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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

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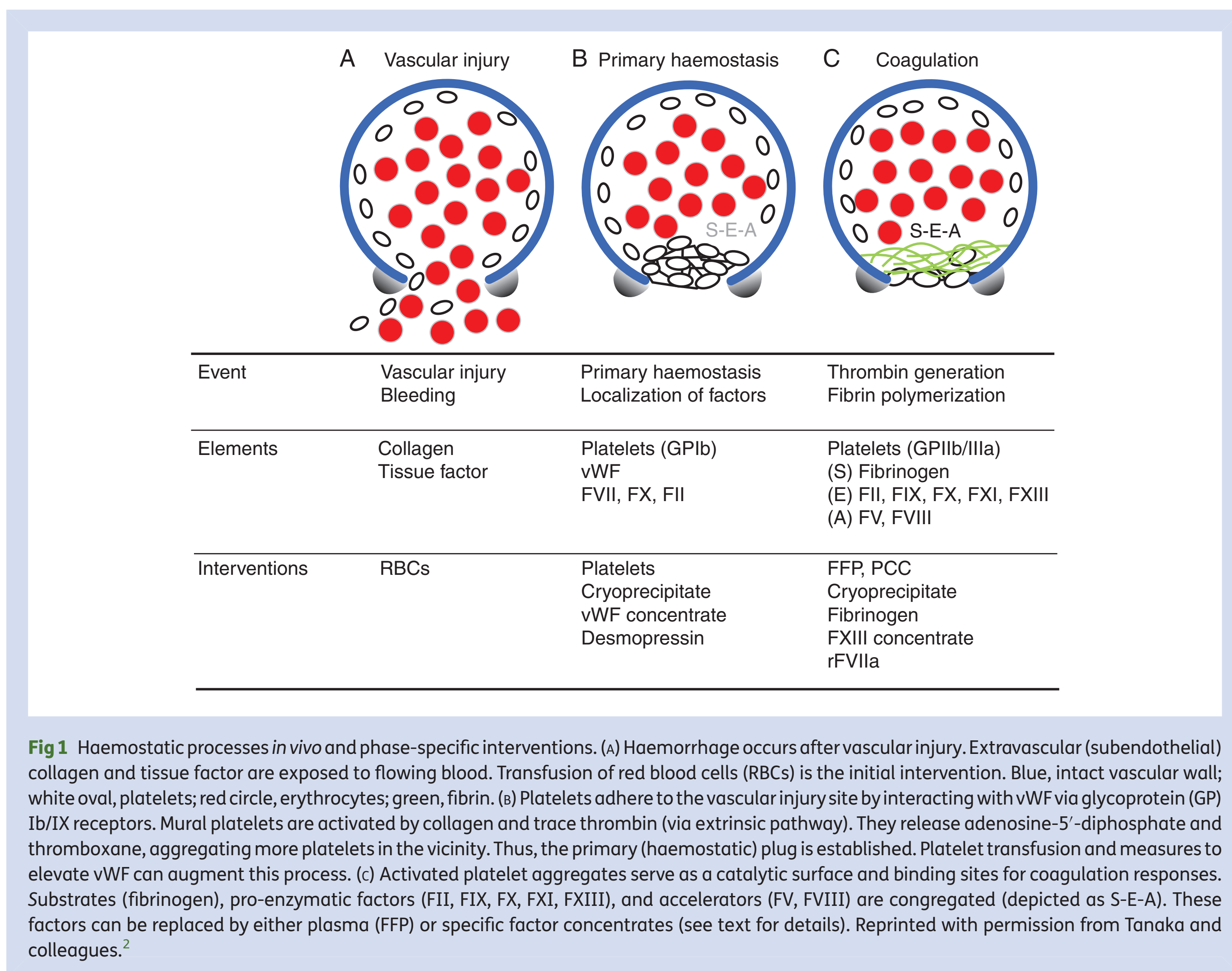

Event	Vascular injury Bleeding	Primary haemostasis Localization of factors	Thrombin generation Fibrin polymerization
Elements	Collagen Tissue factor	Platelets (GPIb) vWF FVII, FX, FII	Platelets (GPIIb/IIIa) (S) Fibrinogen (E) FII, FIX, FX, FXI, FXIII (A) FV, FVIII
Interventions	RBCs	Platelets Cryoprecipitate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

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mediated fibrin formation and its polymerization. The extent of fibrin polymerization has become an important endpoint in perioperative haemostatic management after FIBTEM became routinely used in ROTEM®.[2 34–36] As demonstrated in the examples of thromboelastometric tracings (Fig. 2), early amplitudes (A10) or maximum clot firmness (MCF) of EXTEM and FIBTEM can be used for rapid diagnosis (<15–20 min) of dysfunctional fibrin polymerization, and systemic fibrinolysis.[2 37] Conventional kaolin-TEG® using α-angle is affected by both platelet count and fibrinogen concentration,[38] and functional fibrinogen assay is considered more specific than TEG®-based detection of hypofibrinogenaemia.[39] On the contrary, fibrin clot firmness cannot be assessed by PT, aPTT, or fibrinogen level, and prolonged PT and aPTT are poor predictors of bleeding and plasma transfusion.[40–42] Large amounts of plasma transfusion are required to affect clot firmness in ROTEM® and TEG®,[42 43] and fibrinogen-rich components have recently become the major focus of haemostatic therapy guided by viscoelastic coagulation monitors.[44]

Fibrinogen-rich components

Historical aspects

The prototype of cryoprecipitate dates back to 1956 when a product called fraction I-O was extracted by Blomback[45] from plasma in the presence of glycine in 6.5% ethanol at −3°C. This fraction was used to treat fibrinogen deficiency, haemophilia A (FVIII deficiency), and an unidentified bleeding disorder at that time [von Willebrand disease (vWD)]. A method to produce cryoprecipitate was developed in 1964 by Pool,

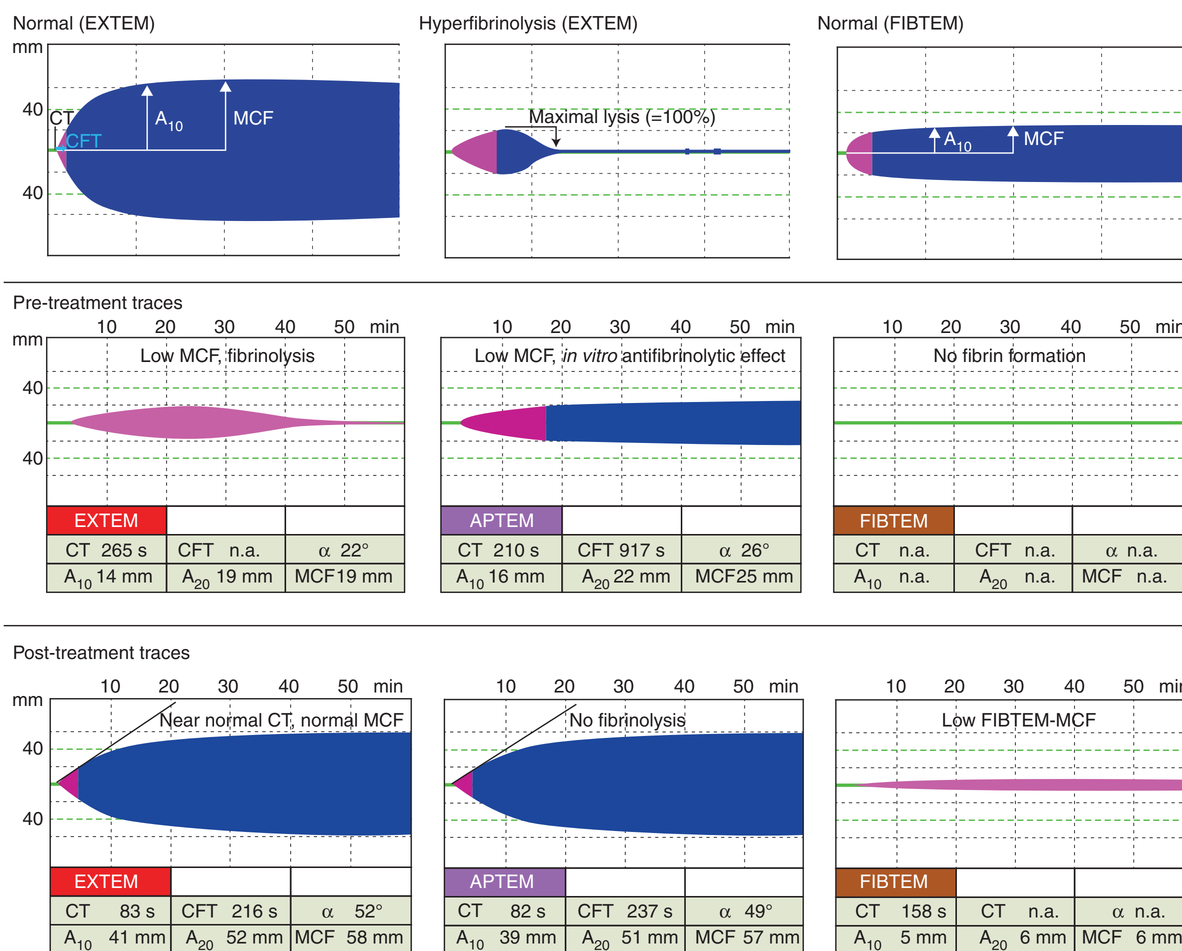

Fig 2 Examples of rotational thromboelastometric tracings. EXTEM reflects the pattern of whole blood clotting, which is triggered by tissue factor. On the FIBTEM test, fibrin-specific clotting after tissue factor activation is demonstrated by inhibiting platelet–fibrin interactions with cytochalasin D.[2] Normal ranges for EXTEM and FIBTEM are as follows; EXTEM-CT 35–80 s, clot formation time (CFT) 35–160, angle 63–81°, A10 50–71 mm, MCF 53–72 mm; FIBTEM-A10 7–23 mm, MCF 9–25 mm.[33] Pre-treatment: traces obtained from a bleeding patient who incurred major blunt trauma. Prolonged CT and early clot breakdown are notable on EXTEM. Fibrinolysis is corrected *in vitro* on APTEM, but CT and amplitude remain abnormal. Severe hypofibrinogenaemia and fibrin breakdown are also observed on FIBTEM. Post-treatment: after treatment with 2 g of tranexamic acid i.v., and transfusion of 20 units cryoprecipitate and 1 units apheresis platelets, CT is nearly normal, and MCF is within normal range on EXTEM. Hyperfibrinolysis is no longer detected (EXTEM = APTEM). Fibrin polymerization is improving, but FIBTEM-MCF remains below normal range.

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who discovered that slowly thawed FFP leaves behind a cold-insoluble precipitate, which contains fibrinogen, FVIII, von Willebrand factor (vWF), and FXIII.[46 47] High volumes of plasma transfusion in haemophilia A patients were obviated by the use of Pool's cryoprecipitate. Although plasma-derived factor concentrates and recombinant proteins have become the standard for the treatment of haemophilia A and vWD, cryoprecipitate has been the mainstay therapy for fibrinogen replacement in congenital and perioperative fibrinogen deficiency in North America. In European countries where cryoprecipitate is unavailable, plasma-derived fibrinogen concentrate (RiaStap®/Haemocomplettan®; CSL Behring, Marburg, Germany) has been approved for both congenital and acquired indications.[44 48] In the USA, plasma-derived fibrinogen has been utilized for many years as a key ingredient for topical fibrin sealants,[49] but i.v. injection of fibrinogen concentrate has only recently been approved by the FDA for the treatment of congenital afibrinogenaemia or hypofibrinogenaemia.[50]

Human plasma-derived fibrinogen concentrate

The characteristics of fibrinogen concentrate, cryoprecipitate, and FFP/FP24 are summarized in Table 1. In contrast to FFP/FP24, fibrinogen concentrate and cryoprecipitate are fractionated (secondary) components of blood, and can be accepted by Jehovah's Witness patients.[51] Fibrinogen concentrate is a lyophilized product, and can be stored at room temperature (<25°C) for up to 30 months.[50] It can be quickly reconstituted and administered intravenously because no thawing or blood type matching is required.[52] In contrast to cryoprecipitate or FFP/FP24, in which fibrinogen content varies, fibrinogen content is standardized in each vial of fibrinogen concentrate (900–1300 mg per vial).[50] Therefore, fibrinogen concentrate (~1000 mg in 50 ml) should be as effective as cryoprecipitate (~300 mg in 20 ml),[53] and superior to FFP/FP24 (~250 mg in 100 ml)[43 47] for fibrinogen replacement. Testing of donor plasma for viral pathogens has reduced the risk of viral transmission with cryoprecipitate and plasma-derived factor concentrate. Pasteurization (60°C for 2 h) and sterile filtrations are applied to fibrinogen concentrate,[54] further reducing the risk of pathogen transmission.[55] The lack of major antibodies in the concentrate reduces the risk of TRALI.

Perioperative hypofibrinogenaemia and monitoring fibrinogen level

Hypofibrinogenaemia is linked to bleeding by several mechanisms (Fig. 1). In primary haemostasis, fibrinogen is crucial in stabilizing vWF-mediated platelet–platelet interactions, and hypofibrinogenaemia results in the formation of small, unstable platelet thrombi.[56 57] In secondary haemostasis, fibrinogen-stabilized platelet thrombi provide a catalytic surface for thrombin generation.[1] Platelet-bound fibrinogen is subsequently converted to fibrin monomer by thrombin, and fibrin monomers are polymerized by thrombin-activated FXIII, a transglutaminase.[44] Paradoxically, hypofibrinogenaemia is associated with thromboembolic complications.[58 59] Plausible mechanisms for this include unstable platelet thrombi,[57] reduced sealing of injured vascular wall,[60] and systemic release of thrombin and FXa.[61] Fibrin is historically referred to as 'antithrombin I' due to these antithrombotic actions.[58 59]

Target plasma fibrinogen level is usually set at 1 g litre^{-1} in congenital fibrinogen deficiency,[62] and similar target levels (0.8–1 g litre^{-1}) have been used for acquired deficiency in the perioperative setting.[3] However, higher thresholds (1.5–2 g litre^{-1}) have been recommended in recent European transfusion guidelines.[3 63] These changes reflect emerging clinical data supporting early fibrinogen replacement and higher

Table 1 Characteristics of plasma, cryoprecipitate, and fibrinogen. TRALI, transfusion-related acute lung injury; FFP, fresh-frozen plasma; FP24, plasma frozen within 24 h; IU, international unit of activity. *Pre-thawed plasma (type AB or A) may be available at major trauma centres in North America. †Pathogen-reduced plasma products are available in North America and European countries

	FFP/FP24[14]	Cryoprecipitate[47]	Plasma-derived fibrinogen (RiaStap®/Haemocomplettan®)[50]
Fibrinogen content per vial or unit	0.5 g	0.3 g	0.9–1.3 g
Volume per vial or unit	250 ml per unit	20 ml per unit	50 ml per vial
Factor concentration	Fibrinogen ~2 g litre^{-1} All other factors in variable amounts (0.5–1.5 IU ml^{-1})	Fibrinogen ~15 g litre^{-1} Factor XIII 2.8 IU ml^{-1} Factor VIII 6.3 IU ml^{-1} vWF 8.0 IU ml^{-1}	Fibrinogen 20 g litre^{-1} Factor XIII 1 IU ml^{-1}
Pre-transfusion procedures	Thawing* Blood-type compatibility	Thawing Blood-type compatibility	Mixing with 50 ml diluent Blood-type free
Storage	Frozen	Frozen	Store at room temp. <25°C
Shelf-life	12 months	12 months	30 months
Pathogen reduction	Donor testing†	Donor testing	Precipitation/adsorption, heat-treated for viral inactivation
Other considerations	Immunoglobulins, cytokines, cell debris	Immunoglobulins, cytokines, cell debris	Minimal immunoglobulins (low TRALI risk)

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target levels after major trauma, perioperative blood loss, and haemodilution.[34 35 48 64]

Owing to unpredictable TAT of plasma fibrinogen assay, POC assessment of fibrinogen function is preferred in the surgical setting; the ROTEM®-based FIBTEM assay is most commonly utilized.[39 65] There are no universally accepted FIBTEM cut-off values for fibrinogen replacement; target fibrinogen levels are different depending on the type and extent of vascular damage (arterial or venous), and levels of other haematological factors (thrombin generation, red blood cell volume, platelet function, etc.).[60] In most adult cardiac surgical patients, a target range of 8–10 mm has been used for FIBTEM-MCF (or A10);[48 66–68] this range roughly corresponds to plasma fibrinogen of 1.5–2 g litre^{-1}.[69]

There are some practical considerations for the use of fibrinogen in surgical patients. First, haemostatic efficacy of fibrinogen depends on enzymatic processes, including platelet activation, endogenous thrombin generation, and activated FXIII-mediated polymerization. The use of fibrinogen at early stages of bleeding appears to work well because enzymatic functions are still intact.[34 35 48 64 70] However, fibrinogen replacement *per se* might be insufficient in the case of advanced or late coagulopathy affecting platelets, proenzymes, and the fibrinolytic system.[35 36 48 60 71 72] In contrast to cryoprecipitate, FXIII is not effectively replaced after fibrinogen infusion (Table 1), and separate FXIII infusion is required in some cases.[73] Hyperfibrinolysis cannot be readily diagnosed by plasma fibrinogen level or PT/aPTT.[74] Profibrinolytic state renders fibrinogen replacement ineffective, so it should be monitored by viscoelastic tests, and antifibrinolytic therapy (tranexamic acid or ε-aminocaproic acid) should be considered (Fig. 2).

Dosing of fibrinogen concentrate

In bleeding associated with acquired hypofibrinogenaemia in adults, plasma fibrinogen is increased by 0.25–0.28 g litre^{-1} (median) per 1 g of fibrinogen administration.[75 76] Gorlinger and colleagues[77] reported that a 25 mg kg^{-1} dose of fibrinogen in an 80 kg patient (total 2 g of fibrinogen) results in a 4 mm increase in FIBTEM-MCF (or A10). An average fibrinogen dose of 7.6 mg kg^{-1} (0.38 ml kg^{-1} vol) is required to increase FIBTEM-MCF by 1 mm in adult cardiac surgical patients with bleeding.[52] In contrast, 11–13 ml kg^{-1} of plasma is required to increase FIBTEM-MCF by 1–1.5 mm.

The dose of fibrinogen concentrate is approximated by the following formula:

$$\text{Dose} = \frac{[\text{target FIBTEM-MCF (mm)} - \text{current FIBTEM-MCF (mm)}] \times \text{weight (kg)}}{140}$$

For example, if the FIBTEM-MCF were 6 mm in a 70 kg patient with clinical bleeding, and the target FIBTEM-MCF were 10 mm, the dose of fibrinogen can be calculated to be:

$$\text{Dose} = \frac{(10-6)\times 70}{140} = 2\ \text{g}$$

A similar calculation can be also applied to calculate the number of pooled units for cryoprecipitate by using a factor of 5 (assuming 1 g of fibrinogen in 5 pooled units of cryoprecipitate):

$$\text{Pooled units of cryoprecipitate} = \frac{(10-6)\times 70}{140} \times 5 = 10\,\text{U}$$

Titrating the dose of fibrinogen concentrate and cryoprecipitate is important in reducing wastage, and potential thromboembolic complications.

Contraindications and adverse reactions

Contraindications to fibrinogen concentrate transfusion include a previous history of anaphylactic reaction to the concentrate,[12] and ongoing (or suspected) thrombosis, or myocardial infarction.[78] Adverse reactions associated with fibrinogen concentrate are most commonly fever and headache, but anaphylactic reactions, deep vein thrombosis, pulmonary embolism, and myocardial infarction are potential risks. Thromboembolic complications directly associated with fibrinogen concentrate seem to be infrequent according to post-market surveillance data. Total usage of fibrinogen over 22 yr has amounted to 1 034 389 g, equivalent to 250 000 doses of 4 g fibrinogen. The rate of thrombosis was estimated to be 3.48 events per 10^5 treatments.[79] However, actual incidence of thromboembolic complications could be underreported, and it is often difficult to prove a causal relationship when multiple haemostatic agents are simultaneously administered.

No case of pathogen transmission has been reported for fibrinogen concentrate that undergoes pasteurization (60°C for 2 h) and sterile filtrations.[55]

Prothrombin complex concentrate

Historical aspects

Prothrombin complex concentrates (PCCs) are lyophilized, human plasma-derived vitamin K-dependent factors containing FII (prothrombin), FVII, FIX, and FX. PCCs were originally used for FIX replacement in patients with haemophilia B.[80] The potency of PCC is standardized to FIX content [~500 international unit (IU) per vial]. Lyophilized PCC can be quickly administered in a low volume (typically, 20–100 ml), and is more effective than plasma in restoring FIX activity. However, repeated administration of PCC to maintain FIX activity in haemophilia B patients results in accumulation of prothrombin and FX due to their long half-lives (40–72 h). Excessive thrombin generation might have occurred in haemophilia B patients when FIX was added to a supra-physiological level of prothrombin.[81] Venous thromboembolic events (VTE), pulmonary embolism, and disseminated intravascular coagulation (DIC) have been reported in haemophilia B after repeated doses of PCC since the 1960s.[82] These complications occur far less frequently since the introduction of plasma-derived FIX concentrate, and more recently recombinant FIX for the treatment of haemophilia B.

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PCCs for acute reversal of warfarin

Acute reversal of warfarin using FFP/FP24 is difficult and time-consuming in the case of bleeding complications or emergency surgery.[27 83] Two commercial PCC products are mainly indicated for the reversal of warfarin anticoagulation. Kcentra® (referred to as Beriplex® in Europe; CSL Behring) has been recently approved by the FDA, and Octaplex® (Octapharma, Lachen, Switzerland) is expected to be approved soon. These and other PCCs have been available in Europe and elsewhere for some years.[84] These PCCs contain therapeutic amounts of prothrombin, FVII, FIX, and FX (thus four-factor PCC), and various amounts of protein C, protein S, and protein Z.[81 84–86] Other commercially available PCCs are Bebulin® (Baxter, Westlake Village, CA, USA) and Profilnine® (Grifols, Los Angeles, CA, USA). These are referred to as three-factor PCC, because of low amounts of FVII relative to FII, FIX, and FX (Table 2).

The use of four-factor PCC is preferred for very high INRs (>4–5) when FVII levels are extremely low (<5%).[87 88] Recombinant activated FVII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsbaerd, Denmark) has been used in an attempt to normalize INR in warfarin-treated patients. However, rFVIIa is only effective in shortening PT/INR, and does not restore thrombin generation due to the absence of FII and FX.[89 90] The use of rFVIIa is no longer recommended for warfarin reversal[91] unless it is used (1–2 mg i.v.) in combination with three-factor PCC.[87 88] Another type of PCC is a haemophilia bypassing agent, factor VIII bypassing agent (FEIBA; Baxter, West Lake Village, CA, USA), which contains prothrombin, FIX, FX, and activated FVII (in addition to traces of thrombin, FIXa, and FXa).[92] FEIBA has also been used for acute warfarin reversal;[93] such use should be cautioned because of underlying thrombophilic issues in warfarin-treated patients (see recent reviews regarding the perioperative implications of rFVIIa[94] and FEIBA[92]). PCCs and FEIBA are considered as a fractionated (secondary) component of blood, and they can be accepted by Jehovah's Witness patients along with recombinant proteins (e.g. erythropoietin, rFVIIa).[51]

PCCs along with FEIBA and rFVIIa have been suggested as a potential reversal agent for novel oral anti-Xa agents (e.g. apixaban, edoxaban, rivaroxaban).[95] However, the supportive data are limited to *in vitro* and animal studies, and *in vivo* haemostatic efficacy of PCCs has not been proven in bleeding patients treated with anti-Xa agents.

Table 2 Prothrombin complex concentrates. Data indicate relative contents of vitamin K-dependent factors for different PCCs. The per cent (%) activity of each factor is shown relative to FIX activity (based on the prescribing information for each product; actual factor contents may vary for each vial). Manufacturers are as follows: Kcentra®/Beriplex® (CSL Behring, Marburg, Germany), Octaplex® (Octapharma, Lachen, Switzerland), Bebulin® (Baxter, Westlake Village, CA, USA), Profilnine® (Grifols, Los Angeles, CA, USA), and Cofact® (Sanquin, Amsterdam, The Netherlands). Other PCC products are also available in different countries. Protein C/S, protein C/protein S; AT, antithrombin; NR, not reported; Yes, contains therapeutic amounts[11]

Product name	FII	FVII	FIX	FX	Protein C/S	Additive
Kcentra®/ Beriplex®	111	57	100	150	Yes	Heparin, AT
Octaplex®	98	66	100	96	Yes	Heparin
Bebulin®	120	13	100	139	NR	Heparin
Profilnine®	148	11	100	64	NR	No heparin
Cofact®	106	48	100	103	Yes	No heparin

Dosing of PCC

Haemostatic efficacy and pharmacological activity of four-factor PCC compared with FFP have been shown in the multi-centre prospective randomized study of Kcentra® and FFP in warfarin-treated adult patients (INR>2.0) undergoing urgent surgery or invasive procedures (Table 3).[12] I.V. vitamin K (5–10 mg) was administered to both treatment arms. Clinical haemostasis over 24 h was judged to be effective in 72.4% (71/98) with Kcentra® (median infused volume 90 ml), and 65.4% (68/104) with FFP transfusion (i.e. PCC was non-inferior to FFP).[96] The percentage of cases in which INR was reduced to ≤1.3 after 30 min of intervention was clearly higher with Kcentra® than with FFP: 62.2% (61/98) *vs* 9.6% (10/104).

Pharmacological data clearly demonstrate the rapid normalization of vitamin K-dependent factors within 30 min using PCC, while it takes a minimum of 3 h for plasma transfusion (and vitamin K) to bring procoagulant levels to ≥50% (Fig. 3).[96] Prothrombin (FII) and FX are replenished to 80–100% activity, and maintained for 24 h by PCC compared with plasma. These proteins have long half-lives (40–72 h), and their hepatic production cannot be acutely increased by vitamin K administration. Plasma levels of FVII and FIX were increased to 60–80% of normal immediately after PCC, but the differences from plasma transfusion became smaller after 12 h due to vitamin K-stimulated endogenous production. Similar findings were found for the anticoagulant proteins, protein C, and protein S (Fig. 3).[96]

Table 3 Treatments for acute warfarin reversal for the Kcentra® study. This table indicates the study protocol from the Kcentra® study.[96] IU, international unit of factor IX; vit K, vitamin K

INR	PCC treatment (i.v.)	Plasma transfusion (i.v.)
2.0–3.9	PCC 25 IU kg^{-1}+vit K 5–10 mg	Plasma 10 ml kg^{-1}+vit K 5–10 mg
4.0–5.9	PCC 35 IU kg^{-1}+vit K 5–10 mg	Plasma 12 ml kg^{-1}+vit K 5–10 mg
≥6.0	PCC 50 IU kg^{-1}+vit K 5–10 mg	Plasma 15 ml kg^{-1}+vit K 5–10 mg

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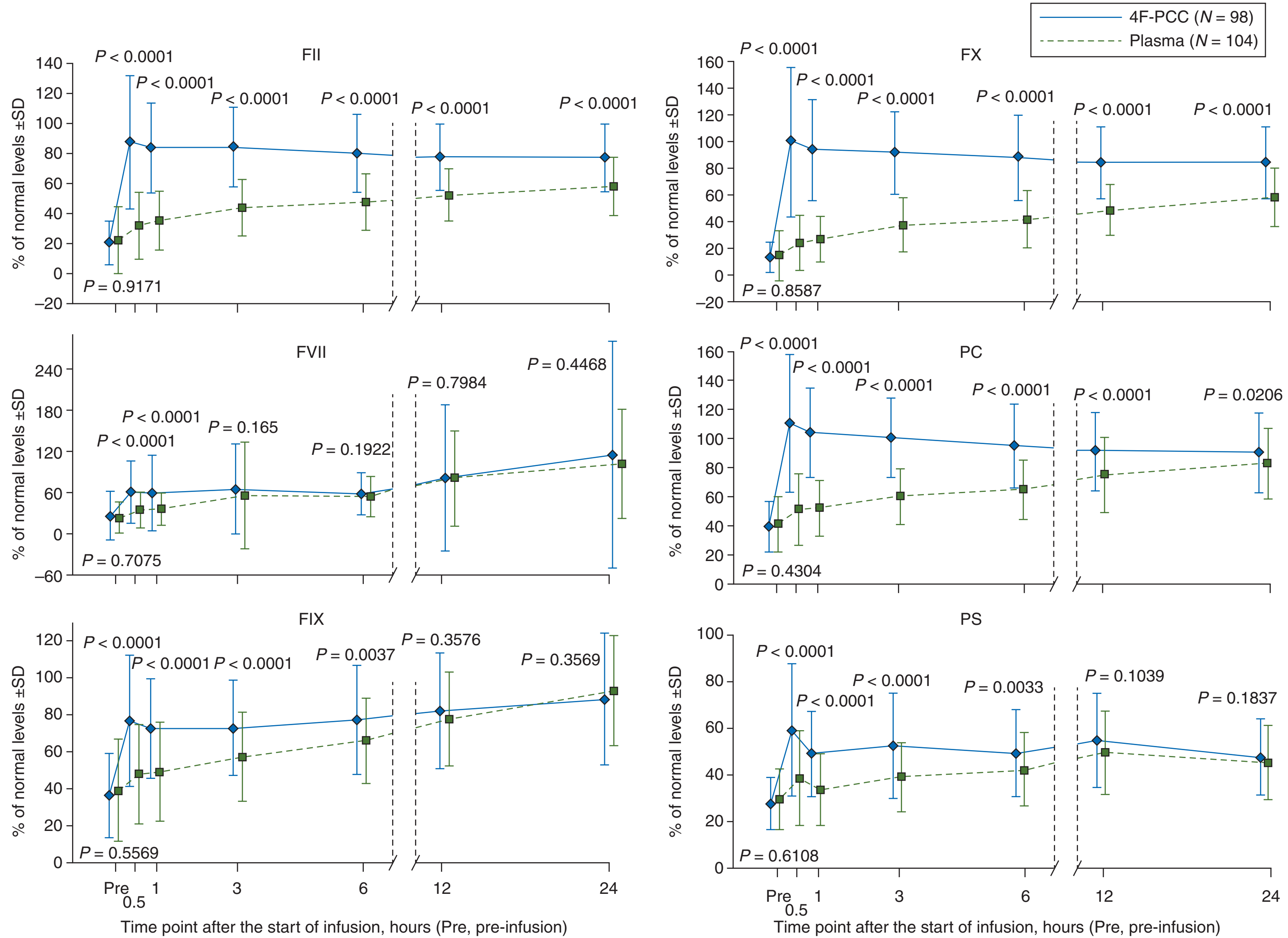

Fig 3 Coagulation factor levels in warfarin-treated patients who received four-factor PCC or plasma transfusion. The mean plasma coagulation factor levels [% of normal activity (SD)] for FII (prothrombin), FVII, FIX, FX, protein C (PC), and protein S (PS) are shown over 24 h after the injection of four-factor PCC (4F-PCC) or plasma transfusion.[96] The elapsed time (h) from the treatment is indicated on the horizontal axis. Pre, baseline; F, factor. *P*-values indicate the significant difference in protein levels between the groups.

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The current indication for four-factor PCC is limited to warfarin-related bleeding, but various PCCs have been utilized in acquired, non-warfarin coagulopathy in major trauma and surgical patients (an off-label indication in North America and Europe).[35 36 48 68] The fibrin polymerization defect is the primary target of this haemostatic intervention, and the enzymatic defect is addressed after hypofibrinogenaemia and fibrinolysis (if any) are corrected according to ROTEM® assays.[6 35 36 48 68] Prolonged clotting time (CT) on EXTEM over 80–100 s (normal 35–80 s) is used as a cut-off for haemostatic intervention with PCC. Lance and colleagues[97] and Tanaka and colleagues[72] recently demonstrated that prothrombin and FX can be decreased to 30–40% of normal after perioperative haemodilution, and bleeding diathesis can continue after fibrinogen replacement. The rationale for using ROTEM®-based assessment in decisions to transfuse PCC, fibrinogen concentrate, or both has been prospectively evaluated by Weber and colleagues[48] compared with centralized laboratory testing in cardiac surgical patients. Four-factor PCC (25 IU kg^{-1}) was administered in the presence of prolonged EXTEM-CT (>80 s) and normal fibrin formation, while plasma or PCC was given if INR >1.4 or after 4 units of erythrocytes was transfused (if INR was unavailable) in the cohort evaluated with laboratory tests. The incidence of plasma transfusion was reduced by half (40% *vs* 80% $P<0.001$) using thromboelastometry guidance. The use of PCC was similar between thromboelastometry and centralized laboratory testing (44% *vs* 52% $P=0.433$). In the collective data analysis from two prospective randomized studies[48 67] and one case–control study[68] in which factor concentrates were part of a transfusion protocol, transfusions of erythrocytes and plasma were reduced, and the use of PCC and rFVIIa were effectively controlled by thromboelastometry (Fig. 4). The use of ROTEM® or TEG® generally results in less plasma transfusion with or without factor concentrates.[98]

Although PCC infusion or plasma transfusion guided by ROTEM® or TEG® is an attractive concept in the management of vitamin K-dependent factor deficiency, there are some precautions. First, the CT of ROTEM® and reaction time of TEG® do not have the same operating characteristics with PT or aPTT.[7 99–101] PT/INR is more standardized than ROTEM® or TEG® for warfarin reversal using four-factor PCCs.[85 86] Kaolin-based reaction time (>8 min) by TEG® was less predictive of vitamin K-dependent factor deficiency (≤50% of normal) compared with an INR >1.5 (positive predictive value, 47% and 84%, respectively).[102] Secondly, optimal cut-off values of ROTEM®-CT and TEG®-reaction time have not been systematically evaluated or standardized.[36 48 68 103 104] Lastly, available haemostatic products vary among different institutions and countries. For example, a timely correction of fibrinogen or vitamin K-dependent factors is difficult when plasma transfusion is the only available source for these factors.

Contraindications and adverse reactions

Thromboembolic complication is a possible risk of PCCs. In a recent meta-analysis of 27 studies (1032 patients) including both three-factor and four-factor PCCs for the reversal of vitamin K antagonists, the overall incidence of thromboembolic complications was 1.4% (95% CI, 0.8–2.1).[105] The use of PCCs was rarely the direct cause of death, but total mortality rate was 10.6%, indicating that patients who received PCCs were often very ill. A low risk of thromboembolic events (1:~31 000) was also described in the pharmacovigilance study of Beriplex®.[106] The lack of major antibodies in PCCs reduces the risk of TRALI.

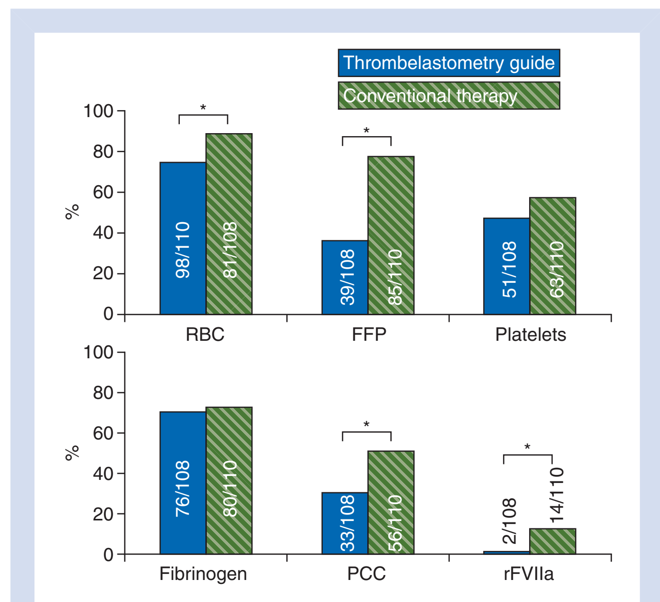

Fig 4 Frequencies of allogeneic blood component transfusion and usage of factor concentrates. Data shown are the percentage of patients who received transfusions of red blood cell (RBC) concentrates, FFP, and platelets in conjunction with fibrinogen concentrate, PCC, or recombinant factor VIIa (rFVIIa) in two randomized controlled studies,[48 67] and in a recent matched case–control trial.[68] Numbers within the columns indicate the number of patients receiving transfusion (or infusion)/total number of patients. Decreased transfusions of RBCs and FFP, and less frequent uses of PCC and rFVIIa were observed in the thromboelastometry-guided group compared with the conventional group (*$P<0.05$ by χ^2 test).

The use of PCCs is contraindicated in the case of ongoing DIC.[78] PCCs are known to increase prothrombin and FX levels (half-lives, 40–72 h) in a dose-dependent manner, and the balance of procoagulant and anticoagulant proteins can be shifted towards a hypercoagulable state.

Most PCCs contain subtherapeutic amounts of heparin and antithrombin (AT), although some contain therapeutic amounts of protein C, protein S, and protein Z.[84] Grottke and colleagues[107] reported that a single dose of PCC (50 IU kg^{-1}; Cofact, Sanquin, Amsterdam, The Netherlands) was associated with multiple pulmonary microcapillary thrombi and signs of DIC (44%) in a porcine model of haemodilution and hepatic injury. Blood loss was reduced in animals that received the lower dose (35 IU kg^{-1}), or in those that did not develop DIC after a dose of 50 IU kg^{-1}. In DIC animals, haemostasis was not improved, while plasma AT activity progressively declined to 20%, and thrombin–AT complex levels continued to increase

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over 2 h. In PCC-treated animals with improved haemostasis, thrombin generation was well regulated as shown in stable AT activity, and limited increases in thrombin–AT complexes. Taken together, based on this animal study, there could be an increased risk of thromboembolic complications when PCCs are administered in haemodiluted, AT-deficient patients. If AT deficiency is suspected (e.g. liver dysfunction) or known (e.g. hereditary AT deficiency), lower doses of PCCs or AT replacement should be considered, but there is no standardized protocol.

Trace amounts (4–75 units per 10 ml vial) of heparin contained in some PCCs make them contraindicated in patients with heparin-induced thrombocytopenia (HIT), but no such case has been reported to date.[106] Notably, Profilnine, Cofact, FEIBA, and rFVIIa do not contain heparin.

AT concentrate

Physiological roles of AT

AT (formerly AT-III) is a 58 kDa glycoprotein that belongs to a family of serine protease inhibitors. AT is synthesized in the liver, and its plasma half-life is 2.5–3.8 days. The primary targets of AT are serine proteases, thrombin (FIIa), and FXa, which are being constantly generated (i.e. idling state) in the circulation. In asymptomatic patients with hereditary AT deficiency (AT activity, 40–60% of normal), prothrombin fragment 1.2 levels (a marker of thrombin activation by FXa) are twice as high as in those in normal subjects (AT activity, 80–120%). The risk of VTE is inversely proportional to plasma AT activity according to the recent population data from Italy.[108] After adjusting for age, gender, body mass index, and hereditary thrombophilia (6% in patients and 1% in controls), the odds ratio for VTE in individuals with AT activity 45–60% of normal was 7.74-fold higher than for those with AT activity >100%. Similar increases in VTE are also associated with nominal decreases in protein C and protein S activities. These data indicate that both hereditary and acquired deficiencies of natural anticoagulants are important risk modifiers of VTE.

Table 4 Acquired AT deficiencies

Iatrogenic AT deficiency
Prolonged heparin infusion
L-asparaginase
AT consumption
Surgery/trauma
Extensive cell salvage use
Haemolytic uraemic syndrome
Sepsis/disseminated intravascular coagulation (DIC)
Preeclampsia
Heparin-induced thrombocytopenia
Decreased AT synthesis
Liver dysfunction
Malnutrition
Prematurity/neonates–infants (up to 6 months)
Increased AT excretion
Nephrotic syndrome
Inflammatory bowel disease

The prevalence of hereditary AT deficiency is estimated to be one in 2000–5000, but acquired deficiency is more frequently diagnosed in clinical practice (Table 4). In cardiovascular patients receiving prolonged heparin infusion (>4–5 days), plasma AT activity decreases progressively to 50–60% of normal. Heparin resistance (or insensitivity) is clinically diagnosed by increased heparin dose requirement, and suboptimal values of aPTT or activated CT (ACT).[109 110] Heparin, low-molecular heparin, and fondaparinux are AT-dependent anticoagulants; therefore, AT deficiency diminishes their antithrombotic efficacies.[111 112]

Currently, plasma-derived AT concentrate (Thrombate III®; Grifols)[113] and recombinant human AT concentrate (ATryn®; rEVO Biologics, Framingham, MA, USA)[114] are commercially available (Table 5). Atenativ (Octapharma, Lachen, Switzerland) and Kybernin (CSL Behring) are plasma-derived AT concentrates available in Europe.[115] Recombinant AT is produced in transgenic goats carrying a human AT gene, and purified from their milk.[116] Both AT concentrates are indicated for prevention of VTE in hereditary AT-deficient patients undergoing surgery and childbirth. Plasma-derived AT concentrate is also indicated for treatment of thromboembolic events in hereditary AT deficiency. For any acquired AT deficiency, it is up to the treating physician to select optimal AT replacement based on clinical

Table 5 Characteristics of AT concentrates. IU, international unit

	Plasma-derived AT[112] (Thrombate III)	Recombinant AT[113] (ATryn)
Half-life	3.8 days (per activity assay) 2.5 days (per immunological assay)	11.6 h (50 IU kg^{-1} dose) 17.7 h (100 IU kg^{-1} dose)
AT content per vial	500 IU	1750 IU
Heparin content per vial	<0.004 units per IU of AT	<0.0002 units per IU of AT
Storage	Store at room temp <25°C	Store refrigerated at 2–8°C
Shelf-life	3 yr	3 yr
Loading dose (IU)	[(120–baseline AT level)×Wt (kg)]/1.4	Surgical patients: [(120–baseline AT level)×Wt (kg)]/2.3 Peripartum patients: [(120–baseline AT level)×Wt (kg)]/1.3
Maintenance dose	60% of the loading dose repeated (bolus) every 24 h	Surgical patients (IU h^{-1}): [(120–baseline AT level)×Wt (kg)]/10.2 Peripartum patients (IU h^{-1}): [(120–baseline AT level)×Wt (kg)]/5.4 (continuous infusion)

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circumstances. Plasma-derived AT is a fractionated (secondary) component of blood, and can be accepted by Jehovah's Witness patients along with recombinant AT.[51] Available clinical data on the management of acquired AT deficiency are discussed below to further our understanding of AT concentrates and other therapeutic options.

Perioperative heparin resistance and AT replacement

Cardiovascular surgery and extracorporeal circulatory support are two clinical situations where heparin insensitivity is frequently encountered. The definition of heparin resistance is rather arbitrary, and depends on the local practice of heparin dosing, different cut-off values for aPTT or ACT, and availability of other diagnostic testing (e.g. preoperative AT activity).[110] Low AT activity ($\leq$60%) is observed in approximately two-thirds of heparin-resistant cases in cardiac surgery, and the remainder is presumably caused by AT-independent mechanisms (e.g. thrombocythaemia).[117–119] Administering more heparin in heparin resistance remains a common practice, and total heparin doses of 800–1200 units kg^{-1} have been reported in cardiopulmonary bypass (CPB) procedures.[109] Potential problems associated with large doses of heparin in cardiac surgery include failure to achieve the target ACT, complicated protamine dose calculations, and an increased risk of heparin rebound. As a source of AT, plasma transfusion (typically 2 units) has been empirically given in heparin-resistant cardiac surgical cases.[120] Expected recovery of AT is merely 2–3% per unit of plasma transfusion in an adult, and thus 2 units of FFP/FP24 would minimally affect plasma AT activity after haemodilution during CPB. Indeed, Avidan and colleagues[121] reported that plasma AT activity decreased to 52% on CPB (baseline AT 74%), and ACTs never improved ($<$450 s) even after 2 units of plasma transfusion. Conversely, AT concentrate products decrease heparin requirement more reliably in heparin-resistant cases. Target ACT values have been achieved in $\sim$95% of heparin-resistant CPB cases after plasma-derived or recombinant AT products.[118,121] In placebo-controlled studies of recombinant AT (75 IU kg^{-1}), the intraoperative incidence of plasma transfusion was decreased in the recombinant AT group compared with placebo (19% *vs* 81%; $P<0.001$).[121,122]

Dosing of AT concentrate

The therapeutic dose of AT concentrate can be calculated from the baseline and target plasma levels of AT (Table 5). For example, if baseline AT is 60%, and the target is 80%, the loading dose of plasma-derived AT for a 70 kg adult is calculated as:

$$\text{Dose} = \frac{(80-60)\times 70}{1.4} = 1000\ \text{IU}$$

In most heparin-resistant cases, plasma-derived AT is empirically administered as 500–1000 IU (1–2 vials). Expected AT increments of 10–20% are generally sufficient to restore heparin sensitivity in patients with baseline AT activity of 50–60%.[118,123] The initial dose of recombinant AT for peripartum patients is similar to plasma-derived AT, but the lower initial dose is used for surgical patients. Continuous infusion is used to maintain plasma levels of recombinant AT because its half-life is shorter than that of plasma-derived AT (Table 5). A single bolus dose of 75 IU kg^{-1} has been tested in clinical trials of recombinant AT for the management of heparin resistance. The mean AT activity was increased from 78% to 130%, and was maintained at 113% at the end of CPB. Higher AT levels decreased intraoperative heparin and FFP requirements, but caused a trend towards increased 24 h postoperative chest tube drainage. A small increase in postoperative bleeding (8 ml h^{-1}) was also reported by Ranucci and colleagues[124] in CPB patients who received plasma-derived AT to the target level of 120% before CPB. In their prospective, randomized study, 100 patients received the median AT dose of 1800 IU ($\sim$22.5 IU kg^{-1}), while 100 control patients received none. AT-treated patients had a mean AT activity $>$90% after CPB, and received significantly less heparin and protamine compared with the control group.[124] However, no differences were observed between the groups in the incidence of allogeneic blood component usage, thromboembolic events, low cardiac output, and in-hospital mortality. Taken together, plasma-derived and recombinant AT concentrates are both effective in reducing heparin and/or plasma transfusion in clinical heparin resistance in cardiac surgery. However, the optimal target AT levels in acquired AT deficiency remain elusive, particularly in high-risk cardiac surgical cases with prolonged CPB ($>$2.5 h).[125] There is a relative paucity of efficacy data of AT replacement in acquired deficiency in liver failure,[126,127] post-trauma,[128] and critical illness.[129] The timing of intervention, co-administration of heparin, and risk–benefit ratio for haemostasis and thrombosis should be carefully considered in these settings.[127,129]

Contraindications and adverse reactions

Plasma-derived and recombinant AT concentrates have relatively few contraindications and side-effects. Recombinant AT concentrate is contraindicated in patients with hypersensitivity to goat or goat milk proteins.[114] Caution should also be exercised for recombinant AT, as it is used with a different dosing regimen in pregnant patients (Table 5). Bleeding complications (haematoma, haemarthrosis, and haemorrhage, etc.) are rare with either AT concentrate, but such risks might be increased after an unintended overdose, or with anticoagulation (excess heparin). Both AT concentrates contain a miniscule amount of heparin, but no association of AT concentrates with HIT has been reported to date. Heat treatment and sterile filtration are applied to plasma-derived and recombinant AT concentrates, minimizing the risk of pathogen transmission.[113,114]

Conclusion

Plasma transfusion has been the mainstay haemostatic intervention for decades for the prevention and treatment of haemorrhagic and prothrombotic conditions, often without clearly defined therapeutic goals.[40,41] Its low therapeutic efficacy, time limitations for thawing and infusion, and potential hazards have been increasingly recognized, particularly in perioperative and critically ill patients.[17] Biotherapeutic and pharmacological factor concentrates have been used for the

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past half-century for treatment of hereditary haematological disorders.[80] Mechanisms of action and safety profiles of these concentrates have been largely defined within the labelled indications through clinical studies, registries, and post-marketing surveillance.[79 105 106] Perioperative use of most factor concentrates is still regarded as non-routine and difficult because multifactorial coagulopathy cannot be diagnosed by standard coagulation tests in a timely fashion, and plasma transfusion is often empirically administered.[9] Early replacement of fibrinogen and correction of hyperfibrinolysis have become widely utilized in Europe after rapid diagnosis of hypofibrinogenaemia and/or fibrinolysis became feasible using thromboelastometry.[3 63 130] The implementation of haemostasis algorithms guided by thromboelastometry appears to reduce allogeneic blood product usage, and leads to rational use of factor concentrates.[48 63] The use of factor concentrates is not intended to eradicate plasma transfusion, which has become increasingly safer.[18 19 131] Preferably, factor concentrates should be included in patient blood management to reduce unnecessary plasma and erythrocyte transfusion.[132 133] The recent FDA approval of a four-factor PCC will change management of acute warfarin reversal, and reduce the need for plasma transfusion in the perioperative period.[12] In many countries, most perioperative uses of PCC, fibrinogen, and AT concentrates are currently considered as 'off-label', but accumulating clinical data indicate that they have important roles in the management of perioperative haemorrhage, and prevention of thrombosis.[110 131]

In contrast to hereditary conditions where a single concentrate is indicated, perioperative coagulopathy often requires multiple haemostatic agents in conjunction with allogeneic blood components.[48 51 72 97] Cumulative clinical data in Europe demonstrate that a combination therapy of factor concentrates and allogeneic blood components is feasible and more efficient using transfusion algorithms based on POC coagulation tests compared with conventional laboratory methods.[48 63] Additional efficacy and safety data are needed to establish proper perioperative indications, target levels for specific factor replacement, and cost implications in diverse perioperative populations (e.g. military casualty, geriatric, and paediatric patients). Ongoing clinical studies on allogeneic components,[134] factor concentrates,[135] and synthetic agents[136 137] will clarify optimal transfusion algorithms and strategies to re-establish the balance of coagulation.[136 137]

Authors' contributions

K.A.T. has put forth the overall concept of this review article. S.E. and D.B. have contributed clinical information, and helped with the manuscript preparation.

Declaration of interest

K.A.T. has served as a consultant for TEM International (Munich, Germany), Grifols (Research Triangle Park, NC, USA), and Octapharma (Hoboken, NJ, USA), and previously received research support from CSL Behring (Marburg, Germany); D.B. received honoraria for lecturing from TEM International, and a non-restricted research grant from CSL Behring (Berne, Switzerland). None of the companies were involved in the manuscript preparation.

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