Prothrombin Complex Concentrates in Trauma and Perioperative Bleeding

Oliver Grottke, M.D., Ph.D., Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M.

CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

PROTHROMBIN complex concentrates (PCCs) are recommended in preference to other treatments such as therapeutic plasma for urgent reversal of vitamin K antagonists.[1,2] PCCs contain either three or four coagulation factors (factors II, IX, and X, with or without factor VII) and, depending on formulation, low doses of coagulation inhibitors such as protein C, protein S, and heparin (table 1). There are considerable variations among countries in the availability and licensing status of PCCs. For example, four-factor PCCs have been used for many years in Europe, where their license is not restricted to vitamin K antagonist reversal—they have broad approval for "treatment and prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors." In the United States, however, the first four-factor PCC was only recently approved, specifically for urgent reversal of vitamin K antagonist therapy.

The mechanism of action of PCCs is important for understanding their therapeutic applications. Vitamin K antagonists such as warfarin function by reducing levels of four coagulation factors: II, VII, IX, and X, with the aim of preventing thromboembolism. For patients with life-threatening bleeding, rapid replacement of these coagulation factors is required, and PCCs serve as a concentrated source of the required coagulation factors. Three-factor as well as four-factor PCCs have been explored for vitamin K antagonist reversal. However, due to the absence of factor VII, it appears that three-factor PCCs are less suitable than four-factor PCCs for patients with an international normalized ratio (INR) greater than 3.7.[3]

In trauma and perioperative bleeding, patients present with a variety of coagulopathies. PCCs increase thrombin generation potential by ensuring adequate levels of the key coagulation factors—notably factor II (prothrombin), whose conversion to thrombin is facilitated by activated factor X and activated factor V. Treatment with PCCs may potentially be effective in facilitating hemostasis in trauma and perioperative bleeding. However, the potential role of PCCs in these settings must be considered in the context of other treatment options and the patient's overall coagulation status. Fibrinogen is generally the first coagulation factor to decrease below critical levels during bleeding.[4] The physiological response to trauma includes an increase in thrombin generation,[5] whereas fibrinogen levels are typically reduced in trauma patients upon admission to hospital.[6] In cardiovascular surgery, it has been shown that fibrin formation is impaired to a greater extent than thrombin generation after cardiopulmonary bypass.[7] Coagulation management algorithms based on coagulation factor concentrates have been published in relation to cardiovascular surgery[8,9] and trauma (fig. 1).[10] Some authors advocate the use of PCC in accordance with implementing such algorithms although it should be noted that, after antifibrinolytic medication, fibrinogen supplementation is recommended as first-line hemostatic treatment.[8,10,11] PCCs may subsequently be considered for patients with ongoing bleeding despite restoration of fibrinogen levels. Throughout the management of coagulopathic bleeding, therapy should be tailored to the patient's coagulation status. Point-of-care assessment, for example using ROTEM® (Tem International GmbH, Germany) or TEG® (Haemonetics Corp., USA), can help determine which of the available hemostatic therapies (*e.g.*, therapeutic plasma, platelets, coagulation factor concentrates, or cryoprecipitate) should be administered. A deficiency in thrombin generation is more likely to arise later during the course of surgery.

Table 1. Labeled Constituents of Commercially Available Prothrombin Complex Concentrates

Product	Availability	Coagulation Factors (IU/ml)				Anticoagulant Proteins (IU/ml)			Heparin (IU/ml)	Volume per Vial (ml)*
		Factor II	Factor VII	Factor IX	Factor X	Protein C	Protein S	Antithrombin		
Bebulin VH (Baxter Healthcare Corporation, USA)	United States	24–38	<5	24–38	24–38	N/A	N/A	N/A	<0.15†	20 ml
Profilnine SD (Grifols, USA)	United States	1.5†	0.35†	100‡	1†	N/A	N/A	N/A	None	5 ml (500 IU); 10 ml (1,000 & 1,500 IU)
Prothromplex TIM 3 (Baxter, USA)	Europe	25	N/A	25	25	N/A	N/A	N/A	3.75	N/A
Uman Complex DI (Kedrion, Italy)	Italy	25	N/A	25	20	N/A	N/A	N/A	N/A	20 ml
Beriplex P/N, Confidex, or Kcentra (CSL Behring, Germany)	Europe, Canada, United States	20–48	10–25	20–31	22–60	15–45	12–38	0.2–1.5	0.4–2.0	10 ml (250 IU); 20 ml (500 IU); 40 ml (1,000 IU)
Cofact/PPSB SD (Sanquin/CAF, The Netherlands)	Europe	≥15	≥5	≥20	≥15	N/A	N/A	N/A	N/A	10 ml (250 IU); 20 ml (500 IU)
Kaskadil (LFB, France)	France	40	25	25	40	N/A	N/A	N/A	N/A	10 ml (250 IU); 20 ml (500 IU)
Octaplex (Octapharma, Austria)	Europe, Canada	14–38	9–24	25	18–30	13–31	12–32	N/A	5–12.5	20 ml
PPSB-human SD/Nano (Octapharma)	Germany	25–55	7.5–20	24–37.5	25–55	20–50	5–25	0.5–3.0	0.5–6.0	10 ml (300 IU); 20 ml (600 IU)
Prothromplex Total/S-TIM 4 (Baxter, Austria)	Europe	30	25	30	30	>20	N/A	0.75–1.5	<15	20 ml
FEIBA NF (Baxter)	United States, Europe	1.3§	0.9§‖	1.4§	1.1§	1.1§	N/A	N/A	None	20 ml (500 IU)

N/A = not available, which indicates that the presence or level of this factor was not provided by the manufacturer.

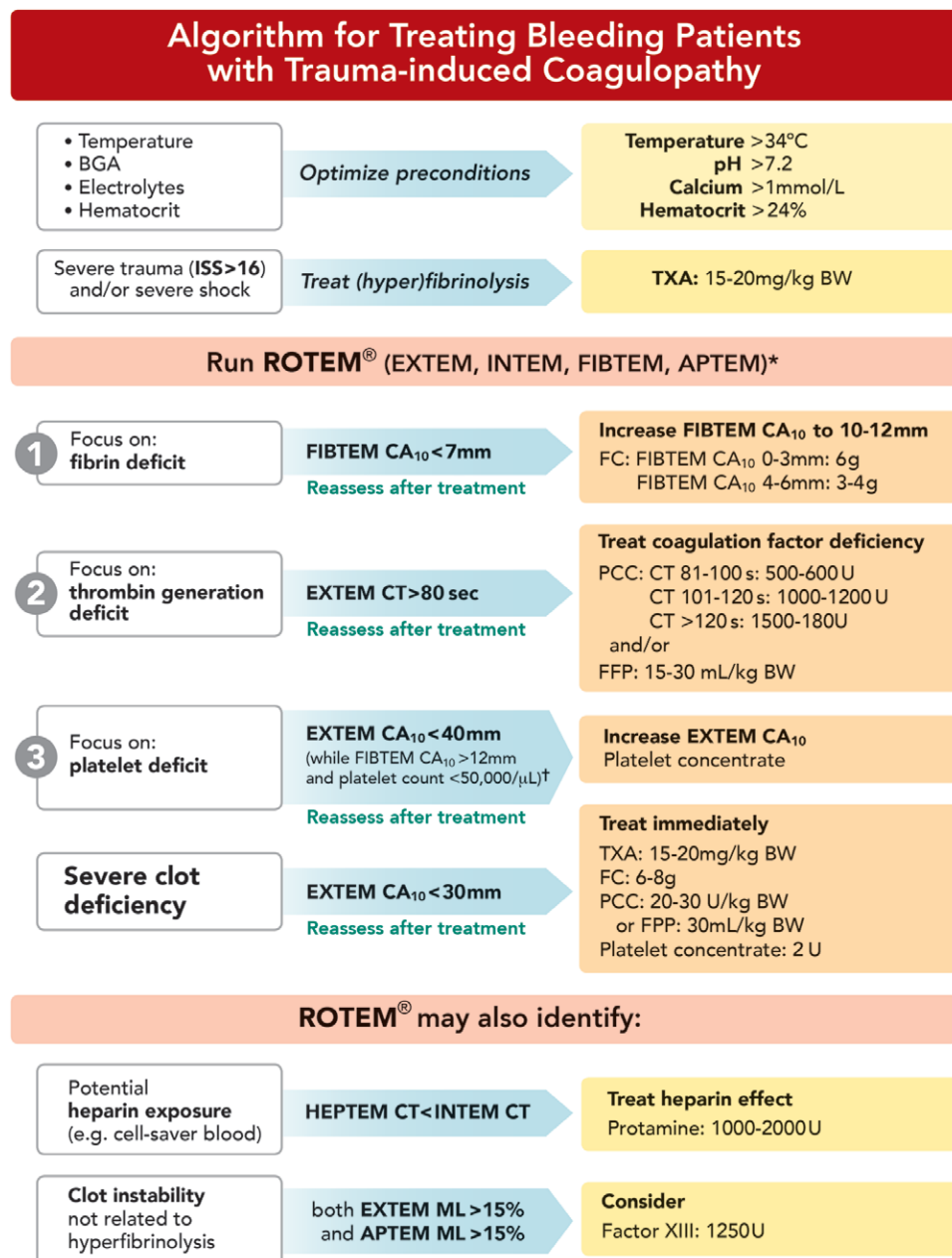* Volume after reconstitution; † Unit: IU/IU factor IX; ‡ Unit: IU per dose; § Unit: U/U; ‖ Mainly in activated form.

Fig. 1. ROTEM®-guided treatment algorithm: managing trauma-induced coagulopathy and diffuse microvascular bleeding (AUVA Trauma Hospital, Austria). *For patients who are unconscious or known to be taking a platelet inhibitor medication, Multiplate tests (adenosine diphosphate test, arachidonic acid test, and thrombin receptor activating peptide-6 test) are also performed. †Traumatic brain injury: platelet count 80,000–100,000/μl. APTEM = extrinsically activated ROTEM® assay with added aprotinin; BGA = blood gas analysis; BW = body weight; CA_{10} = clot amplitude after 10 min; CT = clotting time; EXTEM = extrinsically activated ROTEM® assay; FC = fibrinogen concentrate; FFP = fresh-frozen plasma; FIBTEM = extrinsically activated ROTEM® assay with inactivation of platelets; HEPTEM = intrinsically activated ROTEM® assay with added heparinase; ISS = injury severity score; ML = maximum lysis; PCC = prothrombin complex concentrate; ROTEM® = thromboelastometry; TIC = trauma-induced coagulopathy; TXA = tranexamic acid. Adapted, with permission, from Schöchl H *et al.* J Trauma Acute Care Surg 2013; 74:1587–98.[10] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

The potential risk of thromboembolic complications necessitates a cautious approach when using PCCs in trauma and perioperative bleeding. In these settings—unlike vitamin K antagonist reversal—levels of coagulation inhibitors as well as procoagulants are often decreased. The goal is to enhance thrombin generation and/or fibrin formation to promote clot formation at the site(s) of hemorrhage but not systemically throughout

the circulatory system. Depending on formulation, PCCs contain low doses of coagulation inhibitors such as protein C, protein S, antithrombin, and heparin. However, this does not eliminate the risk of thromboembolic complications; levels of the key inhibitor, antithrombin, are always much lower than those of the coagulation factors.[12–15]

Therapeutic plasma (*e.g.*, fresh-frozen plasma [FFP]) is often used as a means of supplementing coagulation factors. Compared with FFP, PCCs do not require crossmatching, can be rapidly administered, and have minimal risk of infection, transfusion-related circulatory overload, or acute lung injury.[16] Also, with a small administration volume, PCC therapy is unlikely to cause significant dilution of plasma constituents, such as coagulation factors, hemoglobin, calcium, and platelets, or to cause volume overload issues. A shift toward goal-directed use of coagulation factor concentrates may be desirable for safety reasons (minimizing patient exposure to allogeneic blood products) and to maximize the speed of intervention (coagulation factor concentrates can generally be administered rapidly).

Current Evidence

Preclinical Studies of PCC

A number of preclinical studies have investigated the use of PCC in the treatment of trauma-induced bleeding. All studies indicate that PCC can be effective in restoring hemostasis, but the evidence also shows that PCCs can cause procoagulant effects, such as thromboembolic complications and disseminated intravascular coagulation in animal models,[12] so risk *versus* benefit considerations should always be considered. However, uncontrolled hemorrhage is also a potentially fatal event.

A porcine model of dilutional coagulopathy and trauma (spleen incision or bone injury) was used first, and three studies by the same group were published. In the first study, PCC (35 IU/kg) was shown to reduce the time to hemostasis compared with placebo (median 35 *vs.* 82.5 min, *P* < 0.001), and there was a trend toward reduced blood loss in the PCC group (mean 275 *vs.* 589 ml).[17] In the second study, PCC (25 IU/kg) was significantly more effective than FFP (15 or 40 ml/kg) in correcting coagulopathy and controlling bleeding, with significant (*P* < 0.05) reductions in time to hemostasis and blood loss.[18] In the third study, time to hemostasis was significantly shorter with PCC (35 IU/kg) than with recombinant activated factor VII (180 μg/kg) (median 35 *vs.* 94 min, *P* = 0.016).[19]

The effects of PCC on dilutional coagulopathy and kidney trauma (scalpel incision) have also been studied in rabbits, with the aim of assessing thrombogenic potential as well as hemostatic efficacy.[20] PCC (25 IU/kg) increased peak thrombin generation by a median of 104 nM *versus* saline control and by 106 nM *versus* recombinant activated factor VII (180 μg/kg). Similar to the porcine studies, PCC significantly decreased both the time to hemostasis and the amount of blood lost, in comparison with both saline and recombinant activated factor VII.

In a subsequent porcine model of coagulopathy induced by standardized blunt liver trauma and severe hypothermia (33°C), Honickel *et al.*[21] reported a significant reduction in total blood loss with PCC (35 IU/kg) compared with saline control (1,349 *vs.* 2,632 ml, *P* = 0.002). The 2-h survival rate was 100% with PCC and 43% with saline (*P* = 0.022). Increased thrombin generation potential was observed in the PCC group and this was reflected by decreased values for prothrombin time (PT), whereas only small changes in thromboelastometric variables were reported.

The safety as well as efficacy of two PCC doses was explored without hypothermia in the same porcine trauma model as that used by Honickel *et al.*[12] Among pigs receiving either 35 or 50 IU/kg, blood loss was lower and survival was higher than in recipients of saline. However, thromboembolism was observed in all animals receiving the 50 IU/ kg dose of PCC, with 44% of them also showing signs of disseminated intravascular coagulation. In another porcine study published in the same year, dilutional coagulopathy was induced by withdrawing blood and replacing with hydroxyethyl starch, and a standardized liver laceration was performed.[14] Compared with saline, PCC (35 IU/kg) with fibrinogen concentrate (200 mg/kg) shortened clotting time (CT) in the extrinsically activated ROTEM assay (EXTEM), reduced blood loss, and reduced mortality. (EXTEM is the ROTEM assay for assessing coagulation *via* the extrinsic pathway; tissue factor is used as the activator.) However, a fatal thromboembolic complication was reported in 1 of the 10 animals treated with PCC and fibrinogen concentrate.

In a more recently published porcine study, PCC (45 IU/ kg) and FFP (4 U) were investigated *in vitro* for the reversal of dilutional coagulopathy (hemorrhage with ischemia–reperfusion).[22] With both PCC and FFP, significant reductions in PT were observed, from a mean pretreatment level of 23 to 20 s (PCC) and 17 s (FFP) (*P* = 0.001 for both reductions). There were corresponding reductions in INR, from 2.1 to 1.8 (PCC) and 1.5 (FFP).

Clinical Studies of PCC

Three retrospective clinical studies have shown that PCC alone can attenuate bleeding. In the first study, Bruce and Nokes[23] showed that PCC (500 to 4,000 IU) achieved hemostasis in 12 of 16 patients undergoing cardiac and other surgical procedures. In addition, transfusion of allogeneic blood products was reduced after PCC administration. The following year, the effect of PCC (median dose 1,500 IU) was investigated in a cohort of patients with perioperative coagulopathic bleeding.[24] Bleeding cessation followed PCC treatment in 4 of 11 patients (36%) with surgical bleeding and 26 of 27 (96%) of patients with diffuse bleeding. The third study involved patients with bleeding after cardiac surgery involving cardiopulmonary bypass: PCC alone was administered to 24 patients (group I, mean dose

PCC = 10.0 IU/kg), FFP alone was transfused in 26 patients (group II), and 27 patients received both FFP and PCC (group III, mean dose PCC = 14.1 IU/kg).[25] Blood loss during the first hour was different between the three groups ($P = 0.05$; mean blood loss of 224, 369, and 434 ml in groups I to III, respectively). A significant difference in blood loss during the first hour was evident between groups I and III ($P = 0.02$), but not between groups I and II or II and III. There were no significant between-group differences in blood loss at subsequent timepoints. The authors concluded that PCC significantly decreased postoperative bleeding after cardiopulmonary bypass.

Prothrombin complex concentrate has been investigated as part of a concentrate-based approach to coagulation management in trauma and cardiovascular surgery (table 2). In the first study, 131 trauma patients received coagulation factor concentrate-based therapy (fibrinogen concentrate [median dose 6 g] administered as first-line therapy; PCC subsequently administered to 98 patients with prolonged EXTEM CT [median dose 1,800 IU]).[26] The mortality rate was 24%, significantly lower than the 34% rate predicted by the trauma injury severity score. A follow-up study of the same approach to managing trauma-induced bleeding showed that concentrate-based treatment reduced exposure to allogeneic blood products compared with FFP-based therapy.[27] Transfusions of erythrocytes and platelet concentrate were avoided by 29 and 91% of patients receiving concentrate-based treatment compared with 3 and 56% of those receiving FFP-based therapy. Innerhofer *et al.*[28] also assessed concentrate-based therapy in trauma, reporting that fibrinogen concentrate and PCC (PCC administration conditional on bleeding and prolonged CT after fibrinogen supplementation) corrected coagulopathy and reduced transfusion of allogeneic blood products compared with patients also receiving FFP. The median 24-h dose of PCC was zero among patients treated with coagulation factor concentrates only (upper quartile: 1,000 IU), indicating that in this cohort most patients received fibrinogen concentrate alone.

Introduction of a concentrate-based approach to coagulation management in cardiovascular surgery increased the percentage of patients receiving PCC from 4 to 9%.[8] Transfusion of allogeneic blood products was decreased, and the total cost of hemostatic therapy (allogeneic blood products and coagulation factor concentrates) was decreased by 6.5%. Importantly, a significant decrease in the rate of thrombotic/thromboembolic adverse events was also reported (table 2). The last study in this section included a variety of clinical settings including trauma, cardiovascular surgery, and transplantation and spanned three different hospitals. Concentrate-based treatment was again shown to reduce transfusion of allogeneic blood products.[29]

Although clinical outcomes were favorable, these studies were all retrospective or observational. In several of the studies, different patient groups were compared to assess the impact of concentrate-based therapy. However, the extent to which patients were matched across the study groups may be questioned. For example, Schöchl *et al.*[27] selected patients from the German trauma registry with a minimum FFP dose intended to provide comparability with patients treated at their own center. In both studies by Görlinger *et al.*,[8,29] all surgical patients during 1-yr periods before and after implementation of the relevant algorithm were analyzed, without specific selection criteria or matching methods. The study by Innerhofer *et al.*[28] included analysis based on propensity score matching—although this increased comparability of patients' characteristics, the number of patients was reduced, and the potential for differences (*e.g.*, duration of bleeding) remained. Significant weaknesses in all of the comparisons drawn in the studies in table 2 underline the need for prospective, randomized, controlled studies.

Risks of PCC

Prothrombin complex concentrates have been associated with a possible risk of thromboembolic complications, in clinical practice some years ago[13] and in animal studies.[12,14] In the late 1990s, activated factors were removed from most PCCs with the aim of improving safety. Factor II (prothrombin) has been identified as the key determinant of thrombogenicity in today's PCCs, leading to a suggestion that they should be labeled according to the content of factor II instead of factor IX.[15] Circulating levels of anticoagulants are also likely to affect patients' risk of thromboembolic complications. PCCs are sometimes described in the literature as being balanced[19,30–34] or as having high levels of inhibitors including antithrombin.[35] It is important to clarify that, although these products may be balanced regarding the ratios of coagulation factors II, VII, IX, and X, they are not balanced regarding levels of procoagulants *versus* inhibitors (principally, levels of the key inhibitor antithrombin are always far below those of factor II). PCCs are highly potent thrombin-generating drugs: a study in trauma patients has shown that they elicit a significant increase in endogenous thrombin potential for 3 to 4 days, a period that is consistent with the 60 to 72 h half-life of factor II. Until robust evidence has been obtained, we would warn against their portrayal as "a versatile hemostatic agent suitable for use in indications involving multiple clotting factor deficiencies"[19] or "a promising alternative to recombinant activated factor VII monotherapy for uncontrolled coagulopathic bleeding."[20] As with all agents, the risk *versus* benefit profile should be considered carefully.

Pharmacovigilance data indicate that the risk of thromboembolic complications with PCCs may be low,[36] but it must be remembered that the predominant setting from which these data are derived is vitamin K antagonist reversal. Also, no systematic means of screening for adverse events was in place making it likely that some complications were not detected. Well-designed, prospective studies to investigate the safety of PCCs in perioperative bleeding are clearly needed.

Table 2. Studies of PCC as Part of a Concentrate-based Approach to Managing Coagulopathy in Trauma or Perioperative Bleeding

Citation	Study Design	Inclusion/Exclusion Criteria	No. Patients	Criteria for Administering PCC	No. Patients Receiving PCC (%) (Dose)	Main Efficacy Results	Main Safety Results
Schöchl et al.[26]	Retrospective cohort study (trauma)	Patients who received ≥5 units of erythrocytes within 24 h after trauma center arrival	131 (all received concentrate-based therapy)	Prolonged EXTEM CT (>1.5 times normal)	98 (75%) (median 1,800 IU)	Observed mortality of 24 vs. 34% predicted by TRISS (P = 0.032)	Outcome parameters apart from trauma not assessed
Schöchl et al.[27]	Retrospective case–control study (trauma)	Injury severity score ≥16. Concentrate-based therapy group: treated at Salzburg trauma center, received fibrinogen and/or PCC but no FFP. FFP-based therapy group: information obtained from German trauma registry, received FFP but no fibrinogen concentrate or PCC	681 (80 received concentrate-based therapy; 601 received FFP-based therapy)	Prolonged EXTEM CT (>1.5 times normal)	43 (54%) (median 1,200 IU)	Transfusion avoidance rates for concentrate-based therapy vs. FFP-based therapy: erythrocytes, 29 vs. 3%; platelets, 91 vs. 56%. P < 0.001 for both comparisons	Safety aspects not evaluated
Inner-hofer et al.[28]	Prospective cohort study designed to evaluate characteristics and treatment of trauma-induced coagulopathy	Admission to Innsbruck Trauma Center, injury severity score ≥15, multiple blunt injury, survival for at least 24 h, received hemostatic therapy	144 (68 received coagulation factor concentrates only; 78 received concentrates plus FFP)	PT <50% or INR >1.5 and/or EXTEM CT >90 s	Not specified (median 0 IU with concentrates only, 750 IU with concentrates plus FFP)	Patients treated with concentrates only showed sufficient hemostasis and received significantly fewer units of erythrocytes and platelets than patients receiving concentrates plus FFP (median erythrocyte transfusion 2 vs. 9 U; platelets 0 vs. 1 U; P < 0.001 for both comparisons)	Thromboembolism was reported in six recipients of concentrates only (9%) and in six recipients of concentrates plus FFP (8%) (P = ns)
Görlinger et al.[8]	Retrospective case–control study (cardiovascular surgery)	Patients undergoing cardiac surgery before and after implementation of a concentrate-based coagulation management algorithm	3,865 (2,147 treated according to the concentrate-based algorithm; 1,718 controls treated before introduction of the algorithm)	EXTEM CT >90 s, 20–25 IU/kg; CT >100 s, 35–40 IU/kg	191 (9%) (not specified)	The concentrate-based approach decreased the rate of transfusion of any allogeneic blood product from 53 to 42% (P < 0.001), erythrocytes (50 to 40%; P < 0.001), and FFP (19 to 1%; P < 0.001), but increased platelet transfusion from 10 to 13% (P = 0.004)	Rate of thrombotic/thromboembolic events decreased from 3.2 to 1.8% (P = 0.012)
Görlinger et al.[29]	Retrospective case–control study (trauma surgery, cardiovascular surgery, visceral surgery, and liver transplant surgery)	Patients undergoing the defined types of surgery in Essen, before and after implementation of a concentrate-based coagulation management algorithm	Total not specified (data from a 1-yr period after introduction of concentrate-based therapy (n = 7,869) compared with controls treated before the algorithm)	EXTEM CT >80 s	Not specified	Transfusion of blood products was reduced after introduction of concentrate-based therapy, with percentage reductions as follows: 79–98% for FFP; 8–62% for erythrocytes; 65–66% for platelets except in cardiovascular surgery where a five-fold increase in dual antiplatelet therapy increased transfusion of platelets by 115%	Not reported

CT = clotting time; EXTEM = extrinsically activated ROTEM® assay; FFP = fresh-frozen plasma; INR = international normalized ratio; ns = not significant; PCC = prothrombin complex concentrates; PT = prothrombin time; TRISS = trauma injury severity score.

The following considerations may help reduce the risk of complications when administering PCC to control perioperative bleeding—although it must be acknowledged robust evidence to support their implementation is lacking, and no treatment algorithm has been validated in large randomized controlled trials. In major bleeding, fibrinogen deficiency is likely to be the primary cause of coagulopathy because levels of this coagulation factor become critically low before other coagulation factors.[4,8,10] Considering this and the low risk of thromboembolic complications with fibrinogen supplementation, we support the administration of fibrinogen (fibrinogen concentrate or possibly cryoprecipitate/therapeutic plasma) as first-line hemostatic therapy. Correction of fibrinogen levels before administering PCC has been advocated previously and it should help avoid unnecessary administration of PCC (for more detail, see Diagnostic Tests).[12,37,38] The need for fibrinogen supplementation can be assessed at the point of care by testing fibrin-based clot strength (FIBTEM or Functional Fibrinogen assay) or in the laboratory by measuring the plasma fibrinogen level. Although there may be other causes (*e.g.*, platelet deficiency, factor XIII deficiency), persistent bleeding after fibrinogen supplementation is often an indication that endogenous thrombin generation might be deficient. At present, EXTEM CT represents the best means of assessing whether restoration of thrombin generation is needed[38] (see Diagnostic Tests). Furthermore, it has been suggested only low doses of PCCs should be administered and to use a theragnostic approach for dose titration as required.[21,38] In addition, levels of antithrombin (the most potent inhibitor of the activated forms of the four coagulation factors contained in PCCs) may be measured although there is currently no evidence to support best practice regarding threshold levels or how to manage patients with a deficiency.[38] Finally, for patients believed to be at risk of thromboembolic complications (*e.g.*, individuals with a history of thromboembolic events), close monitoring may be appropriate.[39] Careful consideration of the above steps would result in a notably different approach to using PCCs compared with established practice for emergency vitamin K antagonist reversal.

Research Needs

Clinical Evidence

The lack of prospective, randomized, controlled trials prevents development of robust, evidence-based recommendations for PCC use in perioperative bleeding. High-quality studies are needed to ascertain efficacy, safety, optimum dosing, optimum timing, and whether there is an optimal PCC composition for use in this setting. Studies in this field should include screening for clinically relevant thrombosis and coagulation measurements (*e.g.*, thrombin generation, thrombin–antithrombin complex) to ascertain the true clinical picture and how best to avoid inappropriate administration. In addition, comparisons of PCC with alternative

therapy should be designed so that doses are comparable across treatment arms (among studies performed to date, the few comparing PCC with alternative treatment have not confirmed dose comparability). Although the current lack of robust evidence to support PCC use for trauma and perioperative bleeding is far from ideal, levels of evidence for the alternative therapies should be considered when choosing how to manage patients. Many physicians are familiar with administering allogeneic blood products to control bleeding. However, there is a similar lack of robust evidence to support the use of these products as there is with PCCs. In seeking the best care for our patients, it is important not to confuse familiarity with evidence.

Pharmacoeconomic Evidence

There is a need for robust pharmacoeconomic data to demonstrate that the introduction of PCC for treating trauma and perioperative bleeding will be cost effective. The true costs of using allogeneic blood products are often underestimated, whereas the costs of coagulation factor concentrates are usually clear to purchasers. Many additional factors affect the overall cost, including time taken for hemostasis to be achieved, performance of diagnostic tests, management of adverse events, and duration of stay (*e.g.*, in the operating room, emergency room, or intensive care unit). To date, there have been no major pharmacoeconomic analyses of PCC for the treatment of trauma or perioperative bleeding.

Diagnostic Tests

To avoid unnecessary administration of PCCs, they should be given to patients with an urgent/emergent need for vitamin K antagonist reversal or life-threatening hemorrhage that requires increased thrombin generation. INR (derived from PT) is the principal test in the context of vitamin K antagonist reversal, but it is not designed for use outside this setting. PT and INR assess only the initial phase of clot formation, meaning the results do not provide comprehensive insight into coagulation status. More importantly, PT or INR can be prolonged by hypofibrinogenemia (<1 g/l), that is, by insufficient availability of coagulation substrate. A further consideration is that PT and INR results are time consuming to obtain, which can be problematic considering the need for rapid intervention to control perioperative bleeding.

There is currently no ideal biomarker or diagnostic test available to drive PCC administration in perioperative bleeding. However, EXTEM CT is advocated for establishing patients' need for PCC in concentrate-based coagulation management algorithms.[8,26] In patients without oral anticoagulation, CT prolongation is broadly considered to reflect impaired thrombin generation. Along with the TEG® equivalent (R-time), this is the only parameter with rapid availability that can be considered as a surrogate in this way. However, experimental data have shown that thrombin generation potential as assessed by the Calibrated Automated Thrombogram (in particular the parameters lag time,

7   O. Grottke and J. H. Levy

endogenous thrombin potential, and peak height) may not correlate with the CT.[12,21] This may relate to the fact that CT does not reflect levels of antithrombin. The importance of antithrombin levels was highlighted in a study showing that a physiological ratio between prothrombin and antithrombin is required for normal levels of thrombin generation after PCC administration.[15] Normal levels of antithrombin can be expected in vitamin K antagonist reversal, whereas in trauma and perioperative bleeding, the levels are variable. Decreased quality of the fibrin-based clot due to low fibrinogen is potentially a common cause of prolonged CT. Overall, it seems clear that EXTEM CT alone does not provide the ideal means for guiding PCC therapy, but for now, it may be the best alternative to "blind" administration.

The lack of a rapid, accurate, and readily available test for thrombin generation is currently a major research need. A new test is required which is quick to perform, provides sensitive and specific assessment of the need for PCC therapy, and enables the effect of PCC treatment to be monitored. Derivative parameters from TEG®/ROTEM analysis may be considered as candidates in this regard.[40] The two main derivative parameters of interest with TEG® are maximum rate of thrombus generation and time to maximum rate of thrombus generation; the equivalent ROTEM parameters being maximum velocity and time to maximum velocity. A third derivative parameter (TEG®: total thrombus generation; ROTEM: area under the curve) could also be considered,[40] but this is a measure of clot elasticity and is therefore unlikely to provide more valuable information than standard measurements (*e.g.*, maximum clot elasticity).

The Future

Considering the licensing status of PCCs in Europe and the existing use of coagulation factor concentrate-based treatment algorithms in some centers for patients with perioperative or trauma-related bleeding, increasing use of PCCs for indications other than vitamin K antagonist reversal may be anticipated. However, the current lack of prospective, randomized, controlled trials is problematic—such studies will be needed to enable recommendations with a robust efficacy and safety evidence base. A suitable point-of-care test to confirm the need to administer PCC and monitor the effects of treatment is also needed—in the meantime, EXTEM CT (or perhaps R-time in the RapidTEG® assay [Haemonetics Corp.]) appear to provide the best insight. At present, a cautious approach is required because of the possible risk of thromboembolic complications.

Competing Interests

In the past 5 yr, Dr. Grottke has received research funding from Boehringer Ingelheim (Germany), Novo Nordisk (Denmark), Biotest (The Netherlands), CSL Behring (Germany), and Nycomed (Germany). He has also received honoraria for consultancy and/or travel support from Bayer Healthcare (Germany), Boehringer Ingelheim (Germany), CSL Behring (Germany), and Portola (USA). Dr. Levy serves on Steering Committees for Boehringer Ingelheim (Germany), CSL Behring (Germany), Grifols (USA), Janssen (USA), and is a consultant for Portola (USA).

Correspondence

Address correspondence to Dr. Grottke: Department of Anaesthesiology, RWTH Aachen University Hospital, Pauwelsstrasse 30, D52074 Aachen, Germany. ogrottke@ukaachen.de. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians: Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 suppl):160–98S

2. Tazarourte K, Riou B, Tremey B, Samama CM, Vicaut E, Vigué B; EPAHK Study Group: Guideline-concordant administration of prothrombin complex concentrate and vitamin K is associated with decreased mortality in patients with severe bleeding under vitamin K antagonist treatment (EPAHK study). Crit Care 2014; 18:R81

3. Dentali F, Imberti D, Tamburini Permunian E, Croci E, Ageno W: Risk factors for suboptimal efficacy of 3-factor prothrombin complex concentrates in emergency VKA anticoagulation reversal. Thromb Haemost 2014; 112:621–3

4. Hiippala ST, Myllylä GJ, Vahtera EM: Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995; 81:360–5

5. Dunbar NM, Chandler WL: Thrombin generation in trauma patients. Transfusion 2009; 49:2652–60

6. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K: Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost 2012; 10:1342–51

7. Solomon C, Rahe-Meyer N, Sørensen B: Fibrin formation is more impaired than thrombin generation and platelets immediately following cardiac surgery. Thromb Res 2011; 128:277–82

8. Görlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, Jakob H, Peters J: First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: A retrospective, single-center cohort study. ANESTHESIOLOGY 2011; 115:1179–91

9. Weber CF, Zacharowski K, Meybohm P, Adam EH, Hofer S, Brün K, Volk T, Kreuer S: Hemotherapy algorithms for coagulopathic cardiac surgery patients. Clin Lab 2014; 60:1059–63

10. Schöchl H, Voelckel W, Grassetto A, Schlimp CJ: Practical application of point-of-care coagulation testing to guide treatment decisions in trauma. J Trauma Acute Care Surg 2013; 74:1587–98

11. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, Fries D, Görlinger K, Haas T, Imberger G, Jacob M, Lancé M, Llau J, Mallett S, Meier J, Rahe-Meyer N, Samama CM, Smith A, Solomon C, Van der Linden P, Wikkelsø AJ, Wouters P, Wyffels P: Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2013; 30:270–382

12. Grottke O, Braunschweig T, Spronk HM, Esch S, Rieg AD, van Oerle R, ten Cate H, Fitzner C, Tolba R, Rossaint R: Increasing concentrations of prothrombin complex

concentrate induce disseminated intravascular coagulation in a pig model of coagulopathy with blunt liver injury. Blood 2011; 118:1943–51

13. Levy JH, Tanaka KA, Dietrich W: Perioperative hemostatic management of patients treated with vitamin K antagonists. ANESTHESIOLOGY 2008; 109:918–26

14. Mitterlechner T, Innerhofer P, Streif W, Lödl M, Danninger T, Klima G, Hansson K, Fries D: Prothrombin complex concentrate and recombinant prothrombin alone or in combination with recombinant factor X and FVIIa in dilutional coagulopathy: A porcine model. J Thromb Haemost 2011; 9:729–37

15. Hanker Dusel C, Grundmann C, Eich S, Seitz R, König H: Identification of prothrombin as a major thrombogenic agent in prothrombin complex concentrates. Blood Coagul Fibrinolysis 2004; 15:405–11

16. Rodgers GM: Prothrombin complex concentrates in emergency bleeding disorders. Am J Hematol 2012; 87:898–902

17. Dickneite G, Doerr B, Kaspereit F: Characterization of the coagulation deficit in porcine dilutional coagulopathy and substitution with a prothrombin complex concentrate. Anesth Analg 2008; 106:1070–7

18. Dickneite G, Pragst I: Prothrombin complex concentrate vs fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model. Br J Anaesth 2009; 102:345–54

19. Kaspereit F, Hoffmann S, Pragst I, Dickneite G: Prothrombin complex concentrate mitigates diffuse bleeding after cardiopulmonary bypass in a porcine model. Br J Anaesth 2010; 105:576–82

20. Pragst I, Kaspereit F, Dörr B, Dickneite G: Prothrombin complex concentrate (Beriplex P/N) for control of bleeding after kidney trauma in a rabbit dilutional coagulopathy model. Thromb Res 2010; 125:272–7

21. Honickel M, Rieg A, Rossaint R, Braunschweig T, Spronk HM, ten Cate H, van Oerle R, Tolba R, Grottke O: Prothrombin complex concentrate reduces blood loss and enhances thrombin generation in a pig model with blunt liver injury under severe hypothermia. Thromb Haemost 2011; 106:724–33

22. Porta CR, Nelson D, McVay D, Salgar S, Eckert M, Izenberg S, Martin MJ: The effects of tranexamic acid and prothrombin complex concentrate on the coagulopathy of trauma: An in vitro analysis of the impact of severe acidosis. J Trauma Acute Care Surg 2013; 75:954–60

23. Bruce D, Nokes TJ: Prothrombin complex concentrate (Beriplex P/N) in severe bleeding: Experience in a large tertiary hospital. Crit Care 2008; 12:R105

24. Schick KS, Fertmann JM, Jauch KW, Hoffmann JN: Prothrombin complex concentrate in surgical patients: Retrospective evaluation of vitamin K antagonist reversal and treatment of severe bleeding. Crit Care 2009; 13:R191

25. Arnékian V, Camous J, Fattal S, Rézaiguia-Delclaux S, Nottin R, Stéphan F: Use of prothrombin complex concentrate for excessive bleeding after cardiac surgery. Interact Cardiovasc Thorac Surg 2012; 15:382–9

26. Schöchl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, Kozek-Langenecker S, Solomon C: Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010; 14:R55

27. Schöchl H, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steitz B, Arndt C, Hanke A, Voelckel W, Solomon C: Transfusion in trauma: Thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care 2011; 15:R83

28. Innerhofer P, Westermann I, Tauber H, Breitkopf R, Fries D, Kastenberger T, El Attal R, Strasak A, Mittermayr M: The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury 2013; 44:209–16

29. Görlinger K, Fries D, Dirkmann D, Weber CF, Hanke AA, Schöchl H: Reduction of fresh frozen plasma requirements by perioperative point-of-care coagulation management with early calculated goal-directed therapy. Transfus Med Hemother 2012; 39:104–13

30. Josić D, Hoffer L, Buchacher A, Schwinn H, Frenzel W, Biesert L, Klöcking HP, Hellstern P, Rokicka-Milewska R, Klukowska A: Manufacturing of a prothrombin complex concentrate aiming at low thrombogenicity. Thromb Res 2000; 100:433–41

31. Ostermann H, Haertel S, Knaub S, Kalina U, Jung K, Pabinger I: Pharmacokinetics of Beriplex P/N prothrombin complex concentrate in healthy volunteers. Thromb Haemost 2007; 98:790–7

32. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H; Beriplex P/N Anticoagulation Reversal Study Group: Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: A prospective multinational clinical trial. J Thromb Haemost 2008; 6:622–31

33. Riess HB, Meier-Hellmann A, Motsch J, Elias M, Kursten FW, Dempfle CE: Prothrombin complex concentrate (Octaplex) in patients requiring immediate reversal of oral anticoagulation. Thromb Res 2007; 121:9–16

34. Wiedermann CJ, Stockner I: Warfarin-induced bleeding complications—Clinical presentation and therapeutic options. Thromb Res 2008; 122(suppl 2):S13–8

35. Koster A, Meyer-Jark T, Schirmer U, Sandica E: Fulminant intraoperative right heart and pulmonary artery thrombosis following prothrombin complex concentrate infusion after complex open heart surgery with cardiopulmonary bypass. A A Case Rep 2014; 2:89–91

36. Hanke AA, Joch C, Görlinger K: Long-term safety and efficacy of a pasteurized nanofiltrated prothrombin complex concentrate (Beriplex P/N): A pharmacovigilance study. Br J Anaesth 2013; 110:764–72

37. Schlimp CJ, Solomon C, Keibl C, Zipperle J, Nürnberger S, Ohlinger W, Redl H, Schöchl H: Recovery of fibrinogen concentrate after intraosseous application is equivalent to the intravenous route in a porcine model of hemodilution. J Trauma Acute Care Surg 2014; 76:1235–42

38. Schöchl H, Voelckel W, Maegele M, Kirchmair L, Schlimp CJ: Endogenous thrombin potential following hemostatic therapy with 4-factor prothrombin complex concentrate: A 7-day observational study of trauma patients. Crit Care 2014; 18:R147

39. Sørensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R: Clinical review: Prothrombin complex concentrates—Evaluation of safety and thrombogenicity. Crit Care 2011; 15:201

40. Nielsen VG: Beyond cell based models of coagulation: Analyses of coagulation with clot "lifespan" resistance-time relationships. Thromb Res 2008; 122:145–52