FFP Transfusion in Intensive Care Medicine

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Abstract

Coagulopathies are common in the critically ill but are often mild and short lived. Detailed assessment of haemostasis is normal in many of these cases and there is no evidence and little clinical rationale, for transfusing FFP in the absence of bleeding, even when invasive procedures are planned. The risk of procedure-related bleeding is very low, and evidence suggests that prophylactic plasma does not modify risk for most cases. Pre-procedural FFP should be reserved for patients with significantly prolonged INR (>2.5–3.0) undergoing higher-risk procedures. Currently recommended doses of FFP (10–15 mL/kg) do not generate important improvements in INR or APTT, especially when the INR is <2.5. For patients with more significant abnormalities (e.g. INR >3) or where physiological correction is intended because of high-risk procedures (e.g. CNS procedures), a larger dose of FFP (20–30 mL/kg) is required. The significant volume associated with larger doses requires careful consideration of the rate of administration, the patient's intravascular status and the potential risk of transfusion-associated circulatory overload.

14.1 FFP Use in Critical Illness

It is common for patients in the intensive care unit (ICU) to develop disorders of coagulation in association with their critical illness. Up to 30 % of adult patients admitted to ICUs have an INR (international normalised ratio) greater than 1.5 at some point during their admission [1]. This coagulopathy of critical illness is

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associated with both acute and chronic liver and kidney disease, sepsis, recent blood transfusion and a higher APACHE II score. Disordered coagulation not only increases the risk of bleeding but also leads to microvascular thrombosis, with resulting end-organ hypoperfusion and dysfunction. Fresh frozen plasma (FFP) is commonly administered to coagulopathic, critically ill patients (between 12.7 and 29.9 %) either as part of the treatment of bleeding or prophylactically to prevent bleeding. This chapter focusses on the use of FFP in the ICU setting, specifically in the absence of major bleeding. The management of major bleeding is dealt with elsewhere.

14.1.1 What Is FFP?

Plasma is the noncellular component of blood and may be prepared by either centrifugation of donated whole blood or by plasmapheresis with leucodepletion. FFP can be produced from single donations or pooled donations. Reduction of infection risk, especially for variant CJD (vCJD) and enveloped viruses (e.g. HIV, HBV, HCV) can be achieved by pathogen-reduction techniques; the two commonest approaches are methylene blue treatment or solvent-detergent treatments. The use of these varies between countries and is driven in part by production policies and the risk of vCJD. An important consideration is that pathogen reduction reduces concentrations of procoagulant factors, especially fibrinogen and factor VIII (by approximately 30 %) compared to untreated plasma, which decreases efficacy per unit volume.

When frozen within 8 h to −30 °C, plasma is referred to as fresh frozen plasma (FFP). If frozen later (up to 24 h after preparation), it is known as frozen plasma (F24). Both FFP and F24 contain concentrations of clotting factors that are largely equivalent to those found in vivo (with the exception of pathogen-inactivated FFP as noted above), although the concentration of factors V and VIII is lower in F24 due to their instability prior to freezing. The concentration of all plasma proteins is diluted by the sodium citrate solution used as part of the preparation of FFP/F24. Typical factor concentrations in FFP are given in Fig. 14.1. Besides clotting factors,

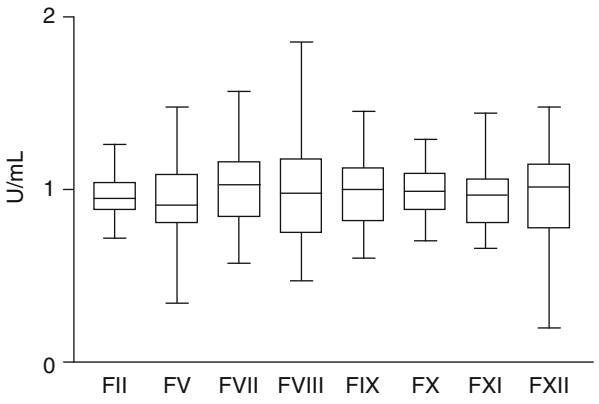

Fig. 14.1 Factor concentrations in white-cell-reduced FFP (Taken from Stanworth et al. [2])

FFP also contains other plasma proteins including acute-phase proteins, von Willebrand factor, donor immunoglobulins and albumin. Donor leukocytes are also present, even following leucodepletion, but at low concentration (typically 1×10^6 leucocytes per component). A typical unit of plasma has a volume of 180–300 mL and may be stored for up to 36 months in most countries. After thawing, the level of factor VIII in plasma falls rapidly, together with factor V levels, but levels of fibrinogen and other haemostatic components are maintained. Guidelines permit the use of plasma that has been thawed for up to 24 h after thawing, but best practice is to order FFP only when required and transfuse it immediately following receipt at the bedside to maximise efficacy. FFP that is not for immediate transfusion following thawing should be stored at 4 °C until transfusion.

14.1.2 Indications for FFP Use in Critical Illness

The use of FFP in critical illness has increased in recent years, although the evidence base supporting its clinical effectiveness is surprisingly lacking. Recommendations in national guidelines [3] are largely based on expert opinion rather than conclusions from well-conducted, randomised trials. Accepted potential indications in critically ill patients include the following:

1. Replacement of multiple coagulation factor deficiencies associated with severe bleeding, disseminated intravascular coagulation and acute traumatic coagulopathy. The treatment of major haemorrhage, in which FFP is administered as part of a protocolised response to massive blood loss, is dealt with in a separate chapter.
2. Correction of coagulopathy in non-bleeding patients.
3. Prophylaxis prior to invasive procedural instrumentation (e.g. central line insertion) in coagulopathic patients.
4. Specific indications, e.g. plasma exchange in thrombotic thrombocytopenic purpura and Guillain-Barre syndrome, treatment of C1-esterase inhibitor deficiency.

The use of FFP for prophylactic correction of coagulopathy prior to procedures is discussed in more detail below.

14.1.3 Situations in Which FFP Transfusion Is Inappropriate

1. *Reversal of warfarin anticoagulation*. In the absence of bleeding, excessive anticoagulation as a result of warfarin administration should be reversed with intravenous or oral vitamin K. In the presence of bleeding and a prolonged INR in a patient taking warfarin, prothrombin complex concentrate is recommended rather than FFP, which is only partially effective in reversing over-warfarinisation.
2. *Correction of single-factor deficiencies*. In this situation, single-factor concentrate is available and should be used.

3. *Volume expansion*. There is no evidence to support the routine use of FFP as a colloid solution, and the risk/benefit balance and cost-effectiveness have never been explored in adequately powered randomised controlled trials.

In addition, FFP is absolutely contraindicated in congenital IgA deficiency in the presence of anti-IgA antibodies and relatively contraindicated in pulmonary oedema.

14.1.4 FFP Use During Critical Illness

Observational studies indicate that approximately 30 % of critically ill patients experience an episode of INR prolongation, although in the majority of cases (70–75 %) the worst INR is less than 2.5, and abnormalities are limited to a single abnormal test result [1, 7]. Despite this, 30 % of episodes of prolonged INR were associated with FFP prescription (10–15 % of all ICU admissions). Typically, 50 % of FFP prescriptions are given to non-bleeding patients, of which half are administered prior to a procedure and half to treat coagulopathy despite no procedure. Observational studies show wide variation in practice, and in response to surveys, clinicians indicate wide variation in beliefs about use of FFP in the absence of bleeding. Clinicians appear more likely to administer pre-procedural FFP when patients have liver disease and other coagulation abnormalities (low platelets; prolonged APTT) or are receiving concurrent red cell transfusions [8, 9].

Observational studies indicate wide variation in FFP dose between clinicians. Concurrent bleeding is associated with higher clinical doses. However, many clinicians prescribe smaller doses than recommended in current guidelines (see below).

14.2 Tests to Assess the Risk of Bleeding

The most commonly used laboratory assay of coagulation factor activity is the prothrombin time (PT). This provides a measure of the extrinsic pathway of coagulation and represents the time taken for plasma to clot after the addition of tissue factor (Factor III). The PT may be standardised to calculate a prothrombin ratio or international normalised ratio (INR). PT ratio is calculated as PT ratio = PT/MNPT and INR as $\text{INR} = (\text{PT}/\text{MNPT})^{\text{ISI}}$, in which MNPT and ISI are the local, laboratory-specific mean normal PT and international specificity index, respectively. Calculating INR therefore provides an adjustment for different thromboplastin sensitivities between different laboratories.

Despite a lack of robust evidence, an INR of greater than 1.5 is frequently recommended as the threshold for considering FFP transfusion and is present in most guidelines. This cut-off is associated with impending haemostatic failure and represents a fall in the activity of some coagulation factors to less than 50 % of normal. As can be seen from Fig. 14.2, there is significant functional reserve in normal coagulation factor levels, and even at an INR of 1.5, there may be normal haemostasis as

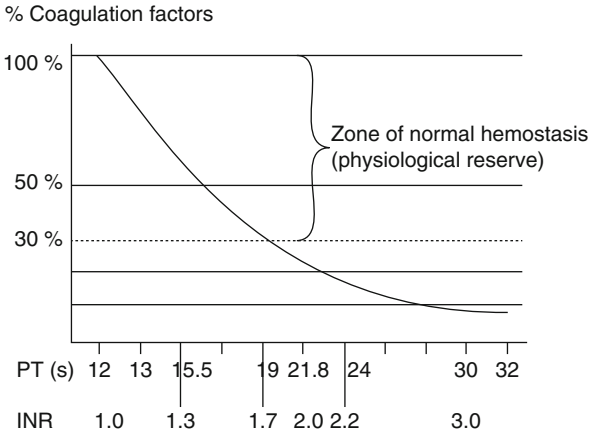

Fig. 14.2 Relationship between coagulation factor concentration and PR/INR (Taken from Yazer et al. [4])

measured by concentrations of individual factor levels. Significant bleeding risk is thought to be increased only when factor levels are less than 30 % of normal ranges. However, this number relates to a single-factor deficiency and may not hold for conditions characterised by multiple factor deficiencies.

There are several well-recognised disadvantages to making FFP transfusion decisions based on PT or INR. In vitro laboratory coagulation tests poorly reflect the complex in vivo haemostatic milieu [5], and there are relatively few studies that support a link between a prolonged PT/INR and bleeding [6]. The long lead time between drawing a sample from a patient to receiving the INR test result (typically in the order of 45 min in many hospitals) means that in a rapidly changing clinical situation, the INR result no longer reflects the patient's current haemostatic status by the time the result is available. Transfusion of FFP in coagulopathic patients, especially those without bleeding, typically results in no change or only a modest improvement in INR when currently recommended doses of 10–15 mL/kg are administered. For example, an 11 mL/kg transfusion of FFP in adults reduced median INR by only 0.2 [7]. Observational data indicates that correction of INR (or equivalent) rarely occurs when the INR is in the 1.5–2.5 range; larger corrections are typically observed at progressively greater derangements. However, correction is typically short lived and limited to less than 24 h.

As the use of point of care, whole-blood viscoelastic tests of coagulation (e.g. ROTEM®/TEG®) increases, it may be possible to recommend thresholds for FFP transfusion based on the results of these technologies. By providing a faster turnaround and allowing the quantification of the interaction between coagulation factors, platelets and red cells in whole blood (rather than utilising plasma only, as with PT and APTT), these tests have several attractive advantages. It is now commonplace to make blood product transfusion decisions in the resuscitation of major trauma based on viscoelastic ROTEM®/TEG® results. There is as yet limited evidence for translating this to non-bleeding patients in intensive care units.

14.3 Utility of FFP During Coagulopathy and in Relation to Invasive Procedures

Invasive procedures such as central venous catheterisation or percutaneous tracheostomies are common in patients admitted to intensive care units. These are potentially associated with bleeding, which could have significant morbidity. Such patients, although not necessarily bleeding, frequently have deranged tests of coagulation. The potential consequences of bleeding depend significantly on the site and nature of the procedure but are generally considered higher in relation to the central nervous system (closed spaces), tracheostomy and major organ biopsy. Other factors such as operator experience and expertise are also relevant. FFP is frequently prescribed with the intention of reducing the likelihood and severity of peri-procedural bleeding.

Observational studies indicate significant variation in use of FFP in relation to procedures between clinicians, ICUs and countries. One case-controlled study found that patients with chronic liver disease, thrombocytopenia or receiving concurrent red cell concentration transfusion were all more likely to be prescribed FFP in relation to central venous cannulation [8, 9].

14.3.1 Dose Recommendations

Endogenous factor concentrations of 25–30 % are typically sufficient for haemostasis. Given a typical plasma volume of 40 mL/kg, dose recommendations are therefore 10–15 mL/kg FFP, which equates to 2–4 units (600–1,200 mL) for most adults [10]. Despite these guidelines, larger doses of 20–30 mL/kg are required to reliably increase individual factor levels; these doses represent significant FFP volumes which may increase the risk of hypervolaemia and TACO in non-bleeding patients.

14.3.2 Evidence-Based FFP Transfusion

Despite being common practice, the evidence base supporting FFP transfusion in non-bleeding patients prior to an invasive procedure or as prophylaxis is weak, with few high-quality studies supporting this practice. A Cochrane systematic review recently found no trials meeting predefined quality criteria that compare a liberal with a restrictive transfusion strategy for FFP use in critically ill patients [11]. Current recommendations are therefore largely based on consensus and expert opinion.

Excluding massive trauma, there is no high-quality evidence that plasma transfusion confers a benefit on mortality [12]. In observational studies, the receipt of FFP is associated with higher mortality, even after adjustment for potential confounders, but these cohort studies are subject to “bias by indication”. There is little evidence that abnormal coagulation tests predict peri-procedural bleeding in critically ill patients, especially for vascular catheterisation [6]. The available evidence for this predominantly relates to observational and other low-quality studies. These suggest

Table 14.1 Factors that may increase justification for using pre-procedural FFP in critically ill patients

Factor	Clinical rationale
INR >2.5–3.0	Individual factor levels are frequently >30 % normal values, consistent with normal haemostasis, when INR is <2.5
Complex coagulopathy	Concurrent thrombocytopenia or DIC may increase bleeding risk
High-risk procedure	Central nervous system procedure
	Biopsy of organ or site with high risk of bleeding or in which consequences of bleeding may be life threatening (e.g. lung, liver)
	Technically difficult procedure anticipated
Evidence of significantly abnormal clot formation	Dynamic tests of clot formation using ROTEM®/TEG® may be useful for discriminating patients at higher risk of bleeding (but evidence to support this is circumstantial)
Concurrent bleeding in a patient with abnormal INR	Loss of factor levels

that central venous cannulation, one of the most common procedures undertaken on critically ill patients, is not associated with significant bleeding in the context of deranged coagulation [13–15]. The increasing use of ultrasound may also modify the risk between coagulopathy and procedural bleeding, but this has not been demonstrated and factors such as operator skill and experience are also important. Similarly, the rate of bleeding in patients undergoing bronchoscopy, percutaneous tracheostomy and thoracocentesis is similar in patients with both normal and deranged coagulation tests. However, the quality of available evidence is low, and the consequences of bleeding and risk-to-benefit ratio within individual patients is a major consideration. Minor bleeding in a noncompressible and/or critical site (e.g. post intracranial bolt insertion) is more serious than that from a compressible bleed following internal jugular vein catheterisation.

Together these data do not support routine use of FFP for patients with prolonged INR or APTT prior to invasive procedures in the ICU. This is particularly the case for central venous catheterisation. The factors that may increase clinical justification for pre-procedural FFP are listed in Table 14.1.

Studies that measured individual factor levels following different doses of FFP in critically ill patients, together with the absence of correction of INR following most FFP transfusions, support the use of higher FFP doses (20–30 mL/kg) when pre-procedural correction is considered necessary.

14.4 Risks Associated with FFP Transfusion

The administration of FFP to critically ill patients is not without risk, and transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI) and allergic reactions are all associated with FFP. TACO and TRALI are considered elsewhere. Both anaphylactic (e.g. secondary to ABO incompatibility)

and anaphylactoid reactions (secondary to residual donor plasma protein, platelets or leucocytes) are associated with FFP transfusion. More mild allergic reactions to FFP may occur in as many as 3 % of all FFP transfusions. Infectious diseases can also be transmitted by FFP, although this is rare because of screening and pathogen inactivation.

14.5 Summary

Prolongation of the INR and APTT is common in the critically ill. In most patients, the derangement is mild and short lived; haemostasis is normal in many of these cases. There is no evidence and little clinical rationale, for transfusing FFP to a non-bleeding patient in whom no procedure is planned. For most procedures, the risk of clinically important bleeding in patients with prolonged INR or APTT is extremely low, and in the absence of high-quality evidence, the risk to benefit balance does not support administration of FFP. Pre-procedural FFP should be reserved for patients with significantly prolonged INR (>2.5–3.0) undergoing higher-risk procedures, including those where the risk from bleeding is high.

Currently recommended doses of FFP (10–15 mL/kg) do not generate important improvements in INR or APTT, especially when the INR is <2.5. This may be in part because these patients do not have haemostatic abnormalities. For patients with more significant abnormalities (e.g. INR >3) or where physiological correction is intended because of high-risk procedures (e.g. CNS procedures), a larger dose of FFP (20–30 mL/kg) is required. The significant volume associated with larger doses requires careful consideration of the rate of administration, the patient's intravascular status and the potential risk of TACO.

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