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Uses and abuses of fresh frozen plasma for the treatment of bleeding

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Background

Transfusion of packed red blood cells (PRBC) to maintain critical oxygen delivery can be lifesaving for patients who have major bleeding. In addition to PRBC, transfusion of blood components, including fresh frozen plasma (FFP), is frequently considered. There is, however, uncertainty about the optimal schedules for FFP administration or the best tests to assess effectiveness. Coagulopathy in patients with major bleeding (who have at least four units of PRBC transfused in the first 2–4 hours of bleeding)[1] is typically defined and monitored by prothrombin time (PT) or international normalised ratio (INR), but these tests have recognised limitations in their ability to provide a relevant or global assessment of haemostatic potential.

The causes of coagulopathy in patients with major bleeding are varied and complex (Table 1). Historically, coagulopathy was thought to result from dilution of procoagulant clotting factors following infusion of PRBC and crystalloids; but it is now recognised that in trauma haemorrhage, a coagulopathy (the 'acute coagulopathy of trauma') might be evident before resuscitation fluids and PRBC have been administered.[2] This discovery promotes early use of plasma for trauma patients, and explains why infusion of FFP before the PT becomes prolonged could be key to preventing (deteriorating) coagulopathy.

How does FFP treat coagulopathy?

Several mechanisms have been proposed for reduction in bleeding and improvement in coagulopathy seen in patients who are transfused with FFP.

1 FFP contains procoagulant and anti-fibrinolytic factors, which might replenish those lost through acute bleeding.
2 When patients are resuscitated with FFP rather than crystalloid or colloid, they are less likely to develop a dilutional coagulopathy.[1]
3 FFP contains fibrinogen, which replenishes losses during bleeding. It is possible that early fibrinogen use could be superior to FFP for patients with major bleeding, but this remains to be determined.[3]

Treating a coagulopathy is not the same as treating bleeding and there is no clear evidence that reversing coagulopathy results in a reduction in bleeding.[4] There are well-recognised risks to FFP transfusion and one study found that when trauma patients who did not require a massive transfusion were transfused with FFP, there was a dose-related increase in adult respiratory distress syndrome, multi-organ failure, pneumonia and sepsis.[5]

Evidence to support FFP transfusion for bleeding patients

The majority of the evidence for the recent change in transfusion practice comes from studies of major bleeding in trauma patients. These studies often involve young patients who have no comorbidities, and their findings can be extrapolated only with caution to other patient groups who might have more complex medical needs – for example, to patients with liver disease or major gastrointestinal bleeding.

Table 1. Mechanisms of coagulopathy in bleeding patients.

Underlying disease	Mechanisms of coagulopathy
All types of major haemorrhage	Consumption of clotting factors
	Dilution (with crystalloid and packed red blood cells)
	Hypoxia (endothelial activation), acidosis and hypothermia (inhibition of clotting factor and platelet function)
	Anaemia (leading to reduced axial blood flow and reduced contact time between clotting factors and endothelium)
Acute coagulopathy of trauma	Local consumption of clotting factors at the site of injury
	Hyperfibrinolysis (increased clot breakdown)
Liver disease	Deficiencies of procoagulant and anticoagulant proteins (both are synthesised in the liver)
	Hypo- or dys-fibrinogenaemia
	Hyperfibrinolysis
	Thrombocytopenia (thrombopoietin is synthesised in the liver)
	Anaemia (reduced axial blood flow)
Disseminated intravascular coagulation	Consumption of clotting factors, fibrinogen and platelets
	Hyperfibrinolysis
	Many precipitants have been identified including sepsis, trauma, severe organ dysfunction (eg pancreatitis), malignancy, severe liver failure, obstetric causes (eg pre-eclampsia) and acute haemolytic transfusion reactions
Warfarin	Inhibition of vitamin-K-dependent procoagulant factors (II VII, IX and X) and anti-coagulant factors (protein C and protein S)

Major bleeding associated with trauma

In the past, 'reactive' infusions of FFP were typically prescribed only after abnormalities of PT were documented, but there is now a move towards the pro-active administration of FFP, aimed at preventing deterioration in coagulopathy. An empirical formula-driven approach is often used, defined by a high ratio of FFP transfusions to PRBC approaching 1:1. Although the results appear promising, the limited evidence to support improved patient outcomes and reduced mortality when this near 1:1 approach has been used should be recognised. The observational studies that have been carried out suffer from survivorship bias (only those that survived long enough were likely to have received FFP).[6] When this was taken into account, Snyder *et al*[7] found no significant reduction in mortality for patients who received high ratios of FFP. It is possible that concentrated sources of fibrinogen, such as cryoprecipitate, might prove superior to FFP in this setting, but their role remains to be determined.[3]

Major bleeding in settings outside trauma

At present, there is a tendency to apply trauma major haemorrhage protocols to other patient groups with bleeding. Therefore, FFP might commonly be given in combination with PRBC as part of a general massive-haemorrhage protocol. But many patients, such as those with gastrointestinal bleeding, are often older than the typical trauma patient and have very different comorbidities.

Patients with gastrointestinal bleeding might have underlying liver disease, which is characterised by complex changes in haemostasis (Table 1). A prolonged PT in a patient with liver disease is often assumed to represent 'auto-anticoagulation', but frequently this is not the case as many of these patients have a propensity towards thrombosis or have balanced haemostasis.[8] Patients with liver disease often have other reasons to bleed, which can be more important than coagulopathy, such as increased portal venous pressure. If extrapolated from trauma practice, early or excessive use of plasma could lead to excessive volume replacement and exacerbate portal hypertension.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is predominantly a prothrombotic condition in which clotting factors, platelets and fibrinogen are rapidly consumed. The most important part of managing DIC is identifying and treating the underlying cause. A bleeding patient with DIC and a PT or activated partial thromboplastin time (APTT) greater than 1.5 times the upper limit of normal should be transfused with FFP, although there is no randomised controlled trial evidence to support this. FFP is not recommended for patients who are not bleeding.[9] An exception to this rule is in the treatment of DIC in patients with acute promyelocytic leukaemia. These patients are at very high risk of bleeding and aggressive treatment of clotting abnormalities until PT or activated partial thromboplastin are normalised is indicated.[10]

Key points

The causes of coagulopathy in patients with major bleeding are varied. They include the dilution and consumption of clotting factors, hyperfibrinolysis, hypoxia, acidosis and anaemia

Some of the protocols for treatment of coagulopathy in trauma advocate using a 1:1 ratio of fresh frozen plasma (FFP) and packed red blood cells (PRBC), but the evidence base for formula driven transfusion strategies is limited. There are concerns about extrapolating these strategies to patients with major bleeding outside trauma

Prothrombin complex concentrate (PCC) rather than FFP should be used to reverse warfarin over-anticoagulation

Patients with disseminated intravascular coagulation (DIC) should only be treated with FFP if they are bleeding

KEY WORDS: coagulopathy, bleeding, fresh frozen plasma

Warfarin reversal

Major bleeding in a patient taking warfarin (defined as life- or limb-threatening bleeding that requires reversal in less than 6–8 hours) should, in preference, be treated with a combination of intravenous vitamin K and prothrombin complex concentrate (PCC).[11] FFP is considerably less effective at reversing warfarin over-anticoagulation than PCC. A commonly referenced study of reversal of warfarin over-anticoagulation recruited and compared 12 patients who received vitamin K and FFP to 29 patients who received vitamin K and PCC. None of the patients who received FFP completely corrected their coagulopathy, whereas all the patients in the PCC group achieved this rapidly.[12] There is, however, much less information on whether more rapid changes in laboratory-defined coagulopathy translate into improved clinical outcomes. FFP is only recommended for the reversal of warfarin over-anticoagulation if PCC is not readily available.

Conclusions

In summary, FFP is commonly used in patients with major haemorrhage. Outside trauma, there is little evidence to inform the optimal use of FFP, and there is a pressing need for new clinical studies to define best transfusion support. Locally agreed major haemorrhage protocols provide a structured framework to guide the transfusion of FFP and all blood components, ensuring that blood components can be accessed rapidly and appropriately. In an emergency situation, delivering blood components, including FFP, rapidly can present logistic difficulties, so the Care Quality Commission recommends that a major haemorrhage protocol should be in place in every hospital.[13]

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