does not reliably reduce the INR and exposes patients to unnecessary risk.

Current guidelines published by multiple organizations consider fresh frozen plasma (FFP) transfusion appropriate only under specific circumstances.[1-15] Although these guidelines vary in the laboratory definition of appropriate FFP transfusion, most suggest a cutoff of a prothrombin time (PT) and/or partial thromboplastin time (PTT) greater than 1.5 times the normal value.

Despite these clear guidelines, requests for FFP are the most frequent inappropriate orders received by the blood bank. Clearly, clinicians do not have confidence in the published guidelines. Reported percentages of inappropriate FFP orders vary from institution to institution and range from 10%[16] to 83%.[17]

The most frequent reason for these inappropriate orders, accounting for at least a third of them, is for correction of a prolonged INR in the absence of bleeding.[18-20] This prophylactic correction of minor laboratory coagulation abnormalities continues in the absence of evidence of its benefit.[21,22]

Segal and Dzik[22] have suggested that inappropriate FFP orders occur because of 3 assumptions: (1) Elevation of the PT/INR will predict bleeding in the setting of a procedure. (2) Preprocedure administration of FFP will correct the prolonged clotting time results. (3) Prophylactic transfusion results in fewer bleeding events. This study seeks to expand previous work[23] and better clarify the second assumption by quantifying the effect of FFP transfusion on laboratory coagulation parameters.

Materials and Methods

Patients receiving FFP and having pretransfusion and posttransfusion PT/INR measurements were considered for inclusion. Patients with acute trauma, in the operating room,

with excessive factor consumption (ie, disseminated intravascular coagulation), or given prothrombin complex concentrate were excluded.

We ultimately included 103 adult patients at OU Medical Center (Oklahoma City, OK) receiving 174 transfusions in our study. The median pretransfusion INR was 2.2 (range, 0.9-11.2); the median posttransfusion INR was 1.5 (range, 0.9-7.1). The number of 500-mL, apheresis FFP units infused per transfusion ranged from 1 to 6 with a median of 1 and an average of 1.6. INR values were available at a median of 5.8 hours (range, 0.5-23 hours) before transfusion and 4.4 hours (range, 0.5-22 hours) after transfusion.

An additional 37 adult patients receiving 62 transfusions at another institution were included for comparison. The median pretransfusion INR of these patients was 2.2 (range, 1.4-12.0), and the posttransfusion median was 1.7 (range, 1.1-4.1). The number of random FFP units (median volume, 310 mL) infused per transfusion ranged from 1 to 4 with a median of 2 and an average of 2.1. INR values were available at a median of 5.3 hours (range, 0.5-26 hours) before transfusion and 4.7 hours (range, 0.5-21 hours) after transfusion.

We also identified 39 patients receiving 59 transfusions at a children's hospital who met the aforementioned criteria. The median pretransfusion INR was 1.5 (range, 1.1-3.9), and the posttransfusion median was 1.4 (range, 1.0-2.4). The number of 250-mL units of FFP infused per transfusion ranged from 1 to 4 with a median of 2 and an average of 1.9. INR values were available at a median of 2.8 hours (range, 0.2-17 hours) before transfusion and 4.2 hours (range, 0.3-9.6 hours) after transfusion.

A control population of adult patients with borderline INR results (1.3-1.6) who did not receive FFP also was identified. Patients with warfarin exposure during the previous week, severe liver disease, or excessive factor consumption (ie, disseminated intravascular coagulation) were excluded. The control group ultimately included 71 patients. The next INR measurement available at least 4 hours later was recorded with repeated measurements available at a median of 8.5 hours (range, 4-23 hours) after the initial measurement.

Given the relatively short time between laboratory measurements, the total variation was assumed to be equal to the analytic variation with no contribution from biologic variation. Within-run variation of INR measurement was calculated by performing PT/INR on plasma from healthy donors with 20 replicates. Between-run variation was calculated for a month from daily measurement of a reference standard. All PT reagents were based on a recombinant thromboplastin with an international sensitivity index (ISI) of essentially 1.0. With this ISI the INR is equivalent to the degree of PT elevation (eg, an INR of 1.5 equals a PT 1.5 times normal).

Statistical analysis was performed with SPSS (version 13, SPSS, Chicago, IL). Potential differences between regression equations were assessed using analysis of variance (ANOVA). The Mann-Whitney U test and t test were used to assess differences in median and mean, respectively. In all cases, a significant change or difference was defined as a P value of less than .05.

Results

The change in INR for control patients not receiving FFP varied with the initial INR: at 1.3, the mean and median decreases were 0.04 and 0.10; at 1.4, the decreases were 0.06 and 0.10; at 1.5, the decreases were 0.09 and 0.10; and at 1.6, the decreases were 0.17 and 0.20, respectively **Figure 1**.

A linear relationship for adult patients between the pretransfusion INR and the decrease in the INR per 500-mL unit of FFP was observed. When expressed in terms of comparable FFP volumes, regression analysis yielded no difference between the slope and intercept of the equations for adult patients at different institutions (ANOVA, $P > .05$). When combined, the 2 adult data sets yield the following equation **Figure 2**:

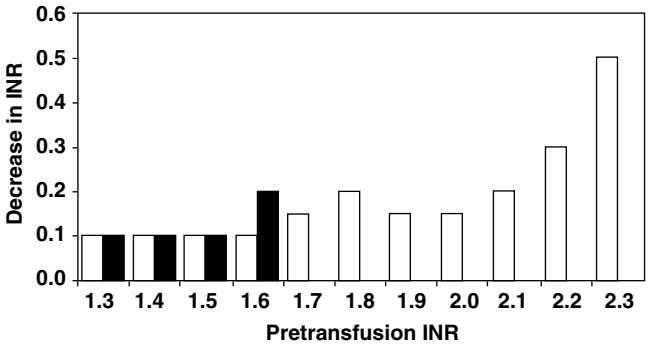

Figure 1 Median international normalized ratio (INR) change with (white bars) and without (black bars) fresh frozen plasma transfusion.

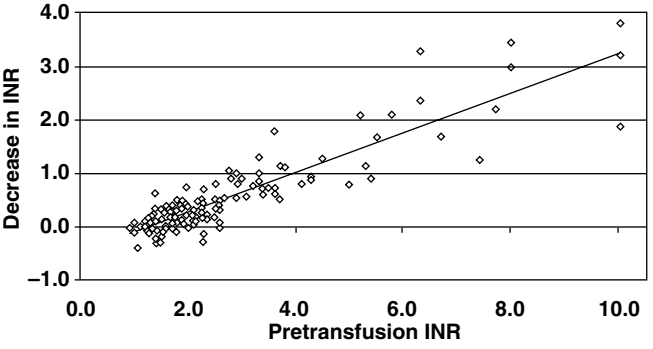

Figure 2 Change in international normalized ratio (INR) per unit of plasma transfused. See Equation 1

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Equation 1

INR Change = 0.37[pretransfusion INR] – 0.47; $r^2 = 0.82$

The observed relationship did not vary with the time of the posttransfusion INR measurement. Indeed, when grouping data into tertiles by time of posttransfusion INR, we found no significant difference in the relationship between the slope and intercept of the equations for data collected less than 3 hours, from 3 to 7 hours, and more than 7 hours after transfusion (ANOVA, $P > .05$).

A similar relationship between the pretransfusion INR and the decrease in INR expressed per 250-mL unit of FFP was noted for pediatric patients:

Equation 2

INR Change = 0.29[pretransfusion INR] – 0.37; $r^2 = 0.67$

To determine the magnitude of a change in INR necessary to be significant, we used the significant change limit (SCL), $z \times \sqrt{2} \times \sigma$. For a 95% confidence interval, z equals 1.96. The observed analytic variation of INR measurement in our study was 3.2% (within run, 3.0%; between run, 1.1%), and this yields an SCL of 8.9%.

Equation 3

Significant Change = 8.9% [pretransfusion INR]

The percentage of adult patients with a change in INR greater than the SCL varies with the pretransfusion INR. Expressed per unit of FFP, this linear relationship is as follows:

Equation 4

% Units With Change More Than SCL =
0.51[pretransfusion INR] – 0.43; $r^2 = 0.82$

A potentially more useful equation can be generated by comparing the pretransfusion INR with change per transfusion. In this case, the change is per physician order with potentially multiple units of FFP transfused **Figure 3**:

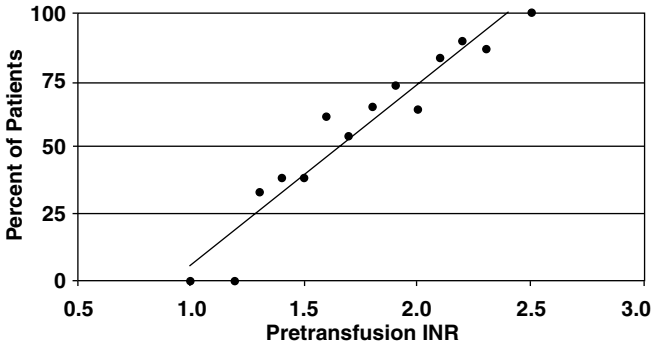

Figure 3 Percentage of patients with significant change in international normalized ratio (INR) following plasma transfusion. See Equation 5.

Equation 5

% Adults With Changes More Than SCL =
0.67[pretransfusion INR] – 0.62; $r^2 = 0.92$

A similar analysis of the pediatric patients shows the following relationship per transfusion:

Equation 6

% Children With Changes More Than SCL =
0.80[pretransfusion INR] – 0.82; $r^2 = 0.88$

Discussion

Significant efforts during the last 20 years have been focused on developing rational criteria for the transfusion of FFP **Table 1**.[1-15] Most guidelines use the laboratory criteria of PT and/or PTT greater than 1.5 times normal paired with the presence of bleeding or anticipated bleeding. Although

Table 1
Fresh Frozen Plasma Transfusion Guidelines

Author	Year	Laboratory Criteria	Dose (mL/kg)
National Institutes of Health[1]	1985	None given	None given
Hong Kong Government Blood Banking Advisory Committee[2]	1990	PT/INR >1.5 times normal	10-15
British Committee for Standards in Haematology[3]	1992	PT/PTT >1.5 times normal; PT >1.8 times normal with liver disease	12-15
Committee Report[4]	1994	PT/PTT >1.5 times normal	15
College of American Pathologists[5]	1994	PT >1.5 times midpoint of normal; PTT >1.5 times upper normal; factor level <25%	2 U (6-7 mL/kg)
American Society of Anesthesiologists[6]	1994	PT/INR >1.5 times normal; factor level <30%	10-15
American College of Obstetrics and Gynecology[7]	1994	PT/PTT >1.5 times normal	2 U (6-7 mL/kg)
Canadian Medical Association Expert Working Group[8]	1997	Significantly increased coagulation time; PT >2.0 with liver disease	10-15
Japanese Ministry of Health and Welfare[9]	1999	PT/PTT >1.5 times normal; factor level <30%	8-12
North Ireland Clinical Resources Efficiency Support Team[10]	2001	PT/PTT >1.5 times normal	12-15
Australia National Health and Medical Research Council[11]	2001	Abnormal coagulation	5-20
American Red Cross[12]	2002	PT/PTT >1.5 times normal	None given
South African National Blood Service[13]	2003	Disturbed coagulation	15-20
British Committee for Standards in Haematology[14]	2004	Multiple factor deficiencies	10-15
New York State Council on Human Blood and Transfusion Services[15]	2004	PT/PTT >1.5 times normal	10-20

INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

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never explicitly stated, it is likely that this ratio was selected based on a number of studies attempting to correlate subjective clinical observation with laboratory values.[24,25] At about the same time, a much larger study proposed an alternative cutoff of 1.8.[26]

A few guidelines offer only vague laboratory criteria such as "abnormal" or "significantly increased" without further explanation. It is unclear whether this omission was coincidental or whether it is tacit admission that a satisfactory laboratory cutoff has not yet been determined.

Regardless of how *appropriate* is defined, it is readily apparent that physicians do not trust the recommendations offered by these guidelines. Multiple studies spanning 25 years from 11 countries document the poor compliance with FFP transfusion guidelines **Table 2**.[16,17,19,27-45] Considering only the studies that defined appropriate as greater than 1.5 times normal, the percentage varies from 31% to 74%.

Definitive results from large, randomized control studies to determine whether elevation of PT/INR predicts bleeding in the setting of a procedure or prophylactic FFP transfusion results in fewer bleeding events are years away. However, the ability to assess the laboratory effect of FFP transfusion on prolonged clotting times is well within reach at this time.

Before examining the effect of FFP on mildly elevated INRs, one must consider the effect of medical treatment without FFP on mildly prolonged coagulation test results. Our findings suggest the natural course of high-normal to mildly elevated INRs (1.3-1.6) is to decrease with supportive care and treatment of the underlying condition alone (Figure 1). The exact reasons for this natural correction are unclear but could relate to correction of the following: (1) dehydration causing hypoperfusion of the liver, (2) anemia causing systemic hypoxia, and/or (3) metabolic disturbances causing pH changes.

Adult patients with INRs in the same range who received FFP showed similar median and mean changes over time (Figure 1). Although patients in the 2 groups were not matched rigorously for demographic characteristics (eg, diagnosis, age, sex), serial INR measurements were taken at similar intervals. The control group measurements were separated by a median of 8 hours, whereas those receiving FFP were separated by a median of 10 hours (time before FFP transfusion plus time after FFP transfusion). Therefore, it seems that transfusion of FFP to patients with mild prolongation of the PT/INR may not be more efficacious for correcting these laboratory abnormalities than usual medical care alone.

More than 20 years ago, Silbert et al[34] noted that only 47% of patients with abnormal coagulation test results showed changes following transfusion of FFP and that these changes were "modest." A later report by the UK National Blood Service showed that in only 23% of patients were mildly abnormal coagulation test results (PT <18 seconds or INR

Table 2
Fresh Frozen Plasma Utilization Reviews

Country	Year	Criteria: PT/PTT*	Intervention	Before (%)	After (%)
Canada[16]	1989	Coagulation defect	Prospective review	NA†	10
United States[27]	1992	>16 s/>60 s		25§	—
Australia[28]	1995‡	>1.5 × normal		31	—
Australia[19]	1997‡	>1.5 × normal	Prospective review	31	15
United States[29]	1985	>2 s more than normal		36	—
Australia[30]	2003	Abnormal		37	—
United States[31]	1988	NIH, 1985	Education; order form modification; prospective review	43	21
Australia[32]	2001‡	>1.5 × normal		43	—
Canada[33]	2002	INR >1.5/none		45	—
United States[34]	1981	Abnormal		48	—
United States[35]	1990	>1.5 × normal/>1.25 × normal	Education	52	22
United States[36]	1986	>1.5 × normal		57	—
India[37]	2004	>1.5 × normal	Education	60	34
England[38]	1991	NIH, 1985		60	—
England[39]	2000	>1.5 × normal		66	—
Belgium[40]	1994	>1.7 × normal/>55 s		67	—
Hong Kong[41]	1996	>1.5 × normal	Order form modification	71	13
India[42]	2005	INR >1.5/none		71	—
Singapore[43]	2003	>1.5 × normal		73	—
Venezuela[44]	1999	>1.5 × normal		74	—
Mexico[45]	1999	>1.6 × normal/none		80	—
Israel[17]	1989	INR >2.0/>50 s		83	—

INR, international normalized ratio; NIH, National Institutes of Health; PT, prothrombin time; PTT, partial thromboplastin time.
* When only 1 value is given, the same criteria were applied to PT and PTT.
† Prospective order approval in place at start of study.
‡ Studies performed at same institution.
§ Based on initial review of orders.

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<1.5) corrected to normal after an average transfusion of 650 mL of plasma.[39] Finally, Abdel-Wahab et al[46] recently found full or partial correction of PT in only about 16% of patients with slightly prolonged clotting times (PT, 13-17 seconds), most of whom received 1 or 2 units of FFP.

However, there is little doubt that FFP transfusion can be effective at correcting laboratory abnormalities under the right circumstances. Our data show that the most important variable determining the amount of change in the INR with FFP transfusion is the pretransfusion INR (Equations 1 and 2 and Figure 2), which accounts for as much as 82% of the variability in INR following FFP transfusion.

The amount of change in a laboratory value that may be significant depends on the variation in measurement of the analyte considered. Many studies have examined variation within PT/INR measurements and potential significant changes in patients taking oral anticoagulants.[47,48] For our patient population, we determined the SCL to be 8.9% of the pretransfusion INR (Equation 3). This value agrees with previous estimates of analytic variation and critical differences of PT/INR values in populations not taking oral anticoagulants.[49,50]

By comparing our equation for change in INR per unit of FFP in adults (Equation 1) with the SCL (Equation 3), we find that the predicted amount of change equals the SCL at an INR of 1.7. The same comparison for pediatric patients (Equation 2) shows the point of equality to be 1.6. Below an INR of 1.7 in adults and 1.6 in children, the potential error in measurement is greater than the observed change, positive or negative, in INR per unit of FFP transfused.

By examining the potential significance of changes in INR with FFP transfusion in another manner, we can compare the percentage of patients with a change in INR greater than the SCL with the pretransfusion INR (Figure 3). Based on our data, we can predict that 50% of adult patients will have a significant change at an INR of 1.8 when the equation is expressed per unit of FFP (Equation 4) and 1.7 when expressed per transfusion (Equation 5). Furthermore, at the conventional cutoff of 1.5, only about 38% of transfusions are predicted to cause a significant change.

A similar analysis of the pediatric cases shows that 50% of patients are expected to have a significant change per transfusion at an INR of 1.7 (Equation 6). As with adult patients, using the common criterion of 1.5, only about 39% of transfusions are predicted to cause a significant change.

Further confounding attempts at appropriate FFP transfusion is the lack of consistency found between FFP transfusion guidelines and recommended doses of FFP. Most suggest dosing by weight, but a few simply recommend a number of units per patient (Table 2). As such, the final dose recommended varies from as low as 5 mL/kg to as high as 20 mL/kg.

Based on our regression line (Equation 1), we have calculated the volume of FFP likely to achieve a target INR assuming no significant change in the synthesis or destruction of clotting factors (eg, vitamin K for warfarin reversal, ongoing disseminated intravascular coagulation) **Table 3**. In addition, based on data from other studies,[51,52] we have estimated the minimum expected factor level increment. In these studies, factors VII and IX had the smallest change, with an increment of about 5% per 500 mL of FFP.

Although the volume of FFP required depends somewhat on the initial INR, the target INR actually has the most significant effect. Indeed, the difference in volume between a goal of 1.3 and 1.7 is 2 L of plasma at all initial INRs (Table 3). This represents a significant volume load for a patient. It is interesting that transfusion of FFP to achieve an INR of 1.7 results in factor levels often cited as hemostatically adequate (20%-30%).[26,53] For example, at an INR of 6.0, factor levels are no more than 5% and administration of FFP to achieve an INR of 1.7 causes an increment of at least 25%. Based on the assumption of 30% factor activity being adequate, Ciavarella et al[26] determined that an INR of 1.8 represented a minimally acceptable level of coagulation in their population.

In addition to the 3 assumptions suggested by Segal and Dzik,[22] another assumption may exist that leads to inappropriate transfusion: the potential for benefit is greater than the

Table 3
Predicted Fresh Frozen Plasma Transfusion Volume, Dose, and Expected Factor Increment for Various Target INR Values

	Target INR											
	1.3			1.5			1.7			3.0		
Initial INR	Volume (L)	Dose (mL/kg)	Factor (%)	Volume (L)	Dose (mL/kg)	Factor (%)	Volume (L)	Dose (mL/kg)	Factor (%)	Volume (L)	Dose (mL/kg)	Factor (%)
6.0	4.5	64	45	3.5	50	35	2.5	36	25	1.5	21	15
5.0	4.3	61	43	3.0	43	30	2.3	32	23	1.0	14	10
4.0	4.0	57	40	2.5	36	25	2.0	29	20	0.5	7	5
3.0	3.5	50	35	2.0	29	20	1.5	21	15	—	—	—
2.0	2.5	36	25	1.5	21	15	0.5	7	5	—	—	—

INR, international normalized ratio.

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negligible risks of FFP transfusion. However, transfusion of FFP is not a therapy of negligible risk. Although publicized risks such as transmission of HIV and hepatitis C virus are calculated to be one in a few million,[54] other equally life-threatening risks of FFP transfusion are far more common. Severe allergic reactions,[55] transfusion-associated circulatory overload,[56] and transfusion-related acute lung injury[56-58] are a few of the serious and potentially overlooked risks of FFP transfusion. All can cause significant morbidity and mortality, and the risk of developing one of these complications is orders of magnitude greater than for transmission of HIV or hepatitis C virus.

The clinical significance of mildly prolonged coagulation test results is likely minimal.[21,22] In the face of this strong but not absolutely definitive evidence, physicians may still be inclined to treat abnormal laboratory values with FFP. However, our study demonstrates that in adult and pediatric patients, the potential benefits of FFP transfusion, in terms of normalization of coagulation test results, are minimal in patients with an INR of less than 1.7 (PT < 1.7 times normal). Therefore, attempting to correct laboratory abnormalities in patients not meeting current FFP guidelines may expose patients to unnecessary infectious and noninfectious risks with no demonstrable benefit.

From the Departments of Pathology, [1]University of Texas Southwestern, Dallas; and [2]University of Oklahoma Health Sciences Center, Oklahoma City.

Address reprint requests to Dr Holland: Dept of Pathology, UT Southwestern Medical Center, Dallas, TX 75390-9072; Lorne.Holland@UTSouthwestern.edu.

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