Anesthesiology 2008; 109:918–26

Perioperative Hemostatic Management of Patients Treated with Vitamin K Antagonists

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Clinicians, including anesthesiologists, surgeons, and intensivists, are frequently called on to correct coagulopathy in patients receiving oral anticoagulation therapy. Before elective surgery, anticoagulation reversal may be undertaken over several days by discontinuing warfarin or vitamin K treatment, but rapid correction is required in an emergency. European and American guidelines recommend prothrombin complex concentrates (PCCs) for anticoagulation reversal in patients with life-threatening bleeding and an increased international normalized ratio. Compared with human fresh frozen plasma, PCCs provide quicker correction of the international normalized ratio and improved bleeding control. Although there are historic concerns regarding potential infectious and thrombotic risks with PCCs, current PCC formulations are much improved. Recombinant activated factor VII is a potential alternative to PCCs, but preclinical comparisons suggest that PCCs are more effective in correcting coagulopathy. Although many patients who require rapid reversal of warfarin are currently treated with fresh frozen plasma, PCCs should be considered as an alternative therapy.

AN increasing number of patients in the developed world are receiving therapy with an oral anticoagulant, such as warfarin, acenocoumarol, fluindione, or phenprocoumon, for preventing thromboembolic complications.[1–3] These agents act as vitamin K antagonists (VKAs) and inhibit γ-carboxylation of coagulation factors II, VII, IX, and X, protein C, and protein S. At therapeutic levels, their net effect is anticoagulation because coagulation factors without the γ-carboxylated domain are not capable of binding to calcium ions on the negatively charged phospholipid surface.

Vitamin K antagonist therapy is often used long-term in patients with prosthetic heart valves, atrial fibrillation, or deep vein thrombosis or in those at risk of thrombotic or embolic events, including stroke. However, there is a need for balance because warfarin and its derivatives can be associated with hemorrhagic complications, and the therapeutic window is narrow.[3–5] A target international normalized ratio (INR) of 2.0–3.0 is recommended based on considerable clinical evidence, although this is less certain for patients with prosthetic heart valves.[6] Maintaining the target therapeutic range of VKA is often difficult because various factors affect anticoagulant responses: age, body weight, dietary habits, sex, and ethnicity.[3] Genetic polymorphisms also influence VKA maintenance dosing requirements and the risk of bleeding.[7] For example, 30% of the population carries variant alleles of cytochrome P450 2C9, which results in slow VKA metabolism. Also, the polymorphism in vitamin K epoxide reductase complex subunit 1, which encodes vitamin K epoxide reductase, affects sensitivity to warfarin.[7] Many patients undergoing VKA therapy have INR values higher than 3.0, presenting considerable risk of bleeding, and patients remaining within the therapeutic range are also at risk. Major bleeding, often involving the gastrointestinal and urinary tracts, affects approximately 1–4% of anticoagulated patients per year.[8–10] Intracranial hemorrhage is the most serious complication because it can lead to death; the reported annual risk for intracranial hemorrhage ranges between 0.25% and 1%.[6,8,10,11]

The risk of hemorrhagic complications in patients receiving oral anticoagulation therapy poses particular problems for surgical patients requiring reversal before the procedure (table 1). With elective surgery, VKA therapy can be discontinued approximately 4 days before the procedure, minimizing the risk of perioperative hemorrhagic complications.[12] The aim is to restore patients' INR to near-normal levels before surgery[12] (*i.e.*, within or close to the range 0.8–1.2).[13] Phenprocoumon, which is used in Europe, has a much longer half-life than warfarin (approximately 160–170 *vs.* 30–40 h).[14] Therefore, INR normalization may take longer in patients receiving phenprocoumon. For patients at intermediate or high risk of thromboembolism, current US guidelines from the American College of Chest Physicians recommend bridging therapy with heparin (either unfractionated or low molecular weight), administered around 2 days before surgery, when the INR is normalized.[12] For elective surgery in patients with a low risk of bleeding, low-dose warfarin therapy need not be discontinued before the procedure, provided the INR is in the range 1.3–1.5.[12] Also, no change in oral anticoagulation therapy is required for most dental procedures.[12] Therefore, it is not always necessary for a patient's INR to be fully normalized.

In most circumstances, emergency surgery or trauma in patients receiving anticoagulation therapy with warfarin or

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

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Received from the Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia. Submitted for publication March 19, 2008. Accepted for publication July 3, 2008. Support was provided solely from institutional and/or departmental sources. Dr. Levy serves as a consultant to CSL Behring, Marburg, Germany, and is a consultant and receives research support from Novo Nordisk, Princeton, New Jersey. Dr. Tanaka receives research support from CSL Behring, King of Prussia, Pennsylvania, and Octapharma, Centreville, Virginia. Dr. Dietrich is a consultant to Curacyte Discovery GmbH, Leipzig, Germany.

David S. Warner, M.D., served as Handing Editor for this article.

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Table 1. Recommendations for Treating Oral Anticoagulation Patients Who Need Their INR Decreased Because of Actual or Potential Bleeding

Condition	Description
INR above therapeutic range but < 5.0; no significant bleeding	Decrease dose or omit dose, monitor more frequently, and resume at lower dose when INR is therapeutic; if only minimally above therapeutic range, no dose reduction may be required. (grade 1C)
INR ≥ 5.0 but < 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR is in therapeutic range. Alternatively, omit dose and give vitamin K_1 (1–2.5 mg orally), particularly if at increased risk of bleeding. (grade 1C) If more rapid reversal is required because the patient requires urgent surgery, vitamin K_1 ($\leq$5 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K_1 (1–2 mg orally) can be given. (grade 2C)
INR ≥ 9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K_1 (2.5–5 mg orally) with the expectation that the INR will be reduced substantially in 24–48 h. (grade 1B) Monitor more frequently and use additional vitamin K_1 if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic.
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K_1 (10 mg by slow intravenous infusion), supplemented with fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation; vitamin K_1 can be repeated every 12 h. (grade 1C)
Life-threatening bleeding	Hold warfarin therapy and give fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa supplemented with vitamin K_1 (10 mg by slow intravenous infusion); repeat if necessary, depending on INR. (grade 1C)
Administration of vitamin K	In patients with mild to moderately elevated INRs without major bleeding, give vitamin K_1 orally rather than subcutaneously. (grade 1A)

If continuing warfarin therapy is indicated after high doses of vitamin K_1, heparin or low-molecular-weight heparin can be given until the effects of vitamin K_1 have been reversed and the patient becomes responsive to warfarin therapy. It should be noted that international normalized ratio (INR) values greater than 4.5 are less reliable than values in or near the therapeutic range. Therefore, these guidelines represent an approximate guide for high INRs.

Reproduced with permission from the American College of Chest Physicians.[12]

its derivatives necessitates rapid preoperative supplementation of vitamin K–dependent coagulation factors. Clotting factor deficiencies associated with certain clinical conditions, such as severe liver dysfunction, can lead to similar therapeutic needs.[15] However, in patients with hepatic dysfunction, a recent study showed that supplementation of coagulation factors may not always be needed because their reduction in coagulation factors may be balanced by reduced levels of inhibitors.[16]

For uncontrolled perioperative bleeding in patients receiving VKA therapy, rapid correction is required (table 1). Because of the specific nature of the deficiency, patients need supplementation of the vitamin K–dependent coagulation factors II, VII, IX, and X for correction. Typically, VKAs reduce levels of factor IX to around 1–3% of normal and levels of factors II, VII, and X to around 30–40% of normal.[12] When choosing treatment, the time needed for administration must be considered, as well as the time taken for INR to normalize. This article will examine the available therapeutic options for anticoagulation reversal.

Anticoagulant Reversal

Treatment Options

Several therapies are available for the reversal of oral anticoagulation, and these include oral or intravenous vitamin K, human fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and recombinant active factor VII (rFVIIa).[12,17] Vitamin K can be considered for nonemergency treatment of coagulopathy associated with VKA therapy.[12,18–20] However, vitamin K therapy alone is inappropriate if rapid normalization of the INR is required, because the onset of action is 4–6 h after intravenous administration and at least 24 h after oral administration.[12,20] The delay before normalization of INR is attributable to the need for coagulation factor proteins to be synthesized *de novo*. Further, a meta-analysis demonstrated that subcutaneously administered vitamin K is ineffective.[18] In addition, high doses of vitamin K are associated with a potential risk (up to 3%) of warfarin resistance (*i.e.*, warfarin administration failing to produce the required therapeutic increase in INR after vitamin K therapy).[18] Because of the frequent need for immediate reversal, anesthesiologists are more likely to administer FFP, PCCs, or rFVIIa to patients who require reversal of anticoagulation. Cryoprecipitate should not be considered as an option, because it does not contain the appropriate coagulation factors.

Fresh frozen plasma is the agent most likely to be used in North America and consists of the fluid portion of 1 unit of human blood, frozen within 8 h after collection and used within 12 months. FFP is generally indicated for treatment of deficiencies of coagulation proteins for which specific factor concentrates are unavailable or undesirable.[21,22] In Europe, a 6-month quarantine of FFP

is commonplace to ensure absence of viral contamination. In the United States, many institutions are converting to the use of 24-h plasma that must be frozen within 24 h of collection. Compared with FFP, 24-h plasma has reduced levels of factor VIII but similar levels of other coagulation factors.[23] Methylene blue–inactivated plasma is virally inactivated (by methylene blue) without the need for pooling; this product is available in several European countries. Solvent- or detergent-treated plasma is manufactured from pooled human plasma and processed to reduce the risk of viral inactivation,[24] although this product is also not currently available in the United States.

Prothrombin complex concentrates are concentrates of essential coagulation factors, often including factors II, VII, IX, and X (though several preparations available in the United States do not contain factor VII).[3,5,25–28] Among products referred to as PCCs, only a small number are formulated and approved specifically for vitamin K deficiency (*e.g.*, Beriplex P/N [CSL Behring, Marburg, Germany], Octaplex [Octapharma, Vienna, Austria]). Although these two products are available in certain countries, neither is approved for marketing in the United States. PCCs available in the United States (FEIBA VH [Baxter, Vienna, Austria], Profilnine SD [Grifols, Barcelona, Spain], and Bebulin VH [Baxter]) are approved for use in hemophilia and contain mainly factor IX.

Table 2 shows the constituents of PCCs commercially available in the United States and Europe. Countries in which each PCC is available are also indicated in the table. All of the PCCs available in the United States are indicated for prevention or control of bleeding in patients with hemophilia B, meaning that their use for emergency reversal of oral anticoagulation would be off-label. The key differences between the US products are that FEIBA contains factor VII in activated form (Profilnine and Bebulin do not), and Bebulin contains only low levels of factor VII. In general, it is considered preferable to administer a PCC containing all four vitamin K–dependent coagulation factors for anticoagulation reversal. Activated coagulation factors are now believed not to be a primary cause of thrombotic complications,[29] but there remains a possibility that administration of activated as opposed to nonactivated coagulation factors could increase thrombotic risk in patients receiving VKA therapy (such patients by definition have an underlying risk of thrombosis).

Viral inactivation steps (filtration, pasteurization, or solvent or detergent treatment) are included in the manufacture of all PCCs to minimize the risk of pathogen transmission. Furthermore, most of the available products contain one or more coagulation inhibitors (protein C, protein S, protein Z, antithrombin III, or heparin). By inhibiting coagulation, these constituents help to maintain hemostatic balance while levels of coagulation factors are increased. For example, PCC administration has

Table 2. Constituents of Commercially Available PCCs (Based on Product Labeling*)

	Factor Content								Antithrombotic Content				
	II		VII		IX		X		Protein C				
Product (Manufacturer); International Availability	Label U/ml	Ratio, %	Label U/ml	Ratio, %	Label U/ml	Ratio, %	Label U/ml	Ratio, %	C Label U/ml	S Label U/ml	Z Label U/ml	ATIII Label U/ml	Heparin Label U/ml
Beriplex P/N (CSL Behring); major western European countries	20–48	133	10–25	69	20–31	100	22–60	161	15–45	13–26	Not in label	0.2–1.5	0.4–2.0
Octaplex (Octapharma); major western European countries	11–38	98	9–24	66	25	100	18–30	96	7–31	7–32	Not in label	Not in label	Not in label
Prothromplex Total/S-TIM 4 Immuno (Baxter); Sweden, Germany, Austria	30	100	25	83	30	100	30	100	>20	Not in label	Not in label	0.75–1.5	<15
Prothromplex TIM 3 (Baxter); Italy, Austria	25	100	Not in label	—	25	100	25	100	Not in label	Not in label	Not in label	Not in label	3.75
Cofact/PPSB SD (Sanquin/CAF); Netherlands, Belgium, Austria, Germany	≥15	75	≥5	25	≥20	100	≥15	75	Not in label	Not in label	Not in label	Present, not quantified	Not in label
Kaskadil (LFB); France	40	160	25	100	25	100	40	160	Not in label	Not in label	Not in label	Not in label	Present, not quantified
Uman Complex D.I. (Kedrion); Italy	25	100	Not in label	0	25	100	20	80	Not in label	Not in label	Not in label	Present, not quantified	Present, not quantified
PPSB-human SD/Nano (Octapharma); Germany	25–55	130	7.5–20	45	24–37.5	100	25–55	130	20–50	5–25	Not in label	0.5–3	0.5–6
Profilnine (Grifols); USA	Present	≤150	Present	35	Present	100	Present	100	Not in label	Not in label	Not in label	Not in label	Not present
Bebulin (Baxter); USA	Present	—	Present (low)	—	Present	100	Present	—	Not in label	Not in label	Not in label	Not in label	0.15 U per U of factor IX
FEIBA (Baxter); USA	Present, not quantified (nonactivated)		Present, not quantified (activated)		500, 1,000, or 2,500 U per vial (nonactivated)		Present, not quantified (nonactivated)		Not in label	Not in label	Not in label	Not in label	Not present

Factor content ratios are based on the content of factor IX.

* In Europe, ranges are usually given on the product label, in accordance with the European Pharmacopoeia; single values are generally from older, national registrations.

PCC = prothrombin complex concentrate.

been shown to increase the plasma level of protein C by 100% in patients undergoing emergency reversal of VKA therapy, whereas levels of factors II, VII, IX, and X were increased by 85, 61, 81, and 115%, respectively.[30] A study of the same product in healthy volunteers showed that levels of protein C and protein S increased by 149% and 59%, respectively, within 5 min of PCC injection.[31] Although evidence directly confirming that inhibitors in PCCs reduce the risk of thrombotic complications, our knowledge of the coagulation cascade and the role played by inhibitors such as proteins C and S[32] indicates that such an effect is highly likely. Nevertheless, PCCs all contain package insert warnings relating to the possible risk of thrombosis after their administration. Administering activated coagulation factors has been suggested as a possible cause of thrombotic complications and myocardial infarction, particularly with FEIBA, which contains activated factor VII.[33,34] However, pharmacovigilance data with FEIBA has indicated the incidence of thrombotic complications to be only 4–8:100,000 infusions.[35,36]

Prothrombin complex concentrates are supplied as a powder and diluent, which are reconstituted before administration. Products stored under refrigeration must be warmed to room temperature before use. The reconstitution method differs between products because different devices are used. Recommended doses vary between products, but they are generally calculated from body weight and based on the units of factor IX. For reversal of anticoagulation, pretreatment INR may be included in the calculation. All PCCs are administered intravenously, and recommended rates vary between products.

Recombinant active factor VII is currently approved for treating bleeding in patients with hemophilia who have antibodies inactivating factor VIII or IX, but has also been investigated and reported in a broader range of applications in life-threatening hemorrhage.[37] There are two principal mechanisms of action of rFVIIa, including the activation of tissue factor at the site of vascular injury to activate factor X and the reversal of platelet defects that are associated with bleeding (it functions *via* the activated platelet surface, further activating the coagulation process).[38] Both postulated mechanisms modulate clotting by generating thrombin, but they are both also dependent on adequate levels of other coagulation factors, notably factor X, prothrombin, and fibrinogen.

Treatment Guidelines and the Emergency Setting

US guidelines (from the American College of Chest Physicians) recommend PCCs as primary treatment for anticoagulation reversal in patients with life-threatening bleeding and increased INR, and suggest rFVIIa as a possible alternative.[12] Such treatment should be accompanied by discontinuing warfarin and its derivatives and administering vitamin K (10 mg by slow intravenous infusion).[12] For patients with serious (as opposed to life-threatening) bleeding and increased INR, the same approach is recommended, albeit with human plasma as a possible alternative to PCC or rFVIIa. Note that in the United States, this approach involves off-label use of a PCC. European guidelines, published by the European Stroke Initiative and the British Committee for Standards in Hematology, contain similar recommendations.[17,39,40] However, many anesthesiologists and surgeons continue to use FFP to reverse an increased INR, even in the presence of major or life-threatening bleeding. In the United States, this is probably related to the approved use of human plasma for this indication, as well as the lack of PCCs approved specifically for anticoagulation reversal. In Europe, where PCCs are approved specifically for the reversal of oral anticoagulation therapy and have greater availability, it has been shown that as few as 19% of physicians follow the guidelines (the majority use FFP instead of PCCs).[41]

Their rapid onset of action make PCCs well suited to emergency reversal of oral anticoagulation therapy. Besides this role, PCCs have been shown to be potentially valuable perioperatively in patients with liver disease.[26,42] In one study, the clinical efficacy of PCC was rated by physicians as "very good," "satisfactory," "doubtful," "none," or "no judgment possible" in 22 liver dysfunction patients with hemorrhage or requiring urgent surgical or invasive diagnostic procedures.[26] In 76% of cases, the PCC was rated as "very good," the Quick test increased from 39% to a maximum of 65%, and there were no PCC-related adverse reactions—although it should be noted that this study was not blinded. Another publication has reported successful use of PCC for hemostasis in two cardiac surgery cases with liver dysfunction, though in these patients PCC was used as an adjunct to standard therapies.[42] A further potential application of PCCs is in critically ill patients who are either bleeding or at risk of bleeding.[15] There may be potential for broader use of PCCs, such as perioperative bleeding in patients without anticoagulant therapy; such use would first need investigation in a research setting because it is currently off-label.

Prothrombin complex concentrate dosing is based on the quantity of factor IX administered. Fixed-dose administration of PCCs is common, and one study indicated that 500 U (typically approximately 7 U/kg) is effective for rapid correction of an INR less than 5, although higher doses are necessary in patients with higher pretreatment INR values (≥ 5).[43] However, other authors have advocated individualized dosing based on body weight and INR values.[5,20,44] In two of these publications, the doses ranged between 25 and 50 U/kg (25, 35, and 50 U/kg for pretreatment INR ranges of 2.0–3.9, 4.0–6.0, and > 6.0, respectively).[5,20]

Monitoring Anticoagulant Reversal

Prothrombin time (PT) is the most commonly used method for monitoring patients' coagulation status. It assesses the extrinsic coagulation pathway, responds to reductions in coagulation factors II, VII, and X, and is standardized using the INR.[12] However, several potential causes of inaccurate INR measurements have been identified, including incorrect PT determination (sampling problems or incorrect normal values), incorrect international sensitivity index of thromboplastin reagent, instrument (coagulometer) effects, lupus anticoagulant effects on some thromboplastin reagents, lack of reliability at onset of warfarin therapy, and lack of reliability of INR values above 4.5 (excluded from international sensitivity index calibration). Prothrombin antigen has been reported as preferable to PT for monitoring the extent of anticoagulation in warfarin-treated patients.[45] Further, PT does not reflect the amount of thrombin generated in plasma. In a study comparing PCC with rFVIIa using *in vivo* rat and *in vitro* human models of anticoagulation, both agents were found to reverse the VKA effects on PT.[46] In contrast, only PCC was shown to normalize thrombin generation. The doses of PCC and rFVIIa used for the *in vivo* model in this study were 50 U/ml and 100 μg/ml, respectively, whereas for the *in vitro* model, samples were spiked with 0.2, 0.4, or 0.72 U/ml PCC or 3.0 μg/ml rFVIIa. The authors of another study, which found no significant relation between INR and levels of coagulation factors II and X, advocated that the treatment of a patient with INR greater than 5.0 should be driven by clinical determinants rather than specific INR values.[47]

In summary, there is clear evidence that INR testing is not perfect. However, the extent of knowledge is undoubtedly related to the fact that this method has been well studied. Other assessments, such as thromboelastography, have not been investigated specifically for monitoring anticoagulant reversal. Ultimately, the aim of anticoagulation reversal is to restore coagulation to the point of allowing adequate thrombin generation, rather than the correction of INR.

PCCs versus *FFP*

Prothrombin complex concentrates rapidly restore INR and facilitate coagulation in a bleeding emergency, even if the patient is overanticoagulated. In a study of PCC (median dose: 3,600 U) in patients requiring emergency anticoagulation reversal for surgery, invasive diagnostic procedures, or active bleeding, a mean baseline INR of 3.4 was reduced to less than 1.3 in seven of eight patients and to 1.4 in the remaining patient, within 10 min of PCC infusion.[30] The clinical effectiveness of PCC was rated as "very good" in seven of eight patients (investigator rating: "very good," "satisfactory," "doubtful," "ineffective," or "impossible to judge"), and there were no thromboembolic or other adverse events. In another study, PCC was administered to a similar but larger cohort of patients (n = 43) at doses of 25, 35, or 50 U/kg, depending on the initial INR.[48] In 93% of cases, INR was reduced below 1.3 within 30 min of PCC administration. Several other studies have reported similar levels of efficacy and safety with PCCs.[20,25,27,49–51]

Comparative studies have also demonstrated that PCCs are more effective than FFP for correcting patients' INRs (table 3). In one such study, the mean posttreatment INR in patients receiving 4 units of FFP was 2.3 (n = 12), compared with 1.3 among patients receiving PCC at a dose of 25–50 U/kg (n = 29).[49] In this study, all patients receiving FFP were regarded as having treatment failures, because the lowest INR reported after FFP therapy was 1.6 (*i.e.*, above 1.5). Also, posttreatment levels of factor IX were much lower in the FFP group compared with the PCC group (19 *vs.* 68.5 U/dl). Similarly, in a second study, only one of six patients receiving 4 units of FFP achieved a safe INR level below 1.5, compared with five of six patients receiving PCC (50 U/kg).[52] In this study, the mean correction time was 41 min with PCC, significantly shorter than the 115 min observed with FFP. Two further studies showed that PCC therapy was associated with significantly reduced clinical progression of intracranial or intracerebral hemorrhage compared with FFP and, as in the other studies, PCC provided greater reduction in INR in less time.[28,53] The time required for INR correction was reported to be four to five times more rapid with PCC.[53] Unlike PCCs, use of FFP for oral anticoagulation reversal in the United States is not off-label.

One study has shown that the time between diagnosis and administration of FFP has a significant impact on the likelihood that INR will be corrected within 24 h of presentation, among patients with warfarin-related intracerebral hemorrhage.[54] This could be relevant when considering whether to use PCCs or human plasma, given the faster preparation time for PCCs.

A major advantage of PCCs *versus* human plasma is that smaller volumes of PCCs are required to reverse anticoagulation.[3,9,20,27,50,55] This is because of the concentration of clotting factors in PCCs being approximately 25 times higher than in human plasma.[55] Although human plasma is often administered at doses around 15 ml/kg,[6] human plasma doses around 30 ml/kg (*i.e.*, 2.4 l in an 80-kg patient) are required to increase coagulation factor levels in critically ill patients.[56] Furthermore, FFP at a dose of 800 ml has been shown to increase median levels of factors II, VII, IX, and X by only 9–14 U/ml among patients requiring emergency anticoagulation reversal.[49] This situation is analogous to that with hemophilia, where FFP was deemed unsuitable many years ago and replaced with factor concentrates. By contrast with FFP, recommended doses of PCC represent injection volumes of 1–2 ml/kg. The reduced volume with PCC minimizes the risk of fluid overload[50]

Table 3. Studies Comparing PCCs with FFP for Anticoagulation Reversal

Study	Study Design	Inclusion Criteria	Study Interventions	Number of Patients	Key Outcomes
Cartmill *et al.*,[52] 2000	Prospective for PCC group, retrospective for FFP group	Life-threatening intracranial hemorrhage necessitating urgent reversal of warfarin therapy	PCC (50 U/kg) plus vitamin K (10 mg) *vs.* FFP (4 units, 800 ml; 2 patients received a further 4 units) and vitamin K (10 mg intravenous)	12 (6 received PCC, 6 received FFP)	Mean preoperative INR in the PCC group was 4.86; this was reduced to 1.32 after treatment. Corresponding values in the FFP group were 5.32 and 2.30. All patients in the PCC group had posttreatment INR below the recommended value of 1.5, compared with one in the FFP group. The mean clinical correction time was 41 min in the PCC group *vs.* 115 min in the FFP group.
Fredriksson *et al.*,[53] 1992	Retrospective analysis	Anticoagulant-related intracranial hemorrhage	PCC (mean dose 32 ml, 1,930 U) *vs.* FFP (mean dose 600 ml); all patients also received vitamin K (10–20 mg intravenous)	17 (10 received PCC, 7 received FFP)	The mean INR improved from 2.83 to 1.22 over a period of 4.8 h in the PCC group, compared with 2.97 to 1.74 (7.3 h) in the FFP group. The rate of improvement was 4.6 times greater after PCC than after FFP ($P < 0.001$). Symptoms and signs of intracerebral hemorrhage, measured on an eight-graded Reaction Level Scale, progressed 0.2 grades in patients given PCC *vs.* 1.9 grades in those given FFP ($P < 0.05$).
Makris *et al.*,[49] 1997	Not defined	Hemorrhage relating to anticoagulation, or other requirement for urgent reversal of anticoagulation	PCC (25–50 U/kg) *vs.* FFP (4 units, 800 ml); all patients also received vitamin K (1–5 mg intravenous)	41 (29 received PCC, 12 received FFP)	Mean preoperative INR in the PCC group was 5.8; this was reduced to 1.3 after treatment. Corresponding values in the FFP group were 10.2 and 2.3. "Complete" INR correction (*i.e.*, < 1.5) was observed in 28 of 29 patients treated with PCC *vs.* none of the patients treated with FFP.
Huttner *et al.*,[28] 2006	Retrospective analysis	Anticoagulant-related intracranial hemorrhage	PCC (alone or in combination with FFP or vitamin K) *vs.* FFP (alone or in combination with vitamin K) *vs.* vitamin K alone (doses of FFP and PCC adjusted according to body weight; vitamin K dose: 5–20 mg)	55 (31 received PCC, 18 received FFP, 6 received vitamin K)	The incidence and extent of hematoma growth were significantly lower in patients receiving PCC (19%/44%) compared with FFP (33%/54%) and vitamin K (50%/59%). However, the difference between PCC and FFP was not present among patients whose INR was completely reversed within 2 h of treatment.

FFP = fresh frozen plasma; INR = international normalized ratio; PCC = prothrombin complex concentrate.

and decreases the time needed for infusion. PCCs are also quicker to prepare than FFP: Some PCCs can be stored at room temperature, allowing administration without warming, whereas FFP must first be thawed and warmed.[20] Unlike human plasma, PCCs do not require cross-matching before administration, saving further time. The time taken from patient presentation or diagnosis to INR correction is greatly reduced with PCCs *versus* FFP—typically around 15 min *versus* 1–2 h.[3,20,30,31]

The safety profiles of human plasma and PCCs differ in ways other than risk of fluid overload. There is a potential risk of viral or prion contamination with human plasma, although this is now low because of improved testing procedures and likely improved safety with virally inactivated preparations.[22] PCCs are also plasma derived, but they undergo viral inactivation steps to reduce contamination—although different methods are used for different products.[9,19,20,26,31,55,57,58] In an *in vitro* study of one PCC, a wide variety of pathogens were shown to be inactivated or removed by the manufacturing process, including human immunodeficiency virus, hepatitis viruses (A, B, and C), herpes simplex virus 1, influenza viruses, poliomyelitis virus type 1, influenza viruses, parvoviruses, West Nile virus, and prions (personal communication, Thomas Nowak, Ph.D., Virologist, Department of Virology, CSL Behring GmbH, Marburg, Germany, July 2007, poster presentation at International Society on Thrombosis and Haemostasis). Therefore, PCCs are associated with minimal risk of transmission of infective agents.[26,57]

One important consideration is the association of FFP with a risk of transfusion-related acute lung injury (TRALI), a major cause of death after transfusion.[59–61] In a series of 298 patients, acute lung injury developed more commonly in patients exposed to transfusion than

in comparator patients not receiving transfusion (25% *vs.* 18%; $P = 0.025$).[60] Two mechanisms have been proposed for developing TRALI: the antigen-antibody model (which suggests that an antigen–antibody reaction triggers a series of events leading to TRALI) and the neutrophil priming model (also termed the two-event hypothesis: the first event causes neutrophils to be primed, and the second event causes primed neutrophils to be activated).[61] FFP reversal of anticoagulation is considered one of the leading patient populations where TRALI is observed.[61] TRALI has not been documented as a safety concern with PCCs.

The primary safety concern with PCCs has been their association with thrombogenic events such as stroke, myocardial infarction, pulmonary embolism, disseminated intravascular coagulation, and deep vein thrombosis.[29,62] The initially low incidence of such events has decreased in recent years, which may be attributable to changes in the composition of commercially available PCCs (inclusion of coagulation inhibitors, reduced use of activated factors, and improved balance of coagulation factors). Several products that are currently available contain inhibitors such as protein C, protein S, and antithrombin III (table 2). It is unfortunate that many products do not have the inhibitor quantities in the label. A recent *in vivo* study compared the constituents of seven PCCs, and inhibitors were included—the findings were interesting in showing considerable variation between the products.[63] Although FFP has the benefit of containing the full range of inhibitors as well as coagulation factors, some PCCs are also balanced in this regard.

Extensive clinical experience with PCCs for anticoagulation reversal in recent years has demonstrated a low risk of thrombotic events,[6] and in several series of patients there have been no such events.[5,25,30,49] Pharmacokinetic studies of 50 U/kg PCC in healthy volunteers have demonstrated rapid increases in coagulation factors II, VII, IX, and X (median increases of 122, 62, 73, and 158%, respectively, within 5 min).[31] In addition, there was no posttreatment increase in levels of the thrombogenicity marker D-dimer and no clinical evidence of thrombosis. However, thrombotic complications are reported to occur in association with PCCs: A review of studies with at least 10 patients revealed seven thrombotic complications in 460 patients.[6] The complications were thrombotic stroke (n = 1), deep vein thrombosis (n = 2), non–Q-wave myocardial infarctions (n = 2), and nonbleeding (ischemic) stroke (n = 2). Despite the apparent association of these events with PCC administration, they may be attributable to patients' underlying risk factors. Conversely, as in one notable publication,[62] thrombotic complications may be attributable to the use of an older PCC that is no longer available. One suggested cause of PCC-associated thrombotic risk is a high level of factor II in the PCC (relative to the other factors), because this has been shown to increase thrombin generation.[29]

PCCs versus *rFVIIa*

Initial studies have indicated positive safety and efficacy outcomes after the use of rFVIIa for anticoagulation reversal.[64–70] Like PCCs, this use of rFVIIa would be off-label in the United States and, unlike PCCs, it would also be off-label in Europe. In a series of patients with warfarin-related life-threatening acute intracranial hemorrhage, rFVIIa reduced the mean INR from 2.7 to 1.08; five of seven patients survived and were dismissed from hospital.[64] The use of rFVIIa in this setting may have similar advantages over FFP as PCCs, including low infusion volume and rapid administration time.

Preclinical data indicate that PCCs may have efficacy similar to that of rFVIIa in acute anticoagulation, but in sustained anticoagulation PCC may be superior.[71] Further preclinical modeling of VKA therapy, using an *in vivo* rat model and an *in vitro* human model, showed that although PCC and rFVIIa were both effective in correcting PT, PCC was superior to rFVIIa with respect to thrombin generation.[46] The doses of PCC and rFVIIa used for the *in vivo* model in this study were 50 U/ml and 100 μg/ml, respectively, whereas for the *in vitro* model, samples were spiked with 0.2, 0.4, or 0.72 U/ml PCC or 3.0 μg/ml rFVIIa. These findings could be related to the fact that PCCs generally contain a balanced ratio of all four vitamin K–dependent clotting factors as opposed to just one (although, as shown in table 2, there are differences between PCCs in coagulation factor content). Comparative investigation of PCC and rFVIIa is needed to ascertain their relative safety, efficacy, and cost effectiveness.

Conclusions

Patients requiring acute anticoagulation reversal are increasingly presenting perioperatively, because the number of people receiving oral anticoagulant therapy is increasing, particularly in the developed world. PCCs designed and approved for anticoagulation reversal are an important treatment option when rapid coagulation correction is required, either preoperatively for emergency surgery or to control bleeding during surgery. Many patients continue to be treated with FFP. However, US guidelines (American College of Chest Physicians) recommend PCCs because they provide a more rapid response than human plasma, are associated with a lower incidence of volume overload, and carry minimal risk of pathogen transmission or TRALI.[12] rFVIIa may be considered as an alternative to PCCs,[12] although further data are required to ascertain the relative roles of these therapies. Future therapies will also need to be developed to determine the best methods to reverse the new oral anti-Xa agents that are under investigation.

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