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REVIEW ARTICLE

Prothrombin Complex Concentrates for Oral Anticoagulant Therapy-Related Intracranial Hemorrhage: A Review of the Literature

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Abstract Warfarin-related intracranial hemorrhage carries a high mortality and poor neurological outcome. Rapid reversal of coagulopathy is a cornerstone of medical therapy to halt bleeding progression; however the optimal approach remains undefined. Prothrombin complex concentrates have promising features that may rapidly reverse coagulopathy, but remain relatively unstudied. We aim to review the literature regarding the use of prothrombin complex concentrates in patients with warfarin-related intracranial hemorrhage. A comprehensive review of the literature was conducted using PUBMED and Google Scholar databases to identify the use of PCC in patients with warfarin-related intracranial hemorrhage. The characteristics abstracted included the type of PCC, dosing, study design, type of intracranial hemorrhage, changes in the INR, and adverse effects. Prothrombin complex concentrates are heterogenous in regards to factor concentration. PCC consistently reversed the INR in patients with intracranial hemorrhage. There is some evidence that PCC may reverse the INR more rapidly compared to fresh frozen plasma. Serious adverse effects were uncommon and included mainly thromboembolism. PCC has features which make it a promising therapy for patients with warfarin-related intracranial hemorrhage, and deserves more rigorous study in prospective-randomized controlled trials.

Keywords Prothrombin complex concentrates · Oral anticoagulation · Vitamin K antagonists · Intracranial hemorrhage · Intracerebral hemorrhage · Coagulopathy · Intracranial bleeding · Warfarin

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Introduction

Oral anticoagulant therapy (OAT) with vitamin K antagonists substantially reduce the risk of thromboembolism in selected patients, but carries a significant risk of a life-threatening hemorrhage, including intracranial hemorrhage. Maintaining VKA therapy within the narrow therapeutic range is challenging, and even within the setting of a closely monitored randomized clinical trial, the international normalized ratio (INR) remains within the therapeutic range about 70% of the time [1].

Intracerebral hemorrhage is the most common (70%) type of OAT-related intracranial hemorrhage, followed by subdural hematoma (SDH), or infrequently subarachnoid hemorrhage (SAH) [2]. The incidence of OAT-related ICH ranges from 0.25 to 1.1%/year, [3] but approaches 2% when the INR exceeds 2.0, and rises dramatically thereafter [4]. Despite the potential hazards of oral vitamin K antagonists, they will likely remain the primary oral-anticoagulant treatment for some time, as attempts to supersede them with other agents have failed so far [5].

The outcome for patients with OAT-related intracranial hemorrhages remains dismal, despite advances in neurocritical care. Patients with OAT-related ICH have a mortality rate approaching 60%, compared to about 40% for their non-anticoagulated counterparts [2, 6, 7]. The poor outcome after OAT-related ICH is related a larger baseline volume of hemorrhage, as well as continued expansion of the hematoma size after admission [8–10]. Early growth of the hematoma occurs more frequently in anticoagulated versus non-anticoagulated patients with ICH, 54 versus 16% respectively, [11] and later in the hospital course [12]. Furthermore, a higher initial INR predicts higher mortality in ICH patients. All of these data support a need for an early and rapid INR correction [13]. In patients with acute

SDH, a coagulopathic state may further worse outcome [14]. For example, among 248 patients with acute SDH patients, coagulopathy (INR > 1.2) independently predicted higher inhospital mortality [14]. The reasons for the association of coagulopathy with worse outcome in SDH patients is not well studied, but may be related to further expansion of the hematoma, worsening mass effect, and elevation of intracranial pressure (ICP).

Medical Management for Reversal of OAT-Related Coagulopathy

The reversal of the vitamin K-antagonizing effects of OAT-therapy depends primarily on the regeneration of vitamin K, which is necessary for the gamma-carboxylation of factors II, VII, IX, X, and protein C and S, producing the active form of these factors. The current treatment options for OAT reversal include fresh frozen plasma (FFP), vitamin K, recombinant factor VIIa (rFVIIa), and prothrombin complex concentrates (PCC).

FFP combined with vitamin K is the traditionally used regimen to reverse the INR, but has many drawbacks. A large infusion volume is required of at least 15 ml/kg to fully correct coagulopathy, and may not be tolerated by patients with cardiac or pulmonary disease. Also, FFP is stored frozen and thawing is a time-consuming process. Other serious adverse effects of FFP may include transfusion related acute lung injury (TRALI), transfusion reactions, and infectious transmission [15, 16].

Vitamin K administration is necessary to maintain prolonged reversal of the INR; however its effects are delayed, therefore is not appropriate alone when rapid reversal is indicated [17–19]. For life-threatening bleeding, vitamin K should be given intravenously or orally, as the subcutaneous or intramuscular routes have unpredictable absorption [20]. Oral vitamin K is usually considered equivalent to intravenous vitamin K [21], however, patients with a higher initial INR, or those with severe liver disease should receive the IV form [22]. When given IV, a dose of 5–10 mg by slow IV infusion is recommended [19, 23]. One should be aware of a small risk of life-threatening anaphylactoid reactions with the IV formulation due to the vehicle.

The use of rFVIIa for intracranial bleeding has been increasing in the United States; however randomized data do not yet support its clinical efficacy in unselected patients with ICH [24, 25]. The lack of efficacy of rFVIIa for improving outcome after ICH may be due to a significant increase in thromboembolic arterial events in the rFVIIa group compared to placebo (9 vs. 4%, $P = 0.04$) [24]. It is important to note that both of the randomized trials of rFVIIa, excluded patients with OAT-related ICH. Evaluation of rFVIIa specifically for patients with OAT-related ICH has not occurred; however, there is a phase II pilot-randomized clinical trial planning to recruit patients with OAT-ICH, to compare the efficacy and safety of rFVIIa and vitamin K versus "standard therapy" [26].

Based on the lack of randomized data, the optimal management for reversal of the coagulopathy in patients with OAT-related intracranial hemorrhages is uncertain, and consequently, there is considerable variability in clinical practice. A survey of 32 British neuroscience intensive care units reported substantial heterogeneity regarding treatment preferences for OAT-ICH [27]. The primary preferred regimens included FFP with vitamin K (28%), FFP only (22%), PCC with vitamin K (19%), PCC and FFP with vitamin K (19%), PCC only (6%), PCC and FFP (3%), vitamin K alone (3%), or rFVIIa (3%) [23].

In regards to national guidelines on VKA reversal in the setting of life-threatening hemorrhages, there is considerable variability [19, 23, 28]. Although all recommend vitamin K as an essential component of the strategy for coagulopathy reversal, there is heterogeniety regarding the use of FFP, rFVIIa, and PCC. The British Committee for Standards of Hematology recommended the combination of PCC and IV vitamin K for reversal of major bleeding rather than FFP [23]. Whereas, the Australasian Society of Thrombosis and Hemostasis recommended using PCC in combination with FFP and vitamin K for any "clinically significant bleeding." The rationale given for including FFP in their recommendation was based on the specific PCC product available in Australia, which is relatively deficient in factor VII [28]. Finally, the American College of Chest Physicians recommended FFP, PCC, or rFVIIa, along with IV vitamin K; however, it is stated that "although FFP can be given in this situation, immediate and full correction can only be achieved by the use of PCC, because the amount of FFP required to fully correct the INR is considerable and may take hours to infuse" [19].

Given the lack of proven therapies for improving patient outcomes after OAT-related intracranial hemorrhage, there is an urgent need to evaluate new strategies for VKA reversal. Since little attention has been given to PCC, it will be the focus of this review.

Early Use of PCC

Historically, PCC was given for patients with congenital factor deficiencies. In 1968, Tullis et al. described the use of PCC containing the factors II, VII, XI, and X, for management of Christmas disease and Stuart-Prower deficiency (Factor X) [29]. Later, case reports appeared regarding the efficacy of PCC for reversal of elevated prothrombin time in patients with warfarin overdosage

[30]. In 1976, an early clinical trial was conducted comparing Prothromplex, a commercially available PCC containing factors II, IX, and X, versus Vitamin K for patients with warfarin overdosage. In this study, PCC reversed coagulopathy more quickly than vitamin K, but had only a transient effect [17].

Composition of PCC

PCC is a heterogeneous mixture of the vitamin K dependent plasma clotting factors, including II, VII, IX, X, and protein C and S, derived from large donor plasma pools by ion-exchange chromatography and cryoprecipitation (Table 1) [31, 32].

The early PCC products contained three clotting factors, II, IX, and X; however, some of the newer formulations, available in some European countries, but not the United States are deemed "four factor concentrates" as they also contain factor VII in a significant concentration [31, 32]. Additionally, some PCC formulations contain protein C and S, protein Z, antithrombin III, and/or heparin. Protein Z may have anticoagulation effects in humans by enhancing the proteolysis of activated factor X [33]. The addition of anticoagulant factors in some PCC products is thought to attenuate excessive thrombogenicity.

The standard reporting of PCC factor concentrations is based on the concentration of factor IX, and the relative potencies of clotting factors within a range of 80–125% of the factor IX potency is recommended [32].

Effect of PCC on Hematological Parameters

Multiple studies have evaluated the effects of PCC on the coagulation system [34–45]. Given the heterogeneity among various PCC formulations, and different methods of measuring coagulation parameters, it is difficult to generalize their hematological effects. Nevertheless, there are some consistent findings among studies. First, most studies show a reversal of the INR to less than 1.5 within 10–30 min. Furthermore, there is an expected rise in the vitamin K dependent factor levels [36, 41]. Other findings include mild thrombocytopenia and transient elevation of the prothrombin fragment 1 + 2. Studies are conflicting regarding elevations of serum D-dimer. The effects of PCC on coagulation parameters are summarized in Tables 2 and 3.

Indications for PCC

As will be discussed in this review, the most important potential application of PCC is for reversal of the INR in patients with OAT-ICH. However, other indications include correction of specific congenital or acquired factor deficiencies including factors II, IX, or X. Of note, in the United States, the only FDA approved indication for PCC is for patients with factor IX deficiency due to hemophilia B. The FDA has not approved any PCC products containing all four procoagulant factors (II, VII, IX, and X), which are available in some European countries. The two PCC products currently available in the United States are Bebulin-VH Factor IX complex (Baxter, Westlake, CA)

Table 1 Composition of prothrombin complex concentrates (IU/ml)

Brand	Bebulin®	Proplex-T[a]	Preconativ	Beriplex P/N®	Kaskadil®	Octaplex®	Cofact®	PPSB-HT Nichiyaku	Konyne	Prothrombinex-HT
Company	Baxter	Baxter	Kabi	CSL Behring	LFFB[b]	Octapharma	Sanquin	Nihon	Bayer	CSL Bioplasma
Factor II	24–38	50 IU	50	31	37	10–40	14–35	20	38	25
Factor VII	<5	400 IU	n/a	16	10	10–40	7–20	20	4	Low
Factor IX	24–38	100 IU	60	29	25	20–31	25	20	25	25
Factor X	24–38	50 IU	50	41	40	10–40	14–35	20	38	25
Protein C				35		10–40		15		
Protein S				25		10–40				
Protein Z				36						
Antithrombin III				0.6			<0.6			1.25
Heparin	<0.15 IU/IU FIX	<1.5		0.5	5	4–15	None			10

[a] Concentration not specified

[b] *LFFB* Laboratoire Français du Fractionnement et des Biotechnologies, France

Data derived from [15, 28, 34–44]

Table 2 Effects of prothrombin complex concentrates on INR

Study/design	PCC name	PCC dose (IU/kg)	VK/route (mg)	FFP	INR
Boulis et al. 1999	Konyne	n/a	10	All	PCC: 0.63 Δ INR/hr
$n = 13$			SQ		FFP: 0.18 Δ INR/hr
Randomized PCC + FFP versus FFP alone					
Cartmill et al. 2000	Factor IXa-BPL	50	10	No	4.9 → 1.3
$n = 6$			IV		Pre, 15 m
Retrospective					
Evans et al. 2001	Beriplex	30	5	No	>20 → 1.1 → 1.1
$n = 10$			IV		Pre, 30 m, 24 h
Prospective, non-randomized					
Fredriksson et al. 1998	Preconativ	26	10–20	No	2.8 → 1.2
$n = 10$					Pre, 4.8 h
Retrospective					
Lankiewicz et al. 2006	Proplex-T	25–50	All, variable	$n = 29$	3.8 → 1.3 → 1.5
$n = 58$					Pre, post, 24 h
Lubetsky et al. 2004	Octaplex	25–50	Variable	No	6.1 → 1.5 → 2.5
$n = 20$					Pre, 10 m, 24 h
Prospective					
Pabinger et al. 2008	Beriplex	25–50	5–20, variable	No	3.2 → 1.2
$n = 43$					Pre, 30 m
Prospective					
Preston et al. 2002	Beriplex	25–50	2–5	No	4.0 → <1.3 (78%)
$n = 42$			IV		Pre, 20 m
van Aart et al. 2006[a]	Cofact	Varied	10	No	3.4 → 1.2 → 1.3
$n = 93$			IV		Pre, 15 m, 5 h
Vigue et al. 2007	Kaskadil	20	5	No	4.0 → 1.2 → 1.3
$n = 18$			PO		Pre, 3 m, 6–12 h
Yasaka et al. 2003	PPSB-HT Nichiyaku	7–27	10–20	No	2.7 → 1.1
$n = 13$			IV		Pre, 10 m

Abbreviations: *PCC* prothrombin complex concentrate; *FFP* fresh frozen plasma; *INR* international normalized ratio; *VK* vitamin K; *SQ* subcutaneously; *IV* intravenous; *PO* per oral; *CFC* clotting factor concentrates (Factor II, VII, and X); Factor IX concentrate given separately; *BPL* Blood products laboratory; *n/a* not applicable

[a] Results for the change in INR is based on a subset of 33 patients in whom PCC was targeted to INR < 1.5, and dosed by weight and initial INR

Data derived from references [34–45]

and Profilnine-SD (Grifols Biologicals, Los Angeles, CA). Both contain factors II, IX, and X, and only have FDA-labeled indications for patients with Factor IX deficiency due to hemophilia B.

Dosing of PCC and Vitamin K

Various dosing regimens of PCC have been reported [45–48] (Table 4). Some use a fixed dose of PCC; however, most are based on weight (kg). Other regimens take into account the initial or target INR, changes in factor levels, hemostatic markers, severity of bleeding, or clinical response. Some have advocated targeting the dose for factor levels of 100% of normal for patients with life-threatening bleeding [49]. Measuring the "in vivo recovery" of PCC factors after infusion, can help guide subsequent infusion if necessary. For factors VII and IX, it is estimated that the "in vivo recoveries" are about 1, meaning that for each 1 IU/kg injection of a given factor, the plasma concentration of that factor will increase by about 1% [49].

The maximum infusion rate of PCC has been studied; however the safe upper limit for rate of infusion is not well-

Table 3 Effects of prothrombin complex concentrates on thrombogenic markers

Study	PTT (s)	D-Dimer (ng/ml)	F 1 + 2 (nmol/l)	Platelets ($\times 10^9$/l)	Fibrinogen (mg/dL)	Thrombin time (s)
Lubetsky et al. 2004	89 → 50 → 74	1,368 → 1940	0.56 → 1.51	322 → 304 → 255	365 → 340	14.7 → 12.4
$n = 20$	Pre, 10 m, 24 h	Pre, 3 h	Pre, 3 h	Pre, 3 h, 3 d	Pre, 24 h	Pre, 24 h
Ostermann et al. 2007[a]		No significant change	1 → 30 → 5 → 1	247 → 246		
$n = 15$		Pre, 15 m, 3 h, 24 h	Pre, 15 m, 3 h, 24 h	Pre, 24 h		
Pabinger et al. 2008			0.19 → 6.37	252 → 235 → 208		
$n = 43$			Pre, 30 m	Pre, 1 h, 24 h		
Preston et al. 2002		<250 → <250		251 → 235 → 224	397 → 348	
$n = 42$		Pre, 2 h		Pre, 1 h, 2 h	Pre, 2 h	
Yasaka et al. 2003		570 → 1640	0.41 → 1.02			
$n = 13$		Pre, 12–24 h	Pre, 10 m			

Abbreviations: F 1 + 2 = prothrombin activation fragments 1 + 2; TAT = thrombin-antithrombin complex
Reported as median values unless otherwise specified

[a]D-Dimer and F 1 + 2 values for Ostermann et al. are approximate based on a graph, as the exact values not specified

Data derived from references: [34, 36, 41, 42, 44]

Table 4 Dosing regimens for prothrombin complex concentrate

Dosing method/study	Formula
Factor level based	
Hellstern et al. 1999	Dose (units) = kg (body weight) × desired increase in factor levels (percent or units/100 mL) × 0.5 (0.66 if hepatic dysfunction)
Boulis et al. 1999[a]	IU requested = kilograms of weight × (target factor level–current factor level) Infusion rate 100 IU/min
INR based	
Preston et al. 2001	Dose of PCC for initial INR of 2.0 to 3.9, 4.0 to 6.0, and >6.0 was 25, 35, and 60 IU/kg, respectively
van Aart et al. 2006	Based on weight (kg), initial and target INR, see Table 1b in referenced article.

[a] Current factor levels estimated based on INR, whereas an INR of 2.0 to 3.0, 3.0 to 4.0, and >4.0, corresponded to factor concentrations of 10, 5, and less than 1%, respectively

Data derived from references: [37, 42, 45, 48]

established. Some suggest not exceeding 75–100 IU/min [34, 50]; however, an infusion rate up to 210 IU/min of PCC was well-tolerated in a study of healthy volunteers [36]. Additionally, a median infusion of 188 IU/min was generally tolerated in patients who needed rapid INR reversal for acute hemorrhage or interventional procedures; six of the patients in one particular study received an infusion of greater than 250 IU/min. Of these 43 patients, two developed thromboembolism, possibly related to PCC [41].

There is some evidence that individualized dosing, may achieve more accurate reversal of the INR. In one study, the 46 patients with major OAT-related hemorrhage, those who received an individualized dose of PCC based desired INR target and body weight achieved the target INR more frequently compared to patients receiving a uniform dose (89 vs. 43%, $P < 0.001$) [45]. In another study, most patients (33 of 42) who received body weight and INR target adjusted PCC doses had reduction in INR to the goal of <1.3 by 20 min post-infusion [42].

It is essential to include vitamin K in the regimen to reverse the INR, since the effects of PCC may be transient [44]. In contrast, vitamin K produces a delayed (6–8 h), but sustained rise in PCC factors assuming intact hepatic function [51]. The recommended dose of vitamin K for life-threatening bleeding due to oral anticoagulant therapy is 5–10 mg and may need to be repeated in some cases. The IV or oral routes are preferred, with the former the first choice in life-threatening bleeding [28]. The intramuscular and subcutaneous routes should be avoided, as erratic absorption of vitamin K occurs. One should be aware of the small risk of an anaphylactic reaction with IV administration; a slow infusion over 30 min is recommended.

It is usually unnecessary to give adjunctive FFP along with PCC. An Australian study retrospectively reviewed the administration of prothrombinex-HT with or without adjunctive FFP. About 70% of the overall patients received vitamin K. The amount of PCC required to correct the INR to the "appropriate level" was not significantly higher in PCC only patients versus the adjunctive FFP group, 13.1 versus 12.3 IU/kg, respectively [52]. However, one should note that if the PCC formulation does not contain significant amounts of factor VII, than INR reversal effect may be less robust. A recent study found that the lack of factor VII in some PCC formulations attenuated the ability to reverse the INR [53].

Table 5 Safety of prothrombin complex concentrates

Study	PCC name	Mortality[a]	Thromboembolism (number events)	Other adverse effects related to PCC
Boulis et al. 1999[b] $n = 13$	Konyne	$n = 3$	None	None
Cartmill et al. 2000 $n = 6$	Factor IXa-BPL	$n = 1$	None	None
Evans et al. 2001 $n = 10$	Beriplex	None	None	$n = 2$, mild thrombocytopenia
Fredriksson et al. 1998 $n = 10$	Preconativ	$n = 2$	Not reported	Not reported
Lubetsky et al. 2004 $n = 20$	Octaplex	$n = 2$	None	$n = 3$, seroconversion to parvovirus B19 (asymptomatic)
Lankiewicz et al. 2006 $n = 58$	Proplex-T	$n = 16$	4 events in 3 patients 2 DVT, 2 MI	None
Ostermann et al. 2007[c] $n = 15$	Beriplex	None	None	None
Pabinger et al. 2008 $n = 43$	Beriplex	$n = 3$	$n = 2$; 1 fatal PE, 1 ischemic stroke	None
Preston et al. 2002 $n = 42$	Beriplex	$n = 8$	$n = 1$; 1 ischemic stroke	None
van Aart et al. 2006 $n = 93$	Cofact	None reported	$n = 2$; ischemic strokes	None
Vigue et al. 2007 $n = 18$	Kaskadil	$n = 4$	None	None
Yasaka et al. 2003 $n = 13$	PPSB-HT Nichiyaku	$n = 3$	None	None
Yasaka et al. 2005 $n = 42$	PPSB-HT Nichiyaku	$n = 1$	None	None

Abbreviations: *PCC* prothrombin complex concentrates; *FFP* fresh frozen plasma; *IU* international units; *DVT* deep venous thrombosis; *MI* acute myocardial infarction; *PE* pulmonary embolism

[a] Unless otherwise specified, mortality was related to underlying disease

[b] Randomized trial of factor IX concentrate versus FFP; all the complications were related to fluid overload in the FFP only arm

[c] Investigators monitored for HIV-1, HIV-2, Hepatitis A, B, C, and parvovirus B19

Data derived from references: [34–45, 47]

Thrombogenicity of PCC

Reported thromboembolic complications of PCC include both venous and arterial thromboembolism, and include ischemic stroke, venous thromboembolism (DVT or pulmonary embolism), myocardial infarction, and disseminated intravascular coagulation (DIC) [54–56]. An early study observed thromboembolic complications in 20 of 188 (11%) patients who received factor IX concentrate for either liver disease or hemophilia B (factor IX) deficiency [57]. Risk factors for PCC-associated thromboembolism are related to the patient's underlying condition, the PCC composition, and method of use. First, patients who require PCC for OAT-related hemorrhage are usually predisposed to thromboembolism due to the underlying medical condition which indicated OAT-therapy including venous thromboembolism, atrial fibrillation, ischemic stroke, or a prosthetic heart valve. Patients with hepatic dysfunction may be at higher risk for thrombosis due to antithrombin III deficiency, or impaired clearance of activated clotting factors. Given heterogeneity in the composition of different formulations of PCC, the risk of thrombogenicity likely varies. This may be related to the relative potencies of procoagulant and anticoagulant factors, as well as the proportion of preactivated factors [58]. Preparations of PCC that contain higher concentrations of factors II, X, or contain the activated form of factor VII may increase thrombogenicity [59, 60]. Some PCC formulations contain protein C and S, with the aim of

shifting the balance of coagulation factors to a more physiological state, and thus preventing excessive coagulation [58]; however, no large scale randomized trials exist to compare the different formulations. The presence of activated clotting factors in some PCC may favor coagulation. In regards to the risk of thrombogenicity of PCC, the Task Force on Clinical Use of Factor IX Concentrates of the International Society of Thrombosis and Hemostasis and the European Pharmacopoeia recommended inclusion of heparin to PCC formulations. Some formulations also contain small amounts of antithrombin III. The inclusion of both antithrombin III and heparin in PCC formulations inhibits the in vivo activation of clotting factors [31, 32]; this presumption is based on the observations from two studies which found that the combination of antithrombin III and heparin neutralized the factor IXa and Xa activity, and prevented thrombin formation, whereas the inclusion of only one of these agents did not provide complete inhibition [61, 62]. PCC may also contain procoagulant phospholipids. Although in isolation these lack intrinsic thrombogenicity, they enhanced clotting in the presence of activated factor Xa [63]. Another potential source of thrombogenicity is heparin-induced thrombocytopenia, which may be triggered due to the small amounts of heparin contained in PCC.

The risk of thromboembolism may increase with higher or repeated dosing of PCC [60, 64]. This may be explained by the different terminal half-lives of factors II, VII, IX, X, and protein C and S which range from 60, 4, 17–24, 31, 8–47, and 42–50 h, respectively [36]. It is thought that due to the relatively prolonged half-lives of factors II and X, repeated dosing of PCC may lead to excessive accumulation of these factors, and favor a procoagulant state [32]. In a small case series ($n = 3$), acute thrombotic complications including DIC and venous or arterial occlusion occurred in some patients who had received higher or repeated (40–100 units/kg) dosing of a brand of PCC (DEFIX, Scottish National Blood Transfusion Service) [65].

In order to address this issue of heterogeneity of PCC, the European Pharmacopoeia established manufacturing guidelines in 1999, regarding standardizing composition. The recommendations were to include a small amount of antithrombin III and heparin, anticoagulant proteins C and S ($>40\%$ factor IX level), avoid excessive levels of factor II and X compared to factor IX, and reduce the ratio of factor VII to factor IX to avoid excessive factor VIIa activity ($<5\%$ of total factor VII) [32, 48].

Other Adverse Effects of PCC

Infectious transmission of viruses including hepatitis A, B and C, HIV, HTLV-1, and parvovirus B19 is a possibility. A variety of techniques substantially reduce the risk of viral transmission; these include vapor heating, hydrophobic gel chromatography, solvent/detergent treatment, pasteurization, nanofiltration, and screening for pathogens with ELISA and polymerase chain reaction. Although these techniques substantially reduce the risk of infection, no technique completely eliminates the risk [31, 34, 66–70]. Probable parvovirus B19 seroconversion, clinically asymptomatic, was reported in 3 of 20 patients who received a commercially produced PCC [34].

Other potential adverse effects include allergic reactions including life-threatening anaphylaxis, transfusion reactions, and a theoretical risk of heparin-induced thrombocytopenia due to the small amounts of heparin contained in PCC. No significant hemodynamic changes have been reported [34] (Table 5).

Potential Advantages of PCC over FFP

There are several advantages of using PCC in preference to FFP for reversal of OAT-related intracranial hemorrhage (Table 6). PCC can be given more rapidly than FFP. PCC does not require blood-type matching; whereas FFP requires ABO blood typing due to the presence of isohemagglutinins. PCC is stored as a lysophilized powder and can be reconstituted in sterile water in minutes. In contrast, FFP is frozen and it takes up to 30–60 min for thawing. Third, PCC contains a much higher concentration of clotting factors. Therefore, a much smaller infusion volume of PCC is required [45]. The volume of FFP per unit is about 250 ml, thus the necessary volume of FFP to correct coagulopathy may exceed 2 l depending on the initial INR. This may be a concern in patients with underlying cardiac or renal failure who are at risk for fluid overload. Most importantly, the INR is corrected very rapidly, within minutes, in some previously conducted studies of PCC (Table 3).

Potential Advantages of PCC over rFVIIa

There are no prospective clinical trials to compare the efficacy of PCC versus rFVIIa. However, there is some laboratory evidence suggesting that PCC may stabilize clot formation more effectively than rFVIIa. Taketomi et al. analyzed clot stability in warfarin-treated plasma after giving either PCC or rFVIIa. With PCC administration, the clot lysis time after administration of rtPA, was restored to normal (40 min), but not after rFVIIa treatment, due to a higher local generation of thrombin after PCC treatment [71]. In a different study, PCC 50 IU/kg, but not 100 μg/kg of rFVIIa stopped bleeding after tail transection in warfarin-overdosed rats, despite a reversal of prothrombin time with both

Table 6 Prothrombin complex concentrates versus fresh frozen plasma

	PCC	FFP
Blood type matching required	No	Yes
Thawing time	None	30–45 min/unit
Infection risk	Yes	Yes
Thrombosis risk	Yes	Yes
Clotting factor concentration	High	Low
Infusion volume	Less than 200 ml	1,000–3,000 ml
Speed of INR correction	Quicker	Slower
Availability	Limited in United States	Available
Expensive	Yes[a]	Moderate

Abbreviations: *PCC* prothrombin complex concentrates; *FFP* fresh frozen plasma

[a] In 1998, Nitu et al. reported a cost of about £1,300 (pounds) = $1,600 (USD) per reversal of INR

Data derived from references: [28, 37, 75]

regimens. The authors suggest that the reversal of the INR may not be an adequate measure of hemostatic response [72].

A theoretical advantage of using PCC compared to rFVIIa for OAT-related hemorrhage is a more balanced replacement of clotting factors. As discussed, some formulations of PCC replace both procoagulant (II, VII, IX, and X) and anticoagulant factors (protein C and S), as well as antithrombin III. The imbalanced activation of the clotting cascade produced by rFVIIa has the theoretical risk of producing an overly active thrombotic state. In a recent phase III randomized clinical trial for ICH observed a significantly higher number of thromboembolic events in treated patients as compared to patients in the placebo group (9 vs. 4%, $P = 0.04$) [24].

Studies of PCC for Intracranial Bleeding

A number of studies have been reported which include at least some patients with OAT-related ICH; however most are heterogenous in regards to presence of hemorrhage, type of hemorrhage (systemic or intracranial), severity of hemorrhage, initial INR, type of PCC used, dosing, and study design. Only those studies which include a significant proportion of patients with intracranial hemorrhage will be discussed [38–43, 73, 74].

Fredriksson et al. reported a case series of 17 patients who received three-factor PCC or FFP for intracranial bleeding related to oral-anticoagulant overdosage. The reversal of the INR was four to five times more rapid in patients treated with PCC as compared to FFP, and there was less symptom progression in PCC treated patients [39].

Cartmill et al. reported a pilot study of six patients who received three-factor PCC for OAT-ICH including ICH, SDH, and SAH. The patients received 50 μg/kg of PCC and 10 mg IV vitamin K, with the goal of decreasing the INR to less than 1.5. The mean INR decreased from 4.86 to 1.32 in the PCC-treated patients, compared to 5.32–2.30 in a historical FFP-treated control group. The time to correction of coagulopathy was significantly shorter in the PCC-treated group (41 vs. 115 min), $P < 0.001$. The INR remained corrected in most (5 of 6) PCC-treated patients, but none of the FFP-treated patients [38].

Preston et al. reported a prospective single arm trial of 42 patients (12 with intracranial hemorrhages) who received a four-factor PCC (Beriplex® P/N, Aventis, UK) to reverse warfarin effect. The dose of PCC ranged from 25 to 50 IU/kg depending on the level of the initial INR, and vitamin K 2 to 5 mg IV was also administered. The mean INR decreased from 3.98 to <1.3 in 33 of 42 patients within 20 min. Regarding safety, major complications included death ($n = 8$) and ischemic stroke ($n = 1$). Death was deemed related to the underlying illness in most (7 of 8) of the patients. Of the three autopsies that were done, there was no observed thromboembolism. None of the patients developed serologically or clinically evident DIC [42].

Lankiewicz et al. retrospectively evaluated the use of a three-factor PCC (Proplex-T, Baxter, USA) in 58 patients, 36 had intracranial hemorrhages (ICH-22, SDH-13, SAH 2). The dose of PCC was 25–50 IU/kg; half of the patients also received FFP, and all received vitamin K. The group INR mean was 11.7 and 1.4, before and after PCC infusion, respectively at 1 h. Only 2 of 58 patients had an INR > 2.0 after treatment. There was no difference in the median INR in the patients who received FFP compared to the overall group, suggesting that supplemental FFP may be unneccesary. Of the patients requiring surgical intervention, none of the patients were noted to have "excessive blood loss." Four PCC-related complications included catheter-associated DVT ($n = 1$), recurrent DVT ($n = 1$), and non-ST elevation myocardial infarction ($n = 2$). Sixteen patients (28%) died during hospitalization, and five other patients were discharged to hospice with death presumed to be imminent, but the outcome was attributed to the underlying disease [40].

Huttner et al. reported a retrospective evaluation of different treatment strategies for reversal of the INR in 55 patients with OAT-ICH. Of patients who received PCC, 84% had reversal of the INR ≤ 1.4 within 2 h, compared to only 39% who received FFP, and 0% who received vitamin K alone, $P < 0.01$. Furthermore, there was significantly less hematoma growth in patients who received

PCC compared to patients who did not receive PCC (19.3 vs. 37.5%, $P < 0.01$); however, there were no differences in long-term outcomes between the groups [73].

Kalina et al. reported a standardized protocol for the rapid reversal of the INR using a four-factor PCC (Proplex-T, Baxter) in 46 patients with traumatic OAT-intracranial hemorrhage. The control group was similar patients seen at the institution during the time period who were not treated by the standarized protocol. Not surprisingly, the protocol increased the proportion of patients who received PCC (54.3 vs. 35.4%, $P = 0.047$). Furthermore, the time to an INR < 1.5 and time to operating room were significantly decreased with the protocol, 331 versus 738 min and 223 versus 351 min, respectively. Regarding adverse events, 3 of 48 patients who received PCC were found to have DVT [74].

Vigue et al. conducted a prospective single arm study of INR reversal for 18 patients with intracranial bleeding (5 with ICH, 12 with SDH, 1 with hydrocephalus) requiring neurosurgical intervention. Patients received a four-factor PCC (Kaskadil®, Laboratoire Français du Fractionnement et des Biotechnologies, France) and IV vitamin K. The dose of PCC was 20 IU/kg in two 10 IU/kg boluses separated by 1 min. The mean INR significantly decreased from a baseline of 4.0–1.4, 1.2, and 1.3 at 1 min, 3 min, and 6–12 h, respectively. The INR was corrected to ≤ 1.5 in all patients after the PCC boluses. At 6 to 12 h after PCC most patients had an INR ≤ 1.5, except for four patients in whom the vitamin K had been omitted from the treatment regimen. A good or moderate outcome was seen in 73% of patients at the 6 month follow-up [43].

Future Studies and Conclusions

Based on the preliminary studies, PCC holds promise for patients with warfarin-related intracranial hemorrhage due to its rapid reversal of the INR. However, there are a number of areas that need further exploration. First, given the concern for thrombogenicity, there is a need for rigorous evaluation of its safety. The optimal dosing and infusion rates to rapidly but safely reverse the INR should be further elucidated. Finally, PCC should be compared directly in randomized controlled trials to other treatment strategies including FFP and rFVIIa evaluating effect on patient outcomes, including the cost-effectiveness of the various approaches.

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