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Perioperative factor concentrate therapy

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Editor's key points

- Use of plasma transfusion in perioperative bleeding and coagulopathy is limited by efficacy, volume, preparation, and serious complications.
- Availability of coagulation factor concentrates and point-of-care testing has led to targeted therapy of haemostatic defects.
- Treatment algorithms appear to reduce transfusion of allogeneic blood products through rational use of factor concentrates.

Summary. Transfusion of allogeneic plasma has been a life-saving measure for decades in patients with severe trauma or suffering from major surgical blood loss. The safety of allogeneic blood components has improved in terms of pathogen transmission, but haemostatic efficacy of plasma is hindered by the large volume and time required for thawing and infusion. Several plasma-derived and recombinant factor concentrates are clinically available and indicated for targeted replacement of missing coagulation elements in hereditary disorders of thrombosis and haemostasis. When used appropriately, factor concentrate therapy can rapidly restore deficient factor(s) without causing volume overload. The haemostatic defect in perioperative patients is often multifactorial, and therefore careful clinical judgement and timely coagulation testing must be exercised before the administration of factor concentrates. In this review, the rationale for including factor concentrates in perioperative haemostatic management will be discussed in conjunction with the limitations of plasma transfusion.

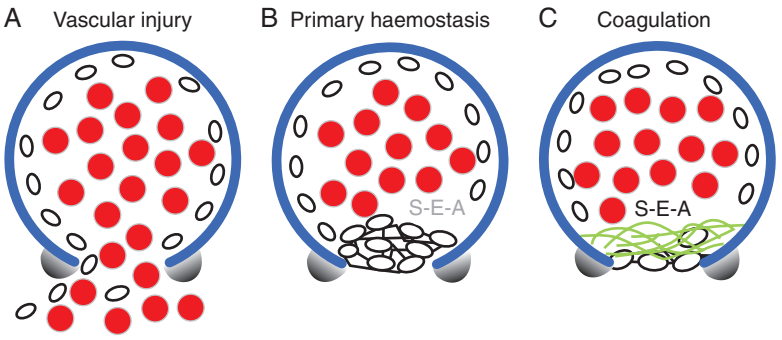
Keywords: antithrombin concentrate; coagulation monitoring; cryoprecipitate; fibrinogen concentrate; fresh-frozen plasma; prothrombin complex concentrate

Haemostasis is a natural defence against vascular injury and haemorrhage.[1] It consists of multiple phases involving both cellular and humoral elements of coagulation (Fig. 1).[2] In the presence of coagulopathy after major trauma and surgery, haemostasis management becomes a major challenge for anaesthesiologists and intensivists.[3–6] The haemostatic defect in perioperative patients is often multifactorial, and coagulation status can deteriorate rapidly. It is thus important to address this problem with comprehensive clinical assessments of coagulopathy, and timely administration of haemostatic therapy.[6–9]

Transfusion of plasma and platelets has been the mainstay of haemostatic therapy for many decades. However, the timing of transfusion is difficult to control, particularly because blood components and laboratory test results are often unavailable in a timely fashion. Delayed decision and administration of transfusion can exacerbate coagulopathy, and potentially affect clinical outcomes. However, premature and overzealous use of haemostatic agents can be equally harmful.[10] For a number of hereditary coagulation factor deficiencies, plasma-derived or recombinant factor concentrates are available to replace the deficient factor(s) without using plasma.[11] The US FDA has recently approved a concentrate of vitamin K-dependent factors for the management of bleeding in patients treated with vitamin K antagonists (e.g. warfarin).[12] When managing perioperative bleeding, these factor concentrates can be more effective than allogeneic plasma, but inappropriate use can be costly and associated with worsening haemorrhage or thromboembolic complications. This article reviews current limitations of plasma transfusion, current concepts of coagulation monitoring, and the roles of factor concentrates as a perioperative therapy for haemostasis and thrombosis.

Plasma transfusion

In the case of perioperative bleeding, transfusion of fresh-frozen plasma (FFP; plasma frozen within 8 h) or frozen plasma (FP24; plasma frozen at 8–24 h after collection) is considered a life-saving measure. Thawed FFP and FP24 contain variable, but near-normal, levels of procoagulant proteins, coagulation inhibitors, albumin, and immunoglobulins.[13 14] For example, if fibrinogen is 2 g litre^{-1} in a unit of plasma (0.25 litre), it is equivalent to 0.5 g of fibrinogen. However, plasma fibrinogen increases by only 0.4 g litre^{-1} after 1 litre of plasma transfusion (median 12.2 ml kg^{-1}) in critically ill patients with bleeding or at risk for bleeding.[15] As much as 2.5 litre of plasma transfusion (median 33.5 ml kg^{-1}) is required to sufficiently increase fibrinogen by 1 g litre^{-1}. This is because the volume of plasma is added to the circulating blood, and as such, fibrinogen is distributed in a larger volume of plasma. Large volumes of plasma transfusion are not tolerated in patients with limited cardiopulmonary reserve, and can be associated with transfusion-associated circulatory overload.[16 17] In addition, transfusion-related acute lung injury (TRALI) is a potentially lethal complication of plasma transfusion, although



Event	Vascular injury Bleeding	Primary haemostasis Localization of factors	Thrombin generation Fibrin polymerization
Elements	Collagen Tissue factor	Platelets (GPIb) vWF FVII, FX, FII	Platelets (GPIIb/IIIa) (S) Fibrinogen (E) FII, FIX, FX, FXI, FXIII (A) FV, FVIII
Interventions	RBCs	Platelets Cryoprecipitate vWF concentrate Desmopressin	FFP, PCC Cryoprecipitate Fibrinogen FXIII concentrate rFVIIa

Fig 1 Haemostatic processes *in vivo* and phase-specific interventions. (A) Haemorrhage occurs after vascular injury. Extravascular (subendothelial) collagen and tissue factor are exposed to flowing blood. Transfusion of red blood cells (RBCs) is the initial intervention. Blue, intact vascular wall; white oval, platelets; red circle, erythrocytes; green, fibrin. (B) Platelets adhere to the vascular injury site by interacting with vWF via glycoprotein (GP) Ib/IX receptors. Mural platelets are activated by collagen and trace thrombin (via extrinsic pathway). They release adenosine-5′-diphosphate and thromboxane, aggregating more platelets in the vicinity. Thus, the primary (haemostatic) plug is established. Platelet transfusion and measures to elevate vWF can augment this process. (C) Activated platelet aggregates serve as a catalytic surface and binding sites for coagulation responses. Substrates (fibrinogen), pro-enzymatic factors (FII, FIX, FX, FXI, FXIII), and accelerators (FV, FVIII) are congregated (depicted as S-E-A). These factors can be replaced by either plasma (FFP) or specific factor concentrates (see text for details). Reprinted with permission from Tanaka and colleagues.[2]

the incidence has recently declined from 1:5000 in 2006 to 1:12 000 in 2009 by preferential use of male donor plasma.[18 19]

Variable amounts of immunoglobulins, inflammatory cytokines, and cellular debris are also undesirable contents of allogeneic plasma.[20 21] The volume of plasma transfusion might not be an issue when it is transfused early in the case of massive haemorrhage without excess resuscitative fluids (crystalloids and colloids).[4 22 23] In haemorrhagic shock, plasma transfusion appears to have protective effects on endothelial glycocalyx and syndecan-1, reducing vascular permeability.[24] However, plasma transfusion at a fixed ratio with erythrocytes has not always yielded improved clinical outcomes, indicating some efficacy and safety limitations.[25 26]

The efficacy of plasma transfusion is affected not only by the dose, but also by the timing of intervention. Commonly used laboratory haemostasis assessment includes prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level (Clauss method), and platelet count. Typical turnaround time (TAT; time from specimen collection to result availability) for these tests is in the range of 30–90 min, which is not optimal in diagnosing coagulopathy or guiding haemostatic interventions. This is particularly an issue when multiple units of FFP/FP24 must be thawed according to the laboratory data, which adds 30–60 min of processing time. Delays in haemostatic intervention could have serious consequences in the case of bleeding involving vital organs (e.g. cerebral haemorrhage).[27 28]

Point-of-care coagulation testing

Rapid TAT (<15 min) for PT/INR and fibrinogen level[29] and prethawed plasma (type AB or A) have been utilized at major trauma centres in the North America to facilitate timely transfusion,[13] but their availabilities are limited elsewhere.[30] Alternative approaches to conventional laboratory diagnosis and transfusion of haemostatic components (FFP/FP24, platelets, and cryoprecipitate) have emerged in Europe since 2005.[31] The primary approach to perioperative diagnosis of coagulopathy is point-of-care (POC) testing using rotational thromboelastometry (ROTEM®) or thrombelastography (TEG®).[32 33] Viscoelastic properties of clotting in whole blood assessed by ROTEM® and TEG® are highly dependent on thrombin-