Indications for and Efficacy of FFP: A Laboratory Study
Introduction

From 1974 to 1984, the use of FFP in the United States increased tenfold, to almost 2 million units annually. A portion of this increase reflected the trend toward using component therapy rather than whole blood. However, the magnitude of the increase clearly indicates changing patterns of therapeutic use as well, and highlights the need for critical review of the indications for and efficacy of FFP administration. There are several specific and well-recognized indications for FFP therapy: (1) replacement of isolated factor deficiencies, (2) rapid reversal of warfarin therapy, (3) antithrombin III deficiency, (4) thrombotic thrombocytopenic purpura, and (5) massive blood transfusion with bleeding not attributable to thrombocytopenia (ref. 6). These indications account for a relatively small percentage of fresh frozen plasma use. In contrast, FFP is a frequently used therapy for bleeding patients with non-specific elevation of screening coagulation parameters. Elevated screening parameters which may be due to multiple factor deficiencies arise in several clinical settings, principally in patients with liver disease, trauma patients, and those undergoing extracorporeal circulation or exchange transfusion (ref. 4). Patients with liver disease may have decreased levels of coagulation factors due to diminished synthesis and chronic consumption. Between 5 and 30% of trauma patients may develop multiple factor deficiencies secondary to a consumptive coagulopathy. Several studies have related development of this coagulopathy to duration of hypovolemia and hypoxia. A subset of patients undergoing extra-corporeal circulation or exchange transfusion develop multiple factor deficiencies. Development of factor deficiencies in this situation seems to depend on patients' ability to respond and compensate rather than on a straight dilutional effect. Clotting factor deficiencies in all these clinical settings may be mild and clinically insignificant; yet, they may still cause significant elevation of coagulation screening tests. A subset of patients with elevated screening tests will actually have dangerously low levels of one or more clotting factors. These patients may benefit from FFP.

Whether elevation of coagulation parameters is due to dilution, lack of production, or consumption of coagulation factors, the theoretical basis for administration of FFP is replacement of the lacking factors. Despite extensive use, the clinical efficacy of FFP in these situations has been difficult to establish. Few studies have attempted to quantify the actual increases in coagulation factor levels which occur with FFP administration. There has also been relatively little investigation concerning what degree of abnormality in screening tests signals dangerously low levels of coagulation factors. Previous studies have suggested that values of PT and PTT less than 1.5X normal do not generally represent hazardous factor levels.

In this study, we examined 30 patients who received FFP. We measured coagulation screening parameters and factor levels at the time of the request for FFP, and then again following the plasma administration. We correlated the patients' screening coagulation tests with the actual factor levels present prior to FFP administration. We then quantified changes in individual factor levels which occurred following FFP therapy.

Materials and Methods

The study was performed on plasma from 30 consecutive patients at the San Francisco Veterans Administration Hospital, for whom requests for FFP were received between April and November 1990. 10 of the 30 patients were status post cardiac or other major vascular surgery. 8 patients had gastrointestinal or intracranial hemorrhage secondary to liver disease (2), warfarin (2), or other causes. 6 patients had
alcoholic liver disease. 4 patients were status post oncologic surgery. All patients were either (1) actually bleeding or (2) had liver disease and were scheduled for an invasive procedure. All patients had screening coagulation parameters which met the criteria for release of FFP at the VAMC. These criteria are a PT or PTT > 1.5X the mid-range of normal. At the VAMC, this corresponds to a PT of 18.5 seconds and a PTT of 45.0 seconds. A PT, PTT, and multiple factor level assays were performed on plasma samples drawn from patients before and after administration of FFP. All 30 patients were included in the analysis of the relationship between screening coagulation tests and coagulation factor levels. Post-transfusion factor levels were not considered to reflect FFP administration if more than 6 hours had elapsed between pre- and post-transfusion samples. This excluded 4 patients. 1 patient never received FFP after it was requested. Thus, analysis of the relationship between FFP administration and change in coagulation factor levels was performed on samples from 25 patients. Patients received either 2 units of FFP (6 patients, 9 episodes) or 4 units (20 patients, 33 episodes). The number of episodes of transfusion per patient ranged from 1 to 4, with a mean of 1.8.

PT and PTT assays were performed on the MLA Electra 700 Automatic Coagulation Timer. The reagent used for the PT was Thromboscreen (rabbit brain with calcium chloride) from Pacific Hemostasis. The reagents for the APTT were Kontact and calcium chloride (Pacific Hemostasis). Coagulation factor assays were performed on the Automated Coagulation Laboratory. Reagents used were from Instrumentation Laboratory (rabbit-calcium thromboplastin for PT and cephalin with activator and CaCl₂ for APTT).

Results

Figure 1 shows pre-transfusion levels of factors VII and X plotted against the corresponding PT values for each patient. 13 of the 30 patients had pre-transfusion assays of both factor VII and X. 3 patients had only factor VII assayed, while 2 patients had only factor X. For factors VII and X, 25% is designated as the minimum hemostatic level, and is marked with a dotted line. The VA screening criteria for release of FFP—PT > 1.5X mid-range of normal—is also marked with a dotted line. This figures show that 16/17 patients with factor VII or X levels less than 25% had elevations of PT > 1.5X normal. Table 1 summarizes the information contained in Figure 1, and forms the basis for calculation of the sensitivity and specificity of this screening criteria for detecting hazardously low levels of factors VII and X. 16/17 patients with low factor levels were detected by screening the PT for this degree of elevation, yielding a sensitivity of 94%. Only 6/14 patients with factor levels > 25% had PT less than 1.5X normal, yielding a low specificity of 43%. The positive predictive value of this screening parameter was 6/24, or 66%, the negative predictive value 6/7, or 85%.

Figure 2 shows the pre-transfusion levels of factors VIII and IX plotted against the corresponding PTT value for each patient. 29/30 patients had pre-transfusion assays of both factors, while 1 patient had only a factor IX assay. For factors VIII and IX, 35% is used as the minimum hemostatic level, and is designated on the graph with a dotted line. The PTT screening criteria for release of FFP —> 1.5X normal — is also marked with a dotted line. Table 2 summarizes the information of the graph, and similarly forms the basis for calculation of the sensitivity and specificity of PTT > 1.5X normal as a screening criteria for detecting low levels of factors VIII and IX. The sensitivity of the
PTT at this level is 100% with a specificity of 40%. The positive predictive value is 31%, and the negative predictive value is 100%.

Figure 3 shows the change in factor VII levels following administration of either 2 or 4 units of FFP. Factor VII was measured before and after 7 episodes of 2 unit transfusions and 19 episodes of 4 unit transfusions. Figures 4, 5, and 6 show changes in levels of factor VIII, IX, and X, respectively, following either 2 or 4 unit transfusions of FFP. Table 3 summarizes the mean and median percent change, the standard deviation, and the interquartile range for each of these 4 factors.

Discussion

Before the relationship of screening coagulation tests and clotting factor levels can be discussed, the question of minimum hemostatic levels of various clotting factors must be addressed. Minimum hemostatic levels vary according to the clinical situation. Less factor is needed to prevent spontaneous bleeding than to re-establish hemostasis after major surgery or trauma. Much of the information about factors II, VII, VIII, IX, and X has come from experiments of nature in which patients with those congenital deficiencies have been monitored for spontaneous bleeding and response to hemostatic stress. Baseline factor levels and therapeutically elevated factor levels have been correlated with clinical course.

Factor VIII has been most extensively studied, but there is still no general agreement about its hemostatic level. Hemophilic patients with factor levels greater than 5% of normal have little difficulty with bleeding in daily life (ref.3). However, Biggs and McFarlane studied hemophiliacs following dental extraction and found that, with a factor VIII level of 25%, almost all patients bled more than normal controls (ref 1). They recommended levels of 30-40% factor VIII to stop major bleeding. The situation for factor IX is probably similar (ref.1). For factor V, evidence has also been extrapolated from patients with an isolated factor deficiency. Factor V deficient patients usually have levels <5%, and fresh whole blood has been effective in controlling their bleeding. It has been estimated that this type of transfusion could not raise the factor V level more than 10% (ref.1). Thus, levels between 5 and 15% are considered hemostatic.

Information on minimum hemostatic levels of factors II, VII, IX, and X has also come from the iatrogenic experiment of warfarin therapy. These factors are routinely reduced to approximately 25% of normal with warfarin therapy, and patients with these levels have rare problems with spontaneous bleeding and do not routinely bleed at surgery. For purposes of this study, minimum acceptable hemostatic levels were conservatively defined as 35% for factors VIII and IX, and 25% for factors V, VII, and X.

At the VAMC, a patient's PT or PTT must be elevated more than 1.5X the mid-range of normal in order to receive FFP. In this study, we evaluate the appropriateness of these screening criteria. For the prothrombin time, elevation greater than 1.5X the mid-range of normal was 94% sensitive for detecting levels less than 25% of factors VII or X. The specificity at this cut-off point was quite low -- 43%. The positive predictive value of PT>1.5X normal was relatively low at 66%. The negative predictive value was 85%. With this degree of elevation as a screening test for release of FFP, 16/17 patients with factor VII or X levels less than 25% would have been treated with plasma. The one patient who remained undetected had a PTT of 35 seconds and an isolated factor VII level of 15% with adequate levels of factors X, VIII, and IX. An isolated defect of the extrinsic coagulation pathway, such as this,
is unlikely to account for a lack of hemostasis. For the PTT, elevation
greater than 1.5X the mid-range of normal was 100% sensitive for
detecting patients with factor VIII or IX levels less than 35%. The
specificity was 40%, the positive predictive value 31%, and the negative
predictive value 100%.

Two previous studies have examined the sensitivity, specificity,
and predictive value of screening coagulation tests with respect to
clinical bleeding tendency. Ciavarella (1987-ref.5) did a prospective
study of 36 massively transfused patients, while Counts (1979-ref.7)
prospectively studied 27 massively transfused patients. Using 1.3X the
control as the minimum value of significantly increased PT or PTT, they
found the sensitivity of the PT to be 89-91% with a specificity of 50-
52% for indicating generalized bleeding. PTT was somewhat less
sensitive and ranged from 56-75%, with a specificity of 56-71%. When
the minimum level for significant elevation was raised to 1.5X (Counts)
or 1.8X (Ciavarella), the sensitivity of an elevated PT fell to 33-44%,
while the specificity rose to 90-96% for indicating generalized
bleeding. Compared to the present study, these studies seemed to find
similar elevations of PT and PTT to be less sensitive in indicating
patients with disorders of hemostasis. There may be several reasons for
this. First, these studies used values of 1.3X or 1.5X control, without
specifying a control value. The present study used a value of 1.5X the
mid-range of normal. These two values may well not be identical. Next,
these two studies looked at the clinical parameter of generalized
bleeding in massively transfused patients, while the present study
looked at the laboratory parameter of diminished clotting factor levels
in relation to PT and PTT. Several studies have shown that in massive
transfusion, thrombocytopenia is the most common cause of generalized
bleeding, and a decreased platelet count is the most valuable indicator
of a tendency to bleed. In the 2 clinical studies mentioned, bleeding
due to thrombocytopenia accounted for much of the bleeding not detected
by significantly elevated coagulation screening tests. Patients with
thrombocytopenia as a primary cause of bleeding often have slight
elevations of PT and PTT, but do not need FFP. In the present study,
thrombocytopenia was somewhat controlled for by selection of the sample
group as patients for whom FFP was requested. 53% of the study group
had 1 or more factor levels below the minimum necessary for hemostasis,
while 20% had platelet counts less than 50,000.

Recommendations for appropriate FFP dosage have generally been
600-2000 ml, or 15-20 ml/kg, administered rapidly over 1-2 hours, with
the hope of raising clotting factor levels to 10-50% of normal
(ref.1,2,4,10). In the present study, the mean increase in factors VII,
IX, and X following 2 or 4 units of FFP ranged from 6.6-9.7%. This is
consistent with the findings reported in several earlier investigations
on the effect of FFP. Bowie (1967-ref.3) transfused FFP into nonbleeding
patients with deficiencies of either factor V, VII, VIII, IX, or X.
Based on an assumed plasma volume of 40 ml/kg, he calculated the
expected % increase in the deficient factor level following FFP
administration. This ranged from 20 to 33%. He then measured the
actual increase following FFP and found it less than expected, ranging
from 7 to 27%. Gazzard (1975-ref.9), Mancucci (1976-ref.11), and
Spector (1966-ref.15) all transfused FFP prophylactically into patients
with liver disease prior to liver biopsy. Two to four hours after
transfusing 600-1800 ml FFP into 13 patients, Spector found mean
increases of 10.5-13% in factors V, VII, and X. Gazzard transfused 15
patients with 600 ml FFP over 30 minutes. One half hour following the
transfusion, mean factor levels had increased 7% for factors V and X,
and 15% for factors VII and IX. Manucci administered 12 ml/kg FFP to 10
Several studies point to the rapid disappearance of clotting factors after administration of FFP. In his study of 13 liver patients, Spector measured the decline of factor levels following FFP transfusion. After 2-4 hours, the net increase had declined by 50%. By 24 hours, factor levels had returned to baseline. Bowie charted the decline of transfused factors following FFP administration to factor deficient patients. For factors V, VII, VIII, and IX, he found the half-life to range between 4-16 hours. He noted that the rapid disappearance of coagulation factors made them unique among plasma proteins. In the present study, the mean time elapsed between pre-transfusion and post-transfusion factor levels was 3.2 hours for 4 unit transfusions and 2.7 hours for 2 unit transfusions. During this time, the requests for FFP were processed, units were thawed, transported to the ward and transfused. These steps take a minimum of 2-3 hours; thus, on average, post-transfusion specimens were drawn within an hour of FFP administration and probably represent peak levels.

In the present study, the mean increase in factors VII, IX, and X following 4 units of FFP ranged from 7.5 to 9.7%. For 2 units of plasma, the mean increase ranged from 6.6 to 9.5%. In this sample, the net increase in factor levels was not significantly different using 2 or 4 units of FFP. No general statement comparing the effect of different doses of FFP can be made from this observation. The number of episodes of 2 unit transfusion (9) was small compared to the number of 4 unit transfusions (33).

In the present study, the change in factor VIII levels bore no relationship to the transfusion of FFP. 20 of the 30 patients studied had factor VIII levels ranging from 100 to 500% of normal, while 6 of the remaining 10 had levels greater than 50%. This is consistent with the role of factor VIII as an acute phase reactant. Given factor levels greater than 100% of normal, the relatively small amount of factor VIII contained in FFP would be expected to make no difference. When the effect of FFP on factor VIII levels less than 100% was analyzed, there was no systematic change. The mean difference following 2 units was minus 18%; following 4 units, it was plus 4%. These findings are consistent with those in the prospective study by Counts of 27 massively transfused patients. Most of the 27 patients had factor VIII levels between 100-250%, and only 5/27 had levels below 50%. He concluded that there was a large physiological reserve of factor VIII, and that deficiency could not be predicted by the number of units transfused.

Conclusion

This study suggests that a significant elevation of PT and PTT can be used as a sensitive screening device for detecting hazardedly low factor levels. A PT>1.5X the mid-range of normal was 94% sensitive in detecting levels of factor VII and X less than 25%, while PTT>1.5X normal was 100% sensitive in detecting levels of factor VIII and IX less than 35%. Previous studies by Ciavarella and Counts demonstrated considerably lower sensitivity of an elevated PT or PTT for indicating generalized bleeding in massively transfused patients. However, these studies may have been confounded by bleeding due to thrombocytopenia in many patients. In the present study, this problem was partially controlled for by the sample selection criteria.

In this study, the mean increase for factors VII, IX, and X following 2 or 4 units of FFP ranged from 6.6 to 9.7%. On average, post-transfusion samples were drawn promptly, and these increases probably represent the peak effect. These findings are consistent with
the results of several earlier studies of the effect of FFP by Bowie(ref.3), Gazzard(ref.9), Mannucci(ref.11), and Spector(ref.15). FFP had no effect on the level of factor VIII, which was significantly elevated in the majority of patients.
Bibliography


Table 1

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<th>Factor Level (VII or X)</th>
<th>(\leq 25%)</th>
<th>(&gt;25%)</th>
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<td>(\geq 1.5x)</td>
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<td>6</td>
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<tr>
<td>(&lt; 1.5x)</td>
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PT

Sensitivity = \(\frac{14}{17} = 94\%\)
Specificity = \(\frac{6}{14} = 43\%\)
Pos Pred Value = \(\frac{16}{24} = 66.7\%\)
Neg Pred Value = \(\frac{6}{14} = 85.7\%\)

Figure 1

70 Factors VII + X
Table 2

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<th>Factor Level (VIII or IX)</th>
<th>≤35%</th>
<th>&gt;35%</th>
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<tr>
<td>&lt;1.5x</td>
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Tests:

- Sensitivity: $\frac{14}{14} = 100\%$
- Specificity: $\frac{18}{45} = 40\%$
- Pos Pred Value: $\frac{14}{14} = 100\%$
- Neg Pred Value: $\frac{18}{18} = 100\%$

Figure 2: PTT

Graph showing factor VIII and IX levels.
% Change in Factor Level following FFP

Figure 3
Factor VII

Figure 4
Factor VIII

Figure 5
Factor IX

Figure 6
Factor X
### Table 3

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<th>Factor</th>
<th>Units of FFP</th>
<th>Mean</th>
<th>Standard Deviation</th>
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<th>Interquartile Range</th>
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