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Chapter 6

Prophylactic Fresh Frozen Plasma: Time for a Re-Think?

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Abstract

Practice guidelines continue to give somewhat conflicting advice regarding indications for Fresh Frozen Plasma (FFP) transfusion and it is therefore not surprising that repeatedly worldwide, audits of FFP usage demonstrate abundant inappropriate transfusion. Nearly half of all FFP transfusions are given prophylactically in order to correct prolonged prothrombin time (PT) and/or international normalized ratio (INR) prior to an invasive or operative procedure in the absence of bleeding. However, the evidence supporting this practice is very poor and will be reviewed in this chapter. Meta-analyses fail to demonstrate that elevated PT and/or INR predict(s) bleeding across a wide range of specialties. Global assays of hemostasis such as viscoelastography may be more useful in predicting bleeding risk but large-scale outcome studies are required. Studies in different patient populations show that coagulation

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factor levels are generally well above the threshold for adequate hemostasis (30%) until the INR exceeds 2.0 x control. In addition, FFP does not reliably correct INR values ≤ 1.8 x control unless given in volumes much larger than conventional doses. Specific clinical scenarios where prophylactic FFP transfusions often occur include patients with liver disease, procedures in critical care, cardiac and liver surgery and warfarin reversal. There is little evidence to support plasma transfusion in any of these situations and the risks of transfusion are not insignificant, including transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), delays in procedures and increased cost. Clinical trials looking at bleeding risks with or without plasma transfusion have been difficult to carry out and the challenges encountered will be reviewed in this chapter. Deeply-engrained personal beliefs and lack of evidence continue to fuel prophylactic FFP transfusion by clinicians; the call for clinical trials has never been greater.

1. Introduction

It is now a requirement of good clinical practice to minimize the unnecessary and inappropriate use of blood and blood products. Patient blood management programs are now addressing this issue, but the focus remains primarily on red blood cell usage. The worldwide use of fresh frozen plasma (FFP), particularly for prophylactic and pre-procedural reasons, remains inordinately high, and has not decreased over the last ten years to any significant extent, in contrast to the falling use of red blood cells as restrictive transfusion thresholds are increasingly adopted (1). A recent retrospective study showed an unchanging rate of FFP use in over 40 hospitals in the US over an eight year period, even though FFP is no longer recommended in many clinical scenarios(2).

A significant proportion of FFP is given prophylactically on the assumption that prolonged coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR) predict an increased bleeding risk, and that FFP transfusion will correct these tests and consequently reduce bleeding risk. This review, which focuses only on the use of FFP in patients who are not actively bleeding, critically questions these assumptions in the context of pre-procedural administration of FFP, and also examines why carrying out high quality trials in this area has been so problematic.

2. Current Practice in FFP Transfusion

Worldwide, FFP is given for two primary indications; prevention of bleeding (prophylactic) or treatment of bleeding (therapeutic). In terms of patients who are actively bleeding, guidelines are reasonably consistent, and trigger thresholds for FFP transfusion are generally set at an $\text{INR} \geq 1.5$. Nevertheless, there is ongoing discussion as to the best trigger threshold/ target INR, and also the volume/ratio of FFP that should optimally be transfused in relation to red blood cells (3-5). There is significantly more variability in the recommendations for pre-procedural thresholds, and this is especially the case in patients with liver disease (see table 1). This is important as the prophylactic use of FFP accounts for nearly 50% of all plasma transfused (1, 6-8). There is a surprising lack of high quality evidence on which guidelines are based, and much is a reflection of expert opinion and observational studies rather than RCTs. Consequently confidence in, and compliance with, existing guidelines tends to be relatively poor (9, 10).

A panel of experts convened by the AABB reported a lack of evidence for FFP transfusion in all settings except massive transfusion and warfarin-associated intracranial hemorrhage (9). A recent systematic review of 80 randomized controlled trials (RCTs) also found a lack of evidence for both prophylactic and therapeutic FFP across a large range of clinical settings (11). The only individual RCTs in the review demonstrating beneficial effects of FFP were in plasma exchange for thrombotic thrombocytopenic purpura (TTP), treatment of early thrombocytopenia in dengue fever, and use of FFP in priming cardiac bypass pumps along with packed red cells prior to cardiac surgery in children. Of concern, in both the 2004 and updated 2012 systematic review, the authors found most trials had large methodological limitations in terms of quality assessment and reporting of adequate randomization, allocation, concealment and blinding (only two of the 21 identified trials fulfilled all criteria). In addition, most trials enrolled small numbers of patients (usually less than 30 patients), and provided inadequate information on the ability of the trial to detect meaningful differences in outcomes between the two patient groups. Doses of FFP used were variable (6-15ml/kg), and the potential for bias was usually very high. In addition, no studies took adequate account of the extent to which adverse effects might have negated the clinical benefits of treatment with FFP. A prophylactic policy aimed at preventing bleeding complications would involve transfusing a large number of patients, many of whom might not bleed even if prophylactic FFP were not given. Studies of prophylaxis must therefore also include an estimate of the adverse

outcomes as well as an estimate of the proportion of patients for whom a significant bleeding problem may be prevented.

Two recent multicenter RCTs to determine if prophylactic FFP is effective in decreasing bleeding complications in patients with $INR \geq 1.5$ were prematurely terminated due to logistics with recruitment (12-14). It appears that the practice of prophylactic transfusion in response to a prolonged PT or INR value is so engrained, and the fear of bleeding (and litigation) so great, that FFP transfusion has not yet been subjected to standard evidence-based scrutiny. Nevertheless, there is a large amount of published information available that questions the validity of these assumptions.

Despite some of the recent blood transfusion guidelines veering away from prophylactic FFP transfusion in light of a lack of evidence (9), audits repeatedly show that variable and high proportions of FFP (ranging from 26% to 83%) are given outside of current indications (6, 15-18). The most common reason for inappropriate orders is a correction of a prolonged INR in the absence of bleeding (1, 6, 15, 16). One of the largest national audits carried out looked at nearly 5000 FFP transfusions (1) and found that 43% of all adult FFP transfusions were given to patients in the absence of any documented bleeding, and that a significant proportion (27%) had a pre-transfusion $INR \leq 1.5$. Over half of FFP transfusions given to patients on warfarin were also in the absence of bleeding. Similarly, in three prospective audits in Canada, 45% of 671 (19) 48% of 547 (20) and 28.6% of 559 (18) FFP transfusions respectively were deemed inappropriate, mainly given to non-bleeding patients with aPTT or INR values $\leq 1.5 \times$ normal. Worldwide this has been a repetitive finding (21-23).. A recent multi regional audit looked specifically at blood component use in over 1300 patients with liver cirrhosis, and 76% of patients given prophylactic FFP received it prior to a procedure (24). For those undergoing a low risk procedure such as central venous catheter insertion or paracentesis, 33% had a pre-transfusion $INR < 2.0$.

Inappropriate transfusion amongst critically-ill patients is a more stubborn problem and a large retrospective US study of over 70000 plasma transfusions found that 80% of transfusions occurred in critical care and medical/surgical wards prior to procedures carried out in those settings rather than the operating room (8). Worldwide 20-30% of critically ill patients receive FFP during the course of their stay on intensive care (ICU) (7, 17). In this environment there is even less adherence to guidelines, wider variation in use and higher inappropriate use (7, 25, 26).

Table 1. Summary of guidelines on plasma transfusion prior to invasive procedures

	British Committee for Standards in Hematology (27)	American Society of Anesthesiologists (28)	Canadian Members of the Expert Working Group (29)	Australian & New Zealand Society of Blood transfusion Ltd (30)	French Security Agency of Health Product Safety (31)	German Medical Association Guidelines (32)	Transfusion Medicine Advisory Group (TMAG) British Columbia, Canada (33)	Cardiovascular and Interventional Radiological Society of Europe Endorsement (34)
Dose	10-15mls/kg	10-15mls/kg	Not stated	10-20mls/kg	10-15mls/kg	20ml/kg	10-15ml/kg	At least 10mls/kg
In Liver Disease	May be advocated by some but response unpredictable	Not stated	If patient bleeding and PT and aPTT > trigger	May be appropriate in the presence of bleeding and abnormal coagulation	If patient bleeding and PT and aPTT > trigger	If risk of massive haemorrhage and/or coagulopathy with Quick value < 50%	Routine use questionable. Response unpredictable	Not stated
Before Invasive procedures	Not stated	Not stated	If INR > 2 for procedures such as liver biopsy, paracentesis, thoracocentes	Can be used in non-bleeding patients who are considered at risk of bleeding in association with PT/aPTT ratio >1.5 or in patients with personal or family history of bleeding	Indicated if significant risk of bleeding and coagulation triggers	Not for Liver biopsy, paracentesis, thoracocentes or central venous puncture. Not for liver transplants if Quick > 50%	Not for mild-moderately high INRs. Factor levels need to be 40%. May be more conservative in lumbar disc space injections, neurosurgery, pulmonary biopsies	“Low risk” procedures, keep INR <2 “Moderate-High Risk” procedures keep INR < 1.5

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transfusion, the principle of a restrictive policy has filtered through to clinical practice and in a recent audit of practice in 47 ICUs across Australia and New Zealand, only 2% of red cell transfusions were considered inappropriate compared to 29% of FFP transfusions (35).

ICU physicians often state bleeding as the reason for transfusion of FFP, but many of these cases are suspected or recent bleeding, or bleeding in the presence of near-normal PT-INR values. In fact physicians often do not agree on the definitions of a major bleeding episode (7) and there is little confidence in available tests to predict bleeding. It is hence unsurprising that so much FFP ends up not being given (in one survey 28% of FFP products were either returned to the transfusion center or wasted (7)). In addition, PT and/or INR values are often not re-checked within six hours after FFP transfusion (32% of cases in one national multicenter study (17)). Chronic liver disease and concurrent red cell transfusion both independently increase the likelihood of prophylactic plasma transfusion regardless of severity of prolonged PT (36).

Walsh et al. (37) looked at patients with prolonged PT values in 29 ICUs in the UK: Half (51%) of FFP transfusions were to non-bleeding patients, and there was high variability in the doses of FFP given (range 2.4 - 41.1ml/kg). PT prolongation was independently associated with higher mortality but these prolongations were often mild, short-lived and naturally corrected themselves with supportive care and treatment of the underlying condition, not with plasma transfusions. This is possibly due to correction of liver hypo-perfusion, dehydration, anemia, hypoxia, hypocalcaemia, hypothermia and acidosis. Holland and Brooks (38) also noted the corrective effect of medical treatment alone on mildly prolonged coagulation factors in stable non-bleeding hospital patients: In their observational study on the effect of FFP on INR values, 179 patients received FFP transfusions and 71 patients acted as a control group (adult patients with INR values 1.3-1.6 x control not receiving FFP transfusions). They reported that mildly elevated INRs (1.3-1.6 x control) decreased without FFP via supportive care after a median time of 8.5 hours. Another systematic review of patients with upper non-variceal gastrointestinal bleeding involving 769 patients did not find INR to predict re-bleeding but it was associated with higher mortality and was possibly more useful as a proxy of co-morbid burden (39). It must be noted alongside this, that the observed higher mortality in patients with higher PT values may partly be caused by FFP transfusions themselves.

3. Risks of FFP Transfusion

In order to be able to assess the risk benefit balance when considering whether or not to transfuse FFP, it is vital that clinicians understand the adverse effect profile of FFP. FFP and platelets are probably the blood components with the highest risk profiles (40) but hemovigilance reports vary highly and this is in part due to passive reporting systems. In France, where reporting is mandatory, the incidence of adverse reactions to FFP has been reported as 1:1700 (41) yet another analysis of over 30,000 FFP transfusions in the US reported it as high as 1:360 (42). Either way, under-reporting worldwide has maintained the practice of transfusion outside of current guidelines (43-45) as there is little appreciation of associated risk. A summary of risks is presented in Table 2.

Table 2. Associated Risks of Plasma Transfusion

- Febrile and Allergic Reaction (1-3% of FFP transfusions) (47)
- Transfusion-Associated Circulatory Overload or TACO (possibly as high as 1 in 10 transfusions in the elderly (44)
- Transfusion-related Acute Lung Injury or TRALI (estimated incidence of 6-23%) (48-50)
- Post Transfusion Purpura (51)
- Viral infection: (estimated risk of hepatitis C transmission 1:50 million and Hepatitis B 1: 1.2 million)
- Nosocomial Infections through detrimental immunomodulation (52, 53)
- Hemolytic Anaemia (ABO compatibility recommended)
-

Morbidity associated with plasma transfusion has been repetitively demonstrated, in particular multi-organ failure and acute lung injury (ALI) across a range of patients; trauma patients, massively-transfused patients, surgical, critically-ill, and pediatric patients (45). The existence and role of transfusion-related immunomodulation is still under debate, but higher pneumonia and nosocomial infection rates have been reported in transfused patients (45, 52-55). Higher rates of venous and arterial thrombosis have also been reported in children but a causal link is difficult to ascertain (2). The largest bodies of evidence regarding mortality stem from reviews of retrospective studies in massively transfused trauma patients rather than RCTs and these mostly show improved survival with aggressive plasma transfusion

although the optimal FFP: RBC ratio remains unclear (56, 57). Studies in civilian trauma and non-massively transfused patients are more inconsistent, some studies showing higher, lower and unchanged mortality and teasing out confounding factors is challenging (45, 58). There is very little regarding morbidity and mortality from prophylactic FFP transfusion specifically.

Both transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) merit some specific consideration. TRALI (48-50) was considered the leading cause of mortality associated with blood product transfusion until recently, occurring 5-6 times more frequently with high plasma volume components such as FFP compared to red cells (59, 60). Dara et al., (61) retrospectively looked at 115 critically-ill patients where there was no difference in new bleeding episodes between those who did and did not receive FFP transfusion prior to invasive procedures, but new-onset ALI was significantly more frequent in the transfused group (18% versus 4% $p = 0.021$). The etiology of TRALI is unclear but most likely involves recipient factors which firstly prime neutrophils on pulmonary endothelium and secondly prime leukocyte antibodies in the donor plasma which then activate these neutrophils and cause a permeability edema (the so called "two hit" hypothesis)(45). There is certainly a higher degree of this allo-immunization in FFP from multiparous women (49, 62) and as a result FFP is now limited to male donors or nulliparous women in many countries. This has resulted in an impressive decline (from 1:4000 to 1:12,000 in one active surveillance study) (63) but not elimination of TRALI (60, 64).

TACO is both under-recognized and under-reported (42, 65). It has only been reported as a separate category since 2007 by the Serious Hazards Of Transfusion (SHOT) group in the UK who have seen a jump in cases per year from 40 in 2010 to 96 in 2013 [59]. The incidence in the literature varies from 1:1566 to 1:68 transfusions or 1-8% (66). This is in part due to changing definitions and recognition/reporting systems. Although often clinically difficult to distinguish from TRALI, the underlying mechanism for hypoxia is a hydrostatic edema rather than permeability one. Recipient factors such as older age, low body weight and co-existing renal/cardiac dysfunction play a role (66) but there are also transfusion factors such as volume transfused and rate of transfusion: Transfusion of as little as 500mls of fluid to patients with congestive heart failure or ischemic heart disease has been shown to increase levels of Brain Natriuretic Peptide (67) (a sensitive marker of volume overload). Of importance, TACO accounts for a large proportion of major morbidity and death associated with transfusion. In the SHOT report of 2013 16 out of 96 episodes of TACO were attributable to plasma transfusion (66)

and strong recommendations were made to increase education and awareness about TACO and identify patients at risk.

4. What Is the Evidence That Prophylactic FFP Transfusion Reduces Bleeding Risk?

4a. Does a Prolonged PT and/or INR Predict an Increased Bleeding Risk in Stable Patients?

The Prothrombin Time (PT)

The conventional tests of coagulation, aPTT and PT, were developed primarily for screening patients with hereditary deficiencies of individual clotting factors or for the monitoring of anticoagulant therapy such as Vitamin K antagonists (VKA) and heparin. These tests were never intended as a model of *in vivo* hemostasis, or as screening tests for bleeding risk in the general population. PT was designed to detect deficiencies of factors II, V, VII and X and therefore to monitor anticoagulant therapy with VKAs and/or detect acquired bleeding disorders such as vitamin K deficiency (68). The aPTT was similarly designed to screen for hemophilia and other coagulation factor deficiencies (69). The endpoint of measurement in both tests is the initial formation of fibrin strands which is detected by optical or electrical means and reported in seconds (70). Neither test reflects the activity of naturally occurring anticoagulants such as antithrombin, protein C, protein S, and tissue factor pathway inhibitor (TFPI). One concern about PT is that *in vitro* it is initiated by high concentrations of tissue factor which does not reflect the lower concentrations *in vivo* (71). In addition, it is not possible to estimate overall strength and stability of the clot because these tests are terminated at very low levels of thrombin (about 5-10nM), and before fibrin is polymerized by activated factor XIII. As such they do not give any information on total thrombin generation, which relies on the balance between pro-coagulants and anti-coagulants. A prolonged aPTT, PT or INR may reflect a reduced level of pro-coagulation factors (such as in liver disease or DIC) or the presence of an inhibitor (such as acquired hemophilia, heparin, direct thrombin inhibitors and anti Xa inhibitors). This may predispose the patient to bleeding, thrombosis or no change in hemostasis despite abnormal PT/aPTT values. For example, factor XII deficiency leads to a prolonged aPTT but does not affect bleeding risk whereas factor XIII deficiency does increase bleeding risk without altering

PT or aPTT. Patients with antiphospholipid antibody or lupus anticoagulant may present with prolonged PT and/or aPTT values but these patients are actually at increased risk of thrombosis. It has also been repetitively shown that patients with acute and chronic liver disease who have prolonged PT or INR values may have normal or even enhanced thrombin generation (72). Finally it must not be forgotten that, pre-analytical error is the most common cause for a prolonged PT value (70): Under-filling of bottles, elevated hematocrit, anticoagulant contamination of lines and variations in instrument-reagent mixtures can all prolong the PT. It is clear there is a significant false positive and false negative rate: The false negatives render the test unhelpful and the false positive tests generate unwarranted investigations. Inappropriate FFP transfusion is associated with the possibility of adverse events, and also has a financial cost. In addition, the risk/benefit equation must involve balancing the inherent logistic issues caused by ordering, defrosting and then transfusing relatively larger volumes of FFP in stable, normovolemic patients which inevitably leads to delays in performing proposed diagnostic or therapeutic procedures, as well as putting some patients at risk of TACO.

The International Normalized ratio (INR)

The INR was developed to monitor VKA therapy and to standardize results in order to account for the highly variable sensitivities of thromboplastin reagents (human, animal or recombinant) used in different centers to measure PT. It is calculated via the formula $[\text{patient PT}/\text{mean normal PT}]^{\text{ISI}}$ where the International Sensitivity Index (ISI) is a value assigned to the thromboplastin reagent when compared with a WHO reference thromboplastin, which is assigned an ISI of 1.0. The threshold of an INR of 1.5 for an increased bleeding risk came out of studies that originally used thromboplastin reagents with high ISIs (≥ 2). Since then, manufacturers have shifted towards more sensitive (lower ISI) reagents to improve inter-laboratory INR reproducibility: Today the reagents have ISIs of 0.9-1.2 and therefore PT values are often prolonged even if factor VII levels are above 40% which is more than adequate for hemostasis (73). The PT-INR ratio literature has not taken this historical shift in thromboplastin reagent sensitivities into account. Data from studies done before the 1990's need some reconsideration. For example, McVay and colleagues observed no increased bleeding in patients with a variety of clinical conditions undergoing paracentesis and thoracocentesis if the PT ratio $\leq 2 \times$ control ratio (74) and the same for percutaneous liver biopsy if the PT ratio $\leq 1.5 \times$ control ratio (75). Apart from concerns about the definition of a bleed in these studies, the thromboplastin

agent used at the time had an ISI index ≥ 2 . This actually translates into an INR threshold range of 2.25 to 4 rather an INR of 1.5 (76) In patients with liver disease there are wide inter-laboratory variations in INR, and it has been suggested that a modified INR using plasma from patients with cirrhosis, would be more appropriate (77, 78).

The INR was calibrated to guide VKA therapy but does not reliably predict bleeding risk even in these patients as suggested by studies looking bleeding events post femoral coronary angiography (79), prostate biopsies (80) or urgent reversal prior to surgery (81). Often a critical INR value of 5 is chosen for indicating an increased risk of spontaneous bleeding but studies show there is a poor correlation with vitamin-K dependent factor levels (82) and the rate and magnitude of factor level decline with INR (83-85). Patient demographics such as age, interacting medications, presence of atrial fibrillation and co-morbidities, as well as being warfarin-naïve are all recognized predictors in patients taking VKA. Bleeding risk scores for warfarinized patients have been devised according to these criteria rather than the absolute INR value although their predictive values are still poor (86).

Clinical Trials Assessing PT-INR As Predictors of Bleeding

There is little hard evidence to support mild to moderate elevations of PT-INR as good predictors of bleeding risk (15, 68, 87). Chee et al., (88) published guidelines on the assessment of bleeding risk prior to invasive procedures in 2008 for the British Committee of Standards in Hematology (BCSH). They found only nine trials involving patients from general surgery and pediatric Ears Nose and Throat (ENT) surgery and these were mainly retrospective case series, with selection bias and imperfect recall. The calculated collective positive predictive value was poor (0.03 - 0.22) and the likelihood ratio (LR) for a positive test ranged from 0.94 to 5.10 with 95% confidence intervals crossing 1.0 in the few trials that were prospective. Segal and Dzik (87) performed a meta-analysis of 25 studies looking at coagulation tests as predictors of bleeding: In 12 out of 14 studies that included patients with normal and abnormal coagulation tests, bleeding rates are almost identical and over a range of procedures (central line placement, thoracocentesis, lumbar puncture, paracentesis, and liver biopsy) (see Figure 1). There was only one RCT, which looked at liver biopsies in 100 patients, and only 2% of patients met their bleeding endpoint criteria despite abnormal coagulation tests. The remaining studies were mainly small retrospective case series and did not report the degree of PT prolongation or have a control group. Only in one study of patients undergoing kidney biopsy were bleeding

complications higher in patients with abnormal tests and in another study of transjugular liver biopsies, the number of bleeding complications was higher in patients with normal coagulation tests.

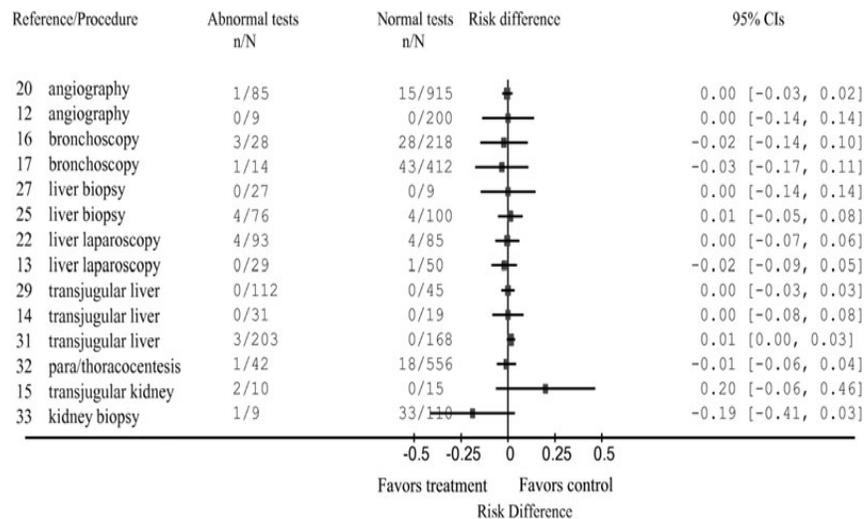


Figure 1. The absolute differences (and 95% confidence intervals) in the proportion of patients with major procedure-related bleeding in the groups with and without abnormalities of pre-procedure coagulation tests. Taken from review of 25 studies by Segal JB and Dzik WH(87).

Ng (76) reports a similar lack of evidence for PT or INR as predictors of bleeding for larger procedures such as aortic surgery, kidney transplant, head and neck surgery, craniotomy and total joint replacements. Eckman et al., (89) pooled results from observational studies in general surgery, adenotonsillectomy, angiography and gynaecological surgery and calculated that the LR for a positive coagulation test result ranged from 0 to 33 and the sensitivity of an abnormal test ranged from 0-100%. Pooling results like this does require cautious interpretation due to heterogeneity in study characteristics, definitions of bleeding outcomes and testing panels. Although the overall level of evidence is poor, these studies collectively suggest that mild to moderate elevations of PT and/or INR are not associated with a significant increase in bleeding risk. The evidence for prophylactic FFP use in specific clinical scenarios such as liver disease and procedures in critical care is outlined later in this chapter.

4b. The Relationship between PT-INR and Coagulation Factor Levels in Different Clinical Settings

Looking more closely at the relationship between coagulation factor levels and coagulation tests may help further understand the utility of these tests in assessing bleeding risk. Studies on patients with hemophilia A and B show that these patients are at increased risk of bleeding during surgery or following trauma if their factor levels fall below 30iu/dl or 30% of normal (73). With these levels of factors, they would be labeled as mild hemophiliacs who would bleed only after surgery or external trauma.

Vitamin K Deficiency

Looking specifically at vitamin K dependent factors, minimum hemostatic levels have been reported as 20-40% for factor II, 25-30% for factor IX, and 10-20% for factors VII and X (82)(90). Studies on patients with congenital multiple factor deficiencies (such as congenital Factor V and Factor VII deficiency “F5F8D” and congenital deficiency of Vitamin K-dependent clotting factors “VKCFD1”) indicate bleeding tendencies are of the same magnitude as those in patients with isolated factor V or factor VII deficiency: this implies multiple deficiencies do not have an additive effect on bleeding risk (76). This is important as multiple factor deficiencies are usually encountered clinically and in addition it has been shown that prolongation of aPTT and PT is significantly greater if there are multiple deficiencies of various clotting factors, and this will occur at levels well above 75% (91). This in part explains the poor correlation of these tests with bleeding risk. Gulati et al., (84) analyzed factor levels in 83 patients on warfarin therapy with INR values ranging from 1.0 to 8.36: They found mean activity levels to be near or above 50% for II, VII, IX and X when the INR was less than 1.5 and that these did not fall below the hemostatic range until INR reached 2.5 (see Figure 2).

Surgery and Critical Care

In a study in neurosurgical patients, Matevosyan et al., (83) found PT values ranging from 12.8 -17.6 seconds (INR 1.3 - 1.7) but in all patients levels of factor II, VII and VIII were above 25% and most above 50% (median (range) for factor II 73% [40-107], factor VII 64% (25-124) and factor VIII 118% [43-547]. Chowdhury et al., (73) measured coagulation factor levels pre and post FFP infusion in critically-ill patients where reasons for prolonged PT and INR were multi-factorial, and found nearly 50% of patients with an INR >1.5 had factor levels above 30iu/dl and hence adequate for hemostasis.

Collins et al., (71) looked at coagulation factor levels in 38 patients with severe sepsis and abnormal coagulation tests. Mean levels of factors II, V, VII, X and XII were lower when compared to controls but only 21% of patients had one or more factor levels below the hemostatic threshold. In addition it is a frequent finding in hospitalized patients that levels of factor VIII and fibrinogen are supra normal (73, 83, 92). Collectively, the evidence from these studies is that over a range of clinical settings, coagulation factor levels are usually adequate for hemostasis at INR < 1.8 x control. Indeed the available data does not support the need to transfuse pre-procedural FFP in patients with mild coagulopathy, defined as an INR \leq 2.0.

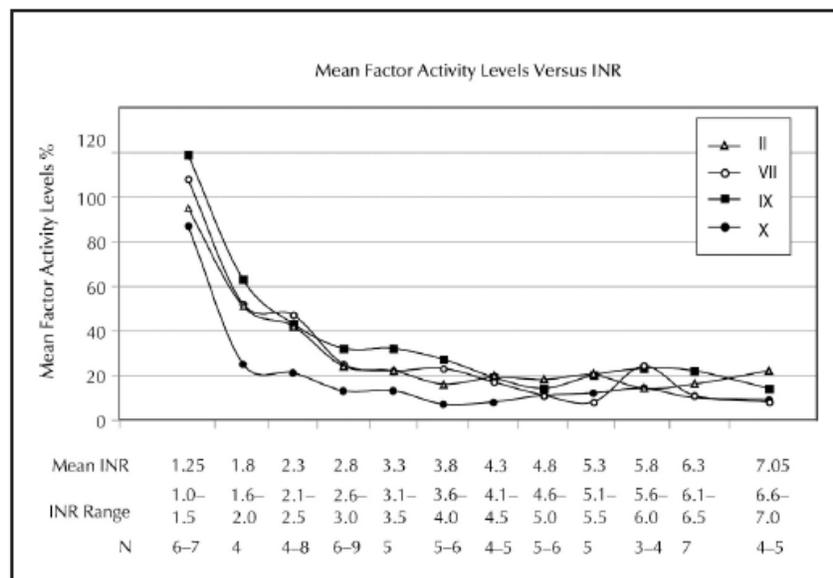


Figure 2. A side by side comparison of mean factor activity levels versus International Normalized Ratio (INR) in 83 patients taking warfarin (INR range 1.0-8.26). Taken from Gulati G, Hevelow M, George M, Behling E, Siegel J(84).

Liver Disease

The liver produces almost all procoagulants exclusively (except for factor VIII and von Willebrand factor) and consequently the INR has become a surrogate marker for liver failure, and is used in scoring systems such as the MELD and UKELD. Deitcher (93) found the INR in liver disease did not reflect the same degree of deficiencies of the same coagulation factors as in patients on warfarin therapy. For any given INR, the degree of factor V and

VII deficiency may be greater in liver disease but the opposite may be true for Factor X. In this study, over an INR range of 1.3 to 1.9, mean factor levels ranged from 31-65% (factor II), 40-70% (factor V) and 22-60% (factor VII). All these levels would be considered adequate for hemostasis. These studies mirror findings from decades ago where Manucci et al., (94) reported factor levels of over 30iu/dl for all of the studied 15 patients undergoing liver biopsy with a prolonged PT. There is also a larger variation in INR values in liver disease relative to the sensitivity of thromboplastin reagent used. Kovacs et al., (95) found that by using different thromboplastin reagents, the INR value in a cirrhotic patient could vary from 1.76 to 2.39. This is clinically important as the INR is used in scoring systems of liver disease and hence in prioritization of patients for liver transplant (78).

It is becoming clear that an INR of 1.6 in a stable cirrhotic patient does not reflect the same bleeding (or thrombotic) risk as in a warfarinized patient, a septic patient with low grade DIC, a patient with traumatic brain injury or a patient undergoing cardiac bypass (96). There are profound local and systemic differences in such coagulopathies. This is quite simply because even if the level of pro-coagulant factors are similar in each setting (resulting in similar PT, INR or aPTT), these tests do not consider activity of tissue factor, natural anticoagulants, ongoing fibrinolysis, platelet activation/consumption, endothelial involvement and an under-estimated degree of cross-trafficking between coagulation and inflammatory molecules (97). The cell-based model of hemostasis (98), as opposed to the traditional description of intrinsic and extrinsic pathways takes this more into account. In sepsis (71) and liver disease (99), a fall in pro-coagulation factors leading to a raised PT/INR is usually accompanied by a concurrent fall in anticoagulants like protein C and antithrombin with preserved thrombin generation. In addition, there is a rise in acute phase proteins like fibrinogen and factor VIII due to constant endothelial activation. This “re-balancing” of coagulation factors often means patients are not at increased risk of bleeding and in fact there is a significant thrombosis rate in such patients (100, 101). All coagulation test abnormalities must be evaluated within a clinical context, and using a single threshold INR that can apply to all patients is possibly the wrong approach, and indeed many guidelines now use different (higher) thresholds for patients with liver disease (see table 1).

4c. Evidence that Conventional Doses of FFP Correct Mild to Moderately Prolonged PT-INR Values

Although there is little hard evidence that a mild to moderate prolongation of PT/ INR is associated with a significantly increased risk of bleeding, the basis of transfusing prophylactic FFP is on the premise that it will correct the PT/INR to a value of <1.5 and so reduce the associated (perceived) risk. However, a multitude of studies have demonstrated that conventional doses of FFP rarely correct these mild abnormalities (1, 8, 38). Studies show that in patients with mildly prolonged clotting times, over a range of clinical settings, including liver biopsy and critical care, only 10-23% of patients will experience adequate correction following FFP transfusion (1, 8, 14, 94, 102-105). In the recent National Audit of FFP transfusion in England and Wales (1) across nearly 5000 transfusions, the median INR correction was only 0.2-0.3 depending on the INR. Another larger study in the US looked at over 70,000 plasma transfusions in 10 institutions, and found a median change in INR of 0.2 with 25% of transfusions resulting in no change or even an increase in INR (8). In a multi-center observational study in critical care, again the median change in PT or INR taken 6 hours post transfusion in 276 patients was minimal and greater with a higher pre-transfusion INR (median change - 0.1, -0.4, -1.0, -2.5 for pre transfusion INRs in ranges <1.5 , 1.6-2.5, 2.6-3.5, and >3.5 respectively) (17). Abdel-Wahab et al., (102) prospectively evaluated the effects of plasma on PT/INR in 121 hospital patients with pre-transfusion PT between 13.1-17 seconds. Less than 1% of patients experienced full correction and only 15% corrected half way to normal, most of whom received one to two units of FFP.

What has become clearer with these studies is that higher INR values (and hence lower coagulation factor levels or more severe coagulopathies) correct more profoundly with FFP. Holland & Brooks (38, 106) reported the effect of FFP on INR values in 179 patients in a retrospective study which excluded trauma and patients in the operating room (see Figure 3). Their data indicated that only at an INR of ≥ 1.8 that patients can be expected to experience a significant post-transfusion reduction in their INR. In addition, with an INR of ≤ 1.7 , factor levels are usually $> 30\%$ and adequate for hemostasis. Similar graphs and findings have been reproduced in other studies (8, 17, 107). At lower levels of INR (1.3 -1.8) only very small changes in clotting factor activity will occur for a given volume of FFP compared to much more significant increases when the INR >2.5 . One reason for this relationship between FFP and INR is the INR of FFP itself which can range from 0.9 to 1.4

(106) due heterogeneity between units derived from different donors. In addition, there are the effects of dilution with citrate and loss of factors incurred by thawing and delays in transfusion.

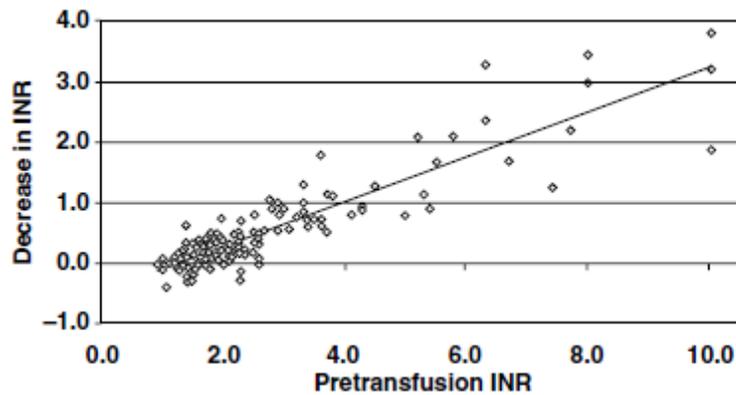


Figure 3a. The linear relationship between pre-transfusion INR and the decrease in INR per 500ml-unit of FFP in adult patients.

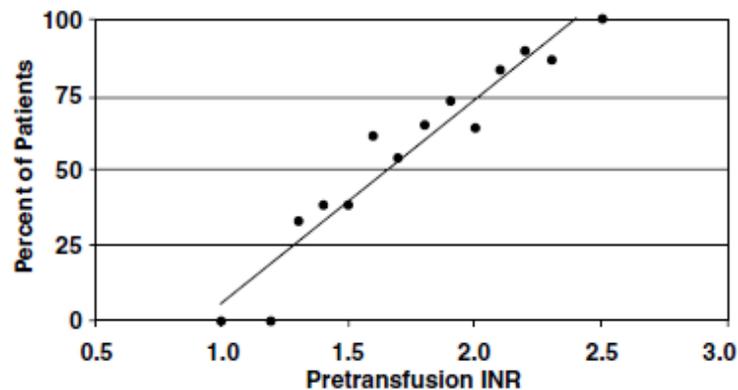


Figure 3b. Percentage of patients experiencing a significant change in INR following FFP transfusion in adult patients. Both taken from Holland LL and Brooks JP(38).

It has become clear that conventional doses of FFP will not correct mildly prolonged PT (less than 17 seconds) or INR (less than 1.8 x control) values. Most guidelines recommend a prophylactic dose of 10-15ml/kg (see Table 1) and studies indicate that doses actually given are often less or that a blanket approach of two to four units is used, particularly in prophylactic transfusion (8, 17). For example, a retrospective study of 70000 plasma transfusions found

that over 75% of transfusions were equal/less than 12mls/kg and that 62% of transfusions consisted of one or two units(8). It is unclear where the recommended dose of 10-15mls/kg comes from but possibly from a trial in 1968 looking at risk of intracranial hemorrhage in neonates with a “thrombotest” of less than 10% (108): Neonates who received 10mls/kg FFP did have reduced risk of death but no data was shown to confirm the assertion that a dose of 10mls/kg corrected the thrombotest. Typically transfusion of one unit per kg of a coagulation factor raises its level by 1%. It follows that conventional doses of 10-15 mls/kg of FFP will only raise levels by 10-15% and indeed studies, many in patients undergoing liver biopsy (94, 109), show that on average FFP transfusions (8-12ml/kg) increased factor levels only by around 10iu/dl. Muller et al., (110) measured factor levels, thrombin generation and viscoelastographic parameters in 38 non-bleeding critically ill patients before and after 12ml/kg FFP transfusion: They also found factor levels increased by around 10% after FFP transfusion but still remained at the lower end of the normal range and that thrombin generation and viscoelastographic parameters were largely unchanged.

Makris et al., (90) showed that in warfarin-treated patients, giving roughly 12mls/kg FFP (or 800mls FFP) raised factors II, VII, IX and X by only 9 -14 iu/dl. Chowdhury et al., (73) in their study on 22 critically-ill patients, found a volume of 12mls/kg FFP did not significantly increment factors V, VIII, IX or X, and that 30mls/kg are required to reliably correct the INR and adequately increment factor levels.. Importantly the volume of FFP required depends not just on the initial INR, but also the target INR; the difference in volume between a goal of an INR of 1.3 and a goal INR of 1.7 is two liters of FFP at all initial INR values (38). Most guidelines do not specify any dose-adjustment based on initial and target values.

4d. Challenges for Trials Evaluating Prophylactic FFP Transfusion and Clinical Outcomes

The call for RCTs looking at bleeding complications in patients receiving prophylactic FFP transfusions has never been greater and voiced repeatedly in the literature (69, 105, 111-113). A recent Cochrane review failed to identify any randomized clinical trials (out of 843 screened) that assessed the effects of liberal and restrictive thresholds of at least one coagulation test used to guide FFP transfusion in critically ill patients (114). Attempts to carry out large RCTs have been abandoned in the past: The Study of Hemostasis in Invasive

Procedures trial (SHIP) (13) was to involve 16 sites and 1,300 participants undergoing invasive hepatic procedures with a pre-procedure INR of 1.3 to 1.9, randomly assigned to plasma or no treatment. It was terminated due to difficulty identifying suitable elective patients. A multi-center open label RCT comparing prophylactic 12ml/kg FFP transfusion to no FFP transfusion in critically-ill patients with an INR in between 1.5 and 3 undergoing an invasive procedure (Transfusion of FFP in non-bleeding ICU patients-TOPIC) also prematurely terminated due to slow inclusion (14). Of the 81 patients randomized in TOPIC, bleeding outcomes were no different between transfused and non-transfused groups. Duration of mechanical ventilation, and incidence of ventilator-associated pneumonia were higher in the transfused group which agrees with other retrospective studies in critical care (61). There was a trend to higher mortality in the non-transfused but this group also had an increased prevalence of liver disease, which was an independent predictor of mortality.

The authors have highlighted the challenges faced in successfully carrying out such trials: Firstly there is a high rate of declined consent as would be expected in critical care and this was 25% in TOPIC: Deferred proxy consent has been suggested to deal with consent issues in emergency and critical care (115). Secondly, clinicians have strong-held beliefs about prophylactic plasma transfusion: A survey carried out after termination of the TOPIC trial showed that almost all clinicians felt the trial was ethically justified and well-designed with clinically relevant outcomes (113). Yet less than half stated the trial was widely supported in their department and more than half felt that certain patient groups should be excluded from the trial. It seems another important barrier to patient inclusion is physician-driven and this is bidirectional; Physicians excluded patients when they felt risk of bleeding was high and they did not want to risk randomization to omission of FFP transfusion but they mainly excluded patients because of concerns about fluid overload and risks of TACO and TRALI if randomized to FFP transfusion. In keeping with this, a RCT looking at bleeding events with and without prophylactic plasma transfusion prior to percutaneous tracheostomy in ICU prematurely terminated as the occurrence of bleeding was so rare in either group that physicians were unwilling to risk randomization to plasma transfusion (116). Lack of knowledge regarding FFP dosage is also a problem. 30% of physicians felt 12mls/kg was too high a dose in the TOPIC trial although this is the lower limit of what is stated in most guidelines and actually nowhere near the 35mls/kg that may be required to correct mildly prolonged PT/INR values (73). It is clear that in order to address these issues, pre-trial questioning and

education of physicians about transfusion indications, dosing and effects is necessary for successful inclusion into trials (113). It has been demonstrated that beliefs about FFP are amenable to change, and education of physicians has been shown to reduce inappropriate FFP use (117)(118) Behavioral interventions such as educational campaigns, prospective audits, and request forms with guidelines printed on them have all been shown to be effective (119-122). In line with this, Matesyovan et al., (83) report an impressive 75% reduction in plasma transfusion after implementation of modified FFP guidelines for neurosurgical patients.

Another challenge in these studies is the choice of primary outcome: Bleeding *per se* is subjective and outcomes need to take into account not only the volume but also its locality, the hemodynamic response to bleeding and the need for red blood cell transfusions (114). Recommendations for potential meaningful clinical end-points of hemostasis have been suggested by Levy and colleagues (96). Different bleeding tools have been validated in different populations: the HEME tool used in the TOPIC trial is well validated in ICU patients but the WHO bleeding scale is validated more in cancer patients. Finally, hemostatic control is itself only a surrogate marker of mortality and so studies need to measure mortality in addition as an outcome (123).

5. The Role of Global Assays in Guiding Prophylactic FFP Transfusion

Most recent guidelines agree that currently the best available predictor of bleeding remains a structured personal and family history of bleeding diatheses with physical examination (88, 124). This is probably reassuring enough for clinicians looking after well and/or uncomplicated patients having minor procedures. However until validated alternatives to conventional coagulation tests become widely available, or well conducted trials are successfully completed, prophylactic correction will probably continue to be practiced in patients with co-morbidities such as liver disease or critical illness and/or in patients having procedures with a moderate to high risk of bleeding.

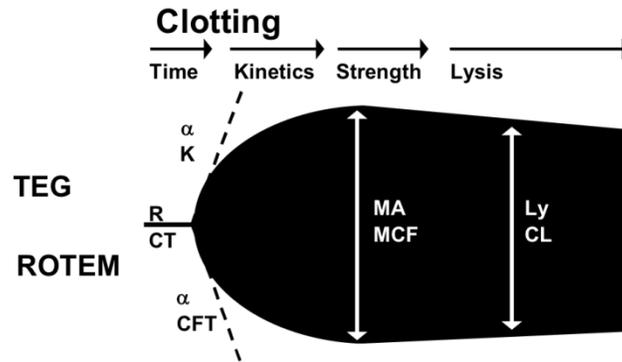


Figure 4a. Schematic TEG (upper trace) / ROTEM (lower trace) traces showing common parameters: reaction (R) time/ Clotting time (CT), Clot Formation Time (k/CFT), alpha angle (α), Maximum Amplitude (MA)/Maximum Clot Firmness (MCF) and Lysis (Ly)/Clot Lysis (CL). Taken from Johansson PI, Stissing T, Bochsén L, Ostrowski SR(125).

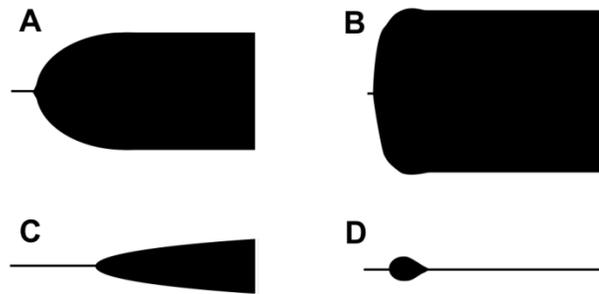


Figure 4b. Schematic presentation of various abnormal viscoelastic tracings. A) Normal B) Hypercoagulability C) Hypocoagulopathy D) Primary Hyperfibrinolysis. Taken from Johansson PI, Stissing T, Bochsén L, Ostrowski SR(125).

Viscoelastography (VET) is a point of care (POC) test that is a dynamic global test of hemostasis with a more rapid turn-around time than conventional coagulation tests. There are two commercially available devices, both based on the original invention of Hartert in 1948 the Thromboelastogram or TEG® (Hemoscope, USA) and rotational elastometry or ROTEM® (Pentapharma, Munich, Germany). Details can be found in the literature (126, 127). In both tests, the rate of polymerization and overall clot strength is displayed visually and numerically on a trace and provides a dynamic assessment of the process of clot initiation, formation, stability, and dissolution (see Figure 4) as described in the cell-based model of coagulation [89]. VETs have become

widely used in orthoptic liver transplantation (OLT) (128, 129), cardiac surgery (130-132), trauma (125, 133, 134) and obstetrics (135) in order to diagnose the causes of established bleeding and allow timely focused interventions. They may also be useful in identifying and monitoring hemophilic patients (136, 137) and other rare bleeding disorders (138). Systematic reviews in trauma, liver transplantation and cardiac surgery do show that VETs decrease transfusion of blood products (139-141) but these studies were not powered to look at outcome or mortality.

A RCT of VETs versus conventional tests to guide transfusion of FFP in liver transplantation, demonstrated a significant reduction in FFP in the group managed with VET (142), however, there is currently little information regarding the use of VET to on guide prophylactic FFP transfusions in these settings. Pietri et al., (143) have yet to publish their RCT looking at cirrhotic patients having invasive procedures with either prolonged PT-INR and/or thrombocytopenia. Patients are randomized to either TEG®- or conventional coagulation test-based care and initial results show far fewer prophylactic blood product transfusion in the TEG® group with no bleeding complications. This is in-keeping with the fact that cirrhotic patients often have coagulation test values that suggest a bleeding tendency with prolonged PT/INR and low platelet values, but VETs and thrombin generation assays often indicate a normal or even hyper-coaguable hemostatic profile, and indeed an increasing number of these patients are able to undergo major surgery, such as liver transplantation without the need for FFP and platelet transfusions (144-146).

Guidelines published by the European Society of Anaesthesiology on management of peri-operative bleeding state there is currently no evidence for VETs as predictors of bleeding but base this statement on four studies in cardiac surgery (147). The French Society of Anaesthesia and Intensive Care have released a similar statement in their guidelines (124) but refer to one paediatric study using a non-VET test of platelet inhibition. However, VETs may be better placed to predict global risk of bleeding than conventional tests, as they reflect pro- and anti-coagulant activity, the contribution of cellular components to clot formation, total thrombin generation and fibrin breakdown (125). To date there are only small prospective studies assessing VETs as predictors of bleeding in non-bleeding patients, and these have conflicting results (148-153). Such studies are too small and heterogeneous with high risks of bias, but in those studies where VETs were shown to be useful predictors, the parameters that look at speed of clot strengthening (alpha angle/Clot Formation Time (CFT) and k value) rather than time to initial clot formation (R time/ Clotting Time (CT)) appear more relevant to bleeding risk.

This would explain the poor correlation of PT and INR with bleeding risk as these tests reflect initiation more than clot kinetics or ultimate clot strength. In sepsis-associated coagulopathy (71) and liver disease (144) it has been shown that although activation of coagulation is delayed (probably reflecting lower levels of pro-coagulants such as factor II, VII and X), thrombin generation is normal or even enhanced despite prolonged PT/INR values and/or low platelet counts. In their prospective observational study of 58 trauma patients Park M.S et al., (154) describe accelerated rate of clot formation (alpha angle) and maximum clot strength (MA) as well as low levels of anticoagulants like protein C and high fibrinogen counts: these all suggest a hyper-coaguable environment which is supported by the high thromboembolic rate in trauma patients despite these same patients having prolonged aPTT and PT values. Varying correlations between PT/INR and the R time/CT and similarly between MA/MCF and platelet count and/or fibrinogen level have been described (144, 155, 156). This variability can be partly explained by different activators and different specimens. However a crucial difference is that conventional tests reflect isolated pathways in clot formation and VETs reflect the balance of both pro- and anti-coagulants and how they all interact with platelets and other blood cells as VETs are done in whole blood. In addition the R time or CT only prolong once factor concentrations dip to 20-30% of normal (157-159) and therefore are less sensitive to PT or INR elevations ≤ 1.7 x control. They may therefore be a better reflection of true bleeding potential than conventional tests and we should more reassured by a lack of, not presence of, a significant correlation between VET parameters and aPTT, PT and INR. This highlights the problem that there is no gold standard test to compare VETs with when assessing bleeding risk. Other challenges in validating VETs include the lack of standardization within and between TEG® and ROTEM® systems (160, 161) as well as lack of definitions for hypo-and hyper-coaguability (162).

6. Evidence for Prophylactic FFP in Specific Clinical Scenarios

6a. Liver Disease

A large proportion of prophylactic FFP is given to patients with liver disease. A national audit of blood product use over 1300 cases of cirrhosis

reported that 76% of patients receiving prophylactic FFP received it prior to a procedure and that 47% of these patients had an $\text{INR} \leq 2.0$ (24). There is now a significant volume of evidence in patients with liver disease that PT, aPTT and INR do not correlate with bleeding risk and that FFP does little to attenuate this risk (163, 164). Specifically looking at liver biopsies, Ewe et al., (165) were the first to observe bleeding times after percutaneous laparoscopic liver biopsy in 200 patients and correlate this to coagulation indices including platelet count. They found no correlation and that the few cases of prolonged bleeding stopped with compression alone if necessary. Gilmore et al., (166) looked at 1500 liver biopsies in England and Wales; and found that of the patients that bled, 89.6% had an $\text{INR} < 1.3$, however, the incidence of bleeding increased from 3.3% to 7.1% if $\text{INR} \geq 1.5$. Several studies since (one looking at over 9000 biopsies (167)), have failed to show a link between hemorrhage and abnormal clotting profiles after liver biopsy (75, 165, 167, 168). Youssef et al., (103) carried out a split retrospective-prospective study in patients with Child-Pugh Class B and C liver disease who received FFP transfusions and only 10-12% of patients achieved the target PT. In their recent systematic review Yang et al., (11) identified seven RCTs addressing prophylactic FFP use in liver disease for a variety indications and outcomes including laboratory correction of coagulopathy (94) and prevention of veno-occlusive disease after stem cell transplantation (169). No significant benefit across all outcomes was reported. It is also becoming more common practice to perform orthotopic liver transplantation without FFP (146, 170), as most centers will only transfuse FFP if there is active bleeding, and avoid prophylactic FFP as the excess volume increases portal hypertension, and paradoxically will increase blood loss (171).

The finding of a prolonged PT ratio or INR is common simply because these tests reflect pro-coagulant levels that are usually decreased in liver disease. There is a “re-balancing” of hemostasis in stable chronic liver disease (99, 172) and patients may not even be vitamin K-deficient as is often assumed (76). Primary hemostasis is relatively preserved and the concentrations of both pro- and anticoagulant factors are both decreased in liver disease (99). Hence, thrombin generation is actually normal (144) and may even be enhanced (173). It is of note that rather than there being lower rates of thromboembolic events, as would be presumed if these patients were indeed “auto-anticoagulated”, there is in fact a similar, or even increased thrombo-embolic rate in patients with cirrhotic and non-cirrhotic liver disease, and the role of pharmacological thrombo-prophylaxis is now being discussed despite prolonged PT-INR values (100, 101). Collectively this evidence supports the notion that plasma should

not be administered to non-bleeding patients with liver disease and an INR ≤ 2 who are undergoing an invasive procedure. In addition, although more evidence is needed, VETs and thrombin generation assays may have better clinical utility in assessing hemorrhagic and thrombotic risk in these patients (145) and large scale clinical trials are urgently needed.

Although acute liver failure (ALF) is defined by a raised PT/INR, clinically significant bleeding is rare, and usually mucosal or superficial in nature (174). It has been found that most patients have normal hemostatic parameters on VETs with no correlation between INR in bleeders and non-bleeders (175). Of interest, hyper-coaguable parameters have been noted in ALF on TEG® in the presence of a systemic inflammatory response syndrome, raised lactate and phosphate, hyperammonemia and encephalopathy (175). In a multi-variant analysis the single most important component determining clot strength in TEG® is the platelet count, followed by fibrinogen concentration and lastly pro-coagulant factor levels (175). Prophylactic administration of FFP simply to correct an abnormal INR is not justified in ALF and will obscure the value of INR as a dynamic indicator or worsening or improving liver function. One randomized trial compared prophylactic FFP transfusion with a control group of no FFP in paracetamol overdose (176). There were only 20 patients but no differences in clinical outcomes was shown. Concerns about coagulopathy arise prior to performing invasive procedures in ALF such as placement of intracranial pressure (ICP) monitors where small studies report success with recombinant factor VIIa (rFVIIa) (177-179). However the evidence as to its efficacy in reducing bleeding complications or for the optimal dose regime is poor as publications are limited to small case series, and there are concerns about the potential for thrombo-embolic complications. Indeed, efficacy has primarily been based on its ability to reverse the PT/INR, rather than on clinical outcomes. Evidence regarding the use of prothrombin complex concentrate (PCC) in a prophylactic role is lacking but similar concerns exist (180). Plasma exchange plasmapheresis with FFP may be beneficial in correcting INR and improving hemodynamics (181). Prior to invasive procedures in patients with ALF, fibrinogen levels $<1\text{g/l}$ should be corrected with cryoprecipitate or fibrinogen concentrate and platelet count of 50000/uL is acceptable (182).

6b. Procedures in Critical Care

Central Venous Access

Central venous access is a commonplace procedure in most hospitals and measures to reduce complication rates include ultrasound-guidance and strict aseptic technique. It is still standard practice in many institutions to correct abnormal PT/INR values with prophylactic plasma despite the fact that studies fail to show a link between these profiles and bleeding episodes (183-187). Della Vigna et al., (187) found no bleeding complications when they retrospectively reviewed 122 CVC line insertions in cancer patients with prolonged PT/aPTT or low platelets. 37% of these patients actually had PT/APTT values $>2.2 \times$ normal and/or platelet count less than 50,000/uL. Weigand et al., (185) report no difference in hemoglobin decreases from 196 patients with and without abnormal PT or platelet counts. Doerfler et al., (188) report similar findings in a prospective study of 104 central line placements and found in the rare cases of superficial bleeding (6.5% of procedures), patients suffered more with severe thrombocytopenia (range 6000/uL to 37,000/uL) rather than abnormal PT and/or aPTT. Mumtaz et al., (183) also found bleeding was limited to the insertion site in the few patients who bled in their study of 330 line insertions, and that a platelet count of less than 50,000/uL was associated with a small risk of bleeding but prophylactic correction of PT was not. Another retrospective review of 490 critical care patients, found that in the rare cases of superficial bleeding, this appeared to be related to the experience of the physician rather than to defects in hemostasis (189). These studies all suggest a platelet count of $> 30,000/uL$ and skill level of the operator are the main determinants of bleeding, not the raised PT/INR, indicating that prophylactic correction with FFP of mildly elevated PT/INR is unlikely to be of benefit, but may be harmful if it results in TRALI or TACO.

Tracheostomy

Veelo et al., (116) report the findings of a small RCT where 35 critically ill patients having percutaneous tracheostomy either with a thrombocytopenia (40-100,000/uL), prolonged PT (14.7-20 seconds), or treatment with acetylsalicylic acid were randomized to correction or no correction with blood products. Not only was the incidence of bleeding very low leading to resistance from physicians to correct values (ultimately prematurely terminating the trial), but correction of PT with FFP was marginal (mean decrease 0.4 seconds \pm 0.56), in keeping with numerous other studies, and there was no difference in median blood loss between the “correction” and “no

correction” groups. Again operator experience and technique have a greater bearing and using multiple or single step dilator techniques may be associated with lower bleeding risk (190, 191)[183, 184].

Thoracocentesis

Over 20 years ago, McVay and Toy (74) retrospectively reviewed 217 patients undergoing thoracocentesis with variable use of ultrasound and operator experience and found no difference in bleeding complications between those with normal and abnormal aPTT or PT values (up to 2.0 x normal) or mild (50-99,000/uL) to moderate (25-49,000/uL) thrombocytopenia. In another retrospective study of 100 patients with malignant pleural effusions, hemothorax complicated thoracocentesis in two patients but none had abnormal clotting profiles (192). Hibbert et al., (193) retrospectively looked at over 1000 episodes of thoracocentesis and found the incidence of hemorrhagic complications to be very low (0.4%) and all four complications occurred in the group of patients given either pre-procedural platelets or plasma. In a retrospective analysis of 1076 ultrasound-guided thoracocenteses, no bleeding complications were observed and pre-procedure INR exceeded 2.0 in 139 cases and exceeded 3.0 in 32 cases (194). Finally Puchalski et al., (195) prospectively observed 312 thoracocenteses where 42% of patients had at least one risk factor for bleeding such as INR > 1.5 x control, platelet count < 50,000/uL, creatinine > 1.5mg/dl or use of clopidogrel or heparin: They found no difference in pre and post hematocrit levels between patients with and without one or more bleeding risk factors. A recent review of risk factors for bleeding following thoracocentesis concluded there was no evidence for correction of mildly elevated INR values or mild to moderate thrombocytopenia and that future studies should focus on patients with INR values 3-5 x control and platelet counts of 10-25,000/uL (196).

Overall, these studies suggest that pre-procedural (prophylactic) administration of FFP is unnecessary if the INR is ≤ 2.0 , and will in any case have a very limited effect in terms of reducing the INR.

6c. Cardiac Surgery

Cardiac bypass brings with it unique coagulation disturbances including platelet dysfunction, hyperfibrinolysis, coagulation factor consumption and effects of anticoagulation. It has been common practice to prime bypass with FFP or to give FFP at the end of surgery irrespective of bleeding or

coagulation indices although this practice is diminishing with the increasing use of VETs. One prospective randomized trial in 20 infants having cardiac bypass found a trend towards reduced blood product transfusion when FFP was used to prime the pump versus no FFP (197) but no difference in 24 hour blood loss. There are also randomized trials reporting reduced blood product transfusion and blood loss when acute preoperative plasmapheresis is used in cardiac surgery (198-200). A systematic review identified six RCTs involving 363 patients that compared FFP with either no FFP, a colloid-like substance, or packed red cells as a control arm either before during or after surgery: The authors commented on poor methodology and heterogeneity in the studies and could not find evidence for reduced 24 hour blood loss with FFP (201). A more recent meta-analysis of eight RCTs (11) also failed to show a difference in 24-hour blood loss between groups given prophylactic FFP and a control arm, (again be it no FFP, a colloid-like substance, or comparing different types of plasma). Overall Yang et al., (202) identified 15 trials which have evaluated prophylactic FFP in non-bleeding patients with cardiac disease and no consistent benefit could be demonstrated.

6d. Neurosurgical Procedures

In neurosurgery, the potential consequences of bleeding into a closed space are catastrophic and many clinicians aim to keep INR < 1.3 x control. A retrospective survey of ICP placement in severe head injury patients with INR of 1.3-1.6 x control showed no differences in bleeding complications with or without FFP and that transfused patients suffered significantly more delays in their procedure (mean 19.2 hours +/- 19.7 hours versus 8.8 +/- 13.9 hours, $p < 0.002$) (203). Several reviews (46, 204, 205) fail to support the use of FFP in a range of neurosurgical scenarios ranging from ICP monitor placement (where depth of monitor seems to play a larger role in bleeding) to traumatic brain injury (TBI). Of concern in TBI, there is an abundance of tissue factor leading to accelerated consumption of coagulant factors and platelets and possible further bleeding (204). Documented coagulopathy is highly variable ranging from 10 to 97.5% [196]. Some advocate the use of prophylactic FFP in severe TBI where Glasgow Coma Scale (GCS) is <6 but this has little evidence-base (46). In a double-blinded RCT comparing FFP with saline, death and delayed ICH were worse in the FFP group (206) and may have been caused by consequent raised intracranial pressures or even a pro-thrombotic effect of FFP with resultant vascular ischemia. Schramm et al., (207) reviewed 1211

neurosurgical patients over one year, 200 of whom had spinal surgery: Prolonged PT or INR was not associated with increased bleeding risk but the combination of prolonged aPTT with a bleeding history (not prolonged aPTT on its own) was. Matevosyan et al., (83) tested plasma from 25 neurosurgical patients with an INR of 1.3-1.7 for levels of factors II, VII and VIII. The median factor level was 57% (range 25 -124%). Based on these findings this group modified their plasma transfusion guidelines and reduced ordering of FFP for mildly prolonged INR in neurosurgical patients by 75%.

Overall these papers demonstrate that neurosurgical patients with mild prolongations of $INR \leq 1.8$ x control have hemostatically normal levels of important coagulation factors and prophylactic plasma does not reduce bleeding risk and can lead to detrimental delay in treatment in TBI.

6e. Reversal of Warfarin Toxicity in the Absence of Bleeding

The majority of guidelines now recommend using PCCs rather than FFP for the urgent reversal of warfarin overdose or prior to emergency surgery (208). The efficacy and rapidity of INR reduction over vitamin K (209) and FFP (90) have been shown although prospective clinical trials comparing therapies are largely lacking. In one study, FFP was compared with PCC in cardiac bypass surgical patients with preoperative INR values of greater than 2.1 (210). There was a trend towards reduced 24-hour chest drain output in the PCC group and a trend towards increased fluid overload, transfusion requirement and ooziness in the FFP group, but mortality was not reported. Stanworth et al., (211) in their systematic review also identified smaller studies comparing conventional FFP with different formulations of pathogen-reduced FFP in warfarinized subjects but did not find any significant difference in laboratory or clinical outcomes. In summary, PCC corrects INR faster and more completely than FFP, which in turn corrects faster than vitamin K but it is unclear if this equates to equivalent reductions in bleeding risk. There is no high quality evidence to support transfusion of FFP or PCC *prophylactically* in warfarin overdose in the absence of bleeding. Most guidelines recommend merely withholding of warfarin or administration of vitamin K if risk of bleeding is deemed high or INR value is very high (above 8 x control) (208).

PCCs are sterile lyophilized concentrates of vitamin-K dependent coagulation factors containing factor II, VII, IX and X and a variable amount of factor VII. PCCs are rapid to mix and administer, avoid volume overload

(as little as 60mls necessary), avoid the risks of TRALI, and produce reproducible and predictable augmentation in coagulation factors (212). Many patients on warfarin therapy are elderly with co-existing cardiac problems, and use of PCC avoids the inevitable volume overload and dilutional problems that accompany FFP administration. The main concerns are cost and an unclear thrombotic risk. The recent addition of anticoagulants and small amounts of heparin to PCC formulations may well have reduced the thrombotic risk [117]. It has been demonstrated that in trauma patients receiving PCC, compared to those that did not, endogenous thrombin potential is increased for several days post operatively, and also that antithrombin (AT) levels remain low, implying a potential pro-thrombotic state not reflected by standard coagulation tests (213). It took a number of years before the increased risk of arterial thrombo-embolic events associated with the use of rFVIIa was recognized, another drug that acts by enhancing thrombin generation (214).

In summary there is a decreasing role for FFP in warfarin reversal as PCC is preferred in emergencies or in bleeding patients, and vitamin K or withholding of warfarin is effective in stable non-bleeding patients or the elective setting.

Overcoming some of these problems will require new, and more novel ways of designing these clinical trials, such as large-scale cohort studies. However, summing all the available evidence to date, it is now clear that the practice of giving FFP in order to reduce a perceived bleeding risk is of little or no benefit in stable patients with mild prolongation of PT/INR, and may in fact be harmful. It is time to move to a much more restrictive, and evidence based practice when transfusing FFP.

Conclusion

There is currently no high quality evidence to support prophylactic FFP transfusion to correct PT or INR values ≤ 1.8 x control in non-bleeding patients across all ranges of specialties. There is also a lack of confidence in current guidelines for both prophylactic and therapeutic FFP use and high levels of inappropriate use worldwide (up to 80%). Conventional coagulation tests such as PT and INR do not accurately indicate bleeding risk and need to be interpreted within their clinical context. Global assays such as viscoelastography may be more useful, but more evidence is needed supported by large-scale clinical trials. In liver disease, many patients VETs show

preserved or enhanced thrombin generation when conventional tests suggest hypercoagulability and many guidelines now use higher threshold INR values of ≥ 2.0 x control in these patients. Standard doses of FFP (10-15mls/Kg) do not adequately correct PT or INR values less than 1.8 x control, and indeed coagulation factor levels, are, in most cases, above the hemostatic threshold of 30% in these patients. It is clear that standard doses of FFP are only effective in correcting profound coagulopathies and physicians need more education about the indications and dosing of FFP as this has been shown to have an impact on practice. RCTs looking at bleeding outcomes and mortality after prophylactic FFP transfusion have been terminated in the past due to challenges in recruiting patients, and resistance from physicians to expose patients to the risks FFP transfusion when bleeding risk is perceived to be low and resistance to expose patients to omission of FFP transfusion when the risk of bleeding is perceived to be high. In addition, bleeding outcomes are variable amongst studies looking at prophylactic FFP and the use of validated tools that incorporate bleeding volume, location, transfusion needs and mortality needs to be promoted. Future studies also need to include mandatory reporting of adverse effects of FFP such as ALI, circulatory overload, thrombosis and infection rates as well as delays incurred in performing procedures. Overcoming some of these problems will require new, and more novel ways of designing these clinical trials, such as large-scale cohort studies. However, summing all the available evidence to date, it is now clear that the practice of giving FFP in order to reduce a perceived bleeding risk is of little or no benefit in stable patients with mild prolongation of PT/INR, and may in fact be harmful. It is time to move to a much more restrictive, and evidence based practice when transfusing FFP.

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