Elective fresh frozen plasma in the critically ill: what is the evidence?

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ABSTRACT

The scientific rationale for administering fresh frozen plasma (FFP) rests on the assumptions that patients are at risk of adverse effects from inadequate coagulation factors, and that FFP transfusions can decrease those risks.

There is a general but unfounded enthusiasm for FFP use across a range of clinical specialties in hospital practice. Plasma for transfusion is most often used when a patient has abnormal results on coagulation screening tests, either as therapy in the face of bleeding, or in patients who are not bleeding as prophylaxis before invasive procedures or surgery.

Laboratory abnormalities of coagulation are considered by many clinicians to help predict bleeding before invasive procedures where bleeding risk exists; FFP is presumed to improve the laboratory results and reduce this risk. However, most guideline indications for the prophylactic use of FFP are not supported by evidence from good-quality randomised trials. In fact, the strongest randomised controlled trial evidence indicates that prophylactic plasma for transfusion is not effective across a range of clinical settings. This is supported by data from non-randomised studies in patients with mild–moderate abnormalities in coagulation tests.

It is also crucial to clearly understand the risks associated with use of FFP, as no studies have taken adequate account of the extent to which adverse effects might negate the clinical benefits of treatment with FFP.

New trials are needed to evaluate the efficacy and adverse effects of plasma, both in bleeding and non-bleeding patients, and to determine whether presumed benefits outweigh the real risks. In addition, new haemostatic tests that better define the risk of bleeding and monitor the effectiveness of FFP use should be validated.

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Fresh frozen plasma (FFP) is human donor plasma, either recovered from a single whole blood donation or obtained by plasmapheresis. It is frozen within 8 hours of collection from a donor and typically stored at –30° C. When appropriately stored, FFP is usable for a year from the date of collection. Standard FFP units derived from a single unit of whole blood have a volume of about 300 mL. After thawing, FFP contains near normal levels of many plasma proteins, including procoagulant and inhibitory components of the coagulation cascades and albumin. The haemostatic factor content of FFP is shown in Table 1.

Evidence for and against effectiveness

The scientific rationale for administering FFP rests on the assumptions that:

- Patients are at risk of adverse effects from inadequate levels of coagulation factors; and
- FFP transfusions can decrease those risks.

The clearest evidence for a direct beneficial effect of FFP would be expected from randomised controlled studies of FFP compared with no FFP. Studies comparing FFP with non-blood products (eg, solutions of colloids or crystalloids) might also assess effectiveness, but would need to be separately evaluated, given that these solutions have different in-vivo and in-vitro effects on coagulation themselves. Of a total of 57 published randomised controlled trials on the use of FFP identified in a systematic review, only 17 compared FFP with no FFP or a colloid/crystalloid solution in adults. When all randomised controlled trials evaluating prophylactic FFP use across a range of settings (including cardiac, neonatal, and other clinical conditions) were considered, the results failed to show evidence for the effectiveness of prophylactic FFP for a range of clinical and laboratory outcomes.[1] Two large well-conducted trials, designed to evaluate the effectiveness of FFP (one in neonates, and the other in patients with acute pancreatitis), found a lack of benefit from the prophylactic use of FFP.[2,3]

Coagulation screening tests and clinical coagulopathy

The commonly used tests of coagulation, such as prothrombin time (PT) and activated partial thromboplastin time (APTT), have been found to be poor predictors of bleeding. The international normalised ratio (INR) is based on PT and was developed to monitor warfarin therapy by standardising results to account for different sensitivities of thromboplastins. It has been argued that the extrapolation of PT to INR is valid only for patients stably anticoagulated

with vitamin K antagonists, and may not be valid for patients with, for example, liver disease.[4]

In a systematic review, Segal and Dzik addressed the problems of relating the standard in-vitro tests to in-vivo haemostasis by asking whether abnormalities in coagulation tests correlate with an increased risk of clinical bleeding. They concluded that the published studies did not provide evidence for a predictive value of PT or INR for bleeding.[5] In patients undergoing invasive procedures who have no history of bleeding, retrospective studies show that abnormal PT and APTT are poor predictors of bleeding.[6,7] Given the understanding that overall haemostasis depends on a complex interrelationship between endothelium, platelets, other inflammatory cells, fibrinolysis and inhibitors, as well as procoagulant factors, it is not surprising that an abnormality in one component of the coagulation cascade is not a sensitive marker of clinical haemostasis. However, laboratory tests to monitor global haemostasis are not readily available at present, and whether newer tests (eg, thromboelastogram and thrombin generation tests) can better predict clinical bleeding risk is unclear.

Table 1. Typical factor concentrations in a freshly thawed unit of fresh frozen plasma (300 mL)

Factor	Concentration (IU/mL)*
Factor II	80
Factor V	80
Factor VII	90
Factor VIII	92
Factor IX	100
Factor X	85
Factor XI	100
Factor XII	83
Factor XIII	100
Antithrombin III	100
Von Willebrand factor	80
Fibrinogen (g/L)	2.67

* Unless otherwise specified.

The series of enzymatic reactions of the coagulation cascade are strongly inhibited by hypothermia, as demonstrated by the dramatic prolongation of PT and APTT in patients with this condition when all factor levels were known to be normal. Unless specifically considered, the contribution of hypothermia to the haemorrhagic diathesis may be overlooked, as coagulation testing is performed at 37° C, rather than at the patient's actual in-vivo temperature.

Although PT and APTT may be abnormal, clinical coagulopathy does not usually occur until replacement exceeds one blood volume (10 units of packed red cells in a 70 kg man), or when the PT and APTT exceed 1.5–1.8 times control values.[8]

Common indications for FFP

Clinical groups in whom FFP administration is commonly indicated include patients with major blood loss, warfarin therapy, deficiencies of coagulation factors, therapeutic apheresis and thrombotic thrombocytopenic purpura and cardiac surgery.

Massive haemorrhage

Blood usually coagulates appropriately at normal temperature and pH when coagulation factor concentrations are at least 20%–30% of normal, and fibrinogen levels are greater than 0.75 g/L.[4] Coagulopathy after trauma is common but is usually attributed to dilution from intravenous fluid therapy and massive blood transfusion, progressive hypothermia, and acidosis. Evidence that coagulation factors can be depleted sufficiently to produce bleeding due to dilutional coagulopathy alone is limited. Replacement of an entire blood volume leaves the patient with about a third of the original concentration of coagulation factors.

Additional factors may play an important role in the development of coagulopathy. Recently published studies showed that a clinically important acute coagulopathy exists after trauma, before and independent of that caused by fluid replacement therapy, hypothermia and acidosis.[9] The release of mediators after tissue trauma activates multiple humoral systems, including the coagulation, fibrinolysis, complement, and kallikrein cascades, which contribute to the systemic inflammatory response syndrome and multiple organ dysfunction. The development of an acute coagulopathy may therefore be an indicator of loss of regulation of the local inflammatory response.[10] Certain injuries in particular are known to interfere with the coagulation system, including brain injuries,[11] due to release of brain tissue thromboplastins, and long bone fractures.[12] Shock, independent of blood loss, may be associated with a consumptive coagulopathy, leading to microvascular bleeding.[13]

Few trials have evaluated the effects of therapeutic FFP in patients with bleeding and deficiencies of multiple coagulation factors, as in disseminated intravascular coagulation or massive transfusion — presumably in part because of the difficulty of designing trials in these settings. Almost all the data to determine whether FFP administration improves clinical outcome in massive haemorrhage comes from simple mathematical models of washout of coagulation factors,[14] and controlled and uncontrolled observational studies. Using these data, various colleges have created expert recommendations. However, these mathematical models are criticised as they assume a stable blood volume and calculate the exponential decay of each blood component when bleeding and replacement rates are constant and equal. In the severely injured patient, most of these assumptions do not apply: blood volume fluctuates, bleeding rates vary with blood

pressure, and replacement typically lags behind blood loss. Therefore, in patients with severe bleeding, replacement guidelines based on washout calculations may underestimate the dilution of clotting factors.

A computer-simulated multicompartment dynamic model of an adult trauma patient with massive bleeding was recently developed.[15] Calculation of changes in intravascular volume, the pressure–volume relationship of the circulation, and the dilution of clotting factors and platelets with ongoing bleeding and transfusion in this model revealed that the key to preventing coagulopathy is plasma infusion before PT becomes subhaemostatic. With the loss of one blood volume, 70% of an individual's coagulation factors are also lost, but the PT remains normal. However, with the loss of approximately two blood volumes, 87% of coagulation factors are lost, and the PT becomes abnormal. The window of opportunity to intervene to prevent coagulopathy is thus quite narrow. Although the precise timing of this window may vary between scenarios, it is an intrinsic attribute of the system, and occurs in any trauma patient with severe blood loss and delayed replacement. Use of an aggressive replacement ratio of FFP to packed red blood cells (RBC), such as 2 : 3, instead of the 2 : 5 to 3 : 5 ratio used in many massive transfusion protocols, effectively prevented the exponential "takeoff" in the PT dilution curve. In support of this model, more recent retrospective trials using higher plasma to RBC ratios were associated with better outcomes.[16,17]

The recommended dose of FFP is calculated to supplement the patient's coagulation factors to give a minimum 30% of the normal concentration of plasma factors. This is usually achieved with administration of 10–15 mL/kg of FFP.

Warfarin reversal

Warfarin and other coumarin anticoagulants act by inhibiting the synthesis of functional vitamin K-dependent coagulation factors II, VII, IX and X. The effective half-life of warfarin ranges from 20 to 60 hours, with a mean of about 40 hours. Over-anticoagulation has been associated with major bleeding, including intracranial haemorrhage, and has been reported in 1.2%–8.1% of patients during each year of long-term warfarin therapy.[18]

In one study, the bleeding rate was found to double as INR increased from 2.0–2.9 to 3.0–4.4, and to quadruple as INR increased to 4.5–6.0.[19] Vitamin K_1 may take up to 24 hours to exert its full effect in reducing INR, even when given in large doses with the intention of complete reversal. For immediate reversal of clinically significant bleeding, the combination of prothrombin complex concentrate (PCC) and FFP covers the period before vitamin K_1 reaches its full effect. However, there is continuing controversy over which component is preferable, and this, in part, reflects a lack of clinical trials comparing the two components. Vitamin K_1 is essential for sustaining the reversal achieved by PCC and FFP.

Warfarin reversal consensus guidelines[18] prepared by the Australasian Society of Thrombosis and Haemostasis recommend that, in clinically significant bleeding where warfarin induced coagulopathy is a contributing factor, warfarin therapy should be ceased, and vitamin K_1 (5.0–10.0 mg) should be given intravenously, as well as PCC (25–50 IU/kg) and FFP (150–300 mL), and the patient should be continuously assessed until bleeding stops and INR is < 5.0. PCC includes all the coagulation factors except factor VII. The smaller doses of FFP are given to add the deficient factor VII.

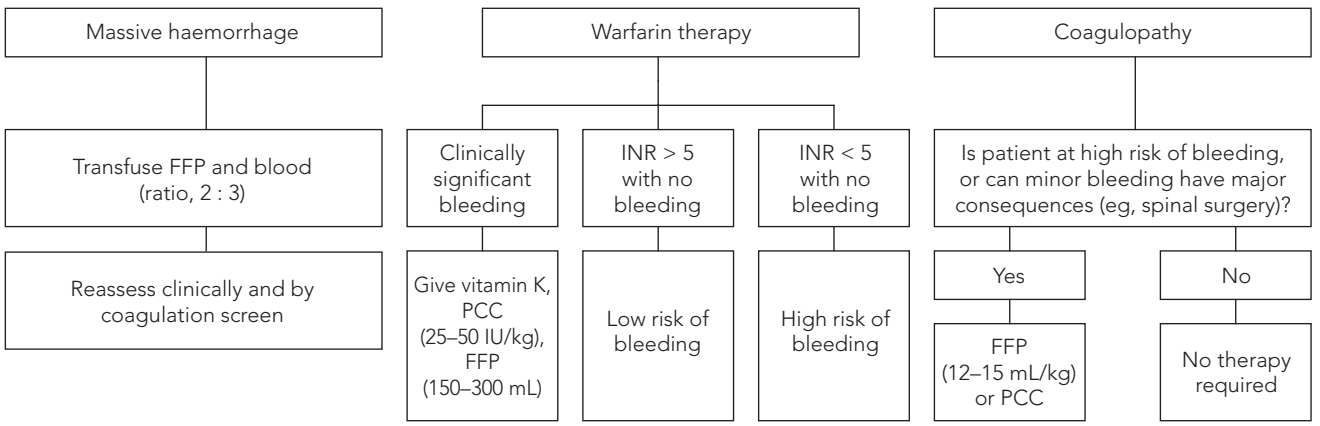
Single and multiple deficiencies of coagulation factors

The coagulopathy of liver disease is complex, with abnormalities of platelets, fibrinolysis and inhibitors of coagulation, as well as coagulation factor deficiencies. A small randomised trial assessed the effects of regular prophylactic transfusions of FFP in patients with paracetamol overdose, compared with a control group of patients who received no FFP. No differences in clinical outcomes were observed between the two groups.[20] Other studies investigating FFP transfusion practice in patients with liver disease have been uncontrolled and observational. It is difficult to correct abnormalities seen on coagulation screening tests unless large volumes of FFP are transfused, as the effects of transfusion are short-lived.[21] Lack of evidence for an association between bleeding and laboratory results for coagulation in liver disease has also been reported in a number of studies.[22] The lack of bleeding in patients with cirrhosis, despite diminished procoagulant synthesis (and abnormal PT and APTT) may be explained by a parallel reduction in the production of anticoagulant proteins, such as protein C and protein S, leading to equivalent potential for thrombin generation on activation of both the procoagulant and anticoagulant pathways.

Therapeutic apheresis and thrombotic thrombocytopenic purpura

FFP may be used as a replacement fluid in patients undergoing therapeutic apheresis procedures. In addition, plasma exchange with FFP has been recommended, based on a single randomised controlled trial,[23] as the first-line treatment of choice for thrombotic thrombocytopenic purpura (TTP). FFP provides the enzyme ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13), which is inhibited or deficient in most cases of TTP. Studies have shown no difference in outcome between FFP and cryodepleted FFP. Of interest, early studies investigating

Figure 1. Algorithm for transfusion of fresh frozen plasma (FFP)



INR = international normalised ratio. PCC = prothrombin complex concentrate.

plasma exchange for conditions other than TTP have reported that no bleeding complications occurred, despite repeated procedures with replacement fluids free of coagulation factors, and marked reductions in levels of coagulation factor.[24]

Cardiac surgery

Epidemiological evidence indicates that significant quantities of FFP are given during cardiac surgery, and a number of published randomised controlled trials have assessed the benefit. However, trials and meta-analyses comparing prophylactic use of FFP with either no FFP or a non-plasma product after cardiopulmonary bypass have not shown evidence of a consistent significant effect on blood loss or transfusion requirements.[25] The haemostatic changes related to cardiac bypass are a product of multiple factors, including contact with synthetic surfaces, use of heparin, hypothermia, thrombocytopenia and defects in platelet function, and are not solely related to coagulation factor deficiency.

Is there an optimal dose for plasma?

Questions about the optimal dose for FFP transfusion generally presuppose that there is evidence of dose-dependent effectiveness in correcting abnormalities seen on coagulation tests. Much of the evidence informing appropriate dose comes from mathematical analyses of physiological assessments of coagulation factor content and effects of plasma infusion. However, FFP may not be effective in correcting mild to moderate abnormalities seen in coagulation screen tests. Abdel-Wahab et al prospectively evaluated the effects of plasma transfusions on PT in hospital patients.[26] They followed up patients who had a PT after re-transfusion of 13.1–17 seconds (INR equivalent, 1.1–1.85). Fewer than 1% of patients had normalisation of PT after transfusion, and only 15% showed a correction of half way to normal. In addition, when all cases of transfusion were reviewed for correction, there was little evidence of a dose–response effect. When other studies or trials do report apparent "correction", the overall absolute or mean changes again appear small. For example, in a randomised controlled trial of patients with liver disease, the median reduction in INR attained after FFP was 0.2 (range, 0–0.7).[27]

Risks of FFP treatment

It is crucial to clearly understand the risks associated with the use of FFP. The most immediate serious — and potentially fatal — complication is transfusion-related acute lung injury, although there are ongoing issues of reporting and diagnosis of this condition that make accurate estimation of prevalence difficult. Prospective trials in ICU patients found a higher incidence of "acute lung injury" during the 48 hours after transfusion with FFP.[28] This association raises the possibility that critically ill patients with systemic inflammatory response syndrome (SIRS) may be more susceptible to transfusion-related acute lung injury after receiving plasma, although distinguishing this lung injury from other clinical problems, such as volume overload, remains problematic. These findings do not prove cause and effect, but emphasise a need for concern about the use of FFP when evidence of efficacy is, at best, questionable.

Other risks are transfusion-transmitted infection, including an unquantifiable risk of prion disease, and fluid overload, which may be a greater issue if larger doses of FFP are transfused to attempt full reversal of abnormal coagulation test results. Allergic reactions to FFP are relatively

uncommon, with a frequency of around 1% to 3% of all transfusions, but can be extremely troublesome and sometimes life-threatening for some patients who receive multiple transfusions.

A prophylactic policy is justified only if the risk of bleeding is greater than the risk of harmful effects. Without evidence of benefit, a policy aimed at preventing uncommon bleeding complications could involve transfusing potentially harmful FFP to a large number of patients, many of whom might not bleed even if not given prophylactic FFP. A suggested algorithm for the use of FFP is shown in Figure 1.

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