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Management of Patients with Gastrointestinal Hemorrhage While Receiving Warfarin: Vitamin K, Prothrombin Complex Concentrates and Others

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Abstract

Introduction: Prothrombin complex concentrates (PCC) has long been used to reverse vitamin K antagonists (VKA) induced coagulopathy rapidly and safely. This article is a review and critical analysis of the most recent literature to analyse treatment with PCC, focusing on gastrointestinal hemorrhage (GIH) in patients on warfarin.

Methods: Currently available literature on the use of PCC in GIH was identified by searches of electronic database. Utilization of PCC was addressed in the literature data found by searches of databases. The indications, efficacy and outcomes associated with the use of the product (three vs four-factors) were reviewed in the articles.

Results: In general, studies point out promising results with respect to PCC use to overcome the VKA–related coagulopathy in GIH. Comparison of different aspects of treatment with PCC and vitamin K, Fresh frozen plasma (FFP) are discussed. PCC is the treatment of choice for normalization of prothtombin time and INR values and resuscitation in emergency setting in patients diagnosed with GIH. Dosing principles are also mentioned.

Conclusion: PCC is the front-line agent to reverse the VKA–related coagulopathy. PCC should be considered for resuscitation in emergency and intensive care in case of severe hemodynamic compromise in GIH associated with high INR values.

Keywords: Prothrombin complex concentrates; Vitamin K antagonists; Warfarin; Coagulopathy; Gastrointestinal hemorrhage

Introduction

Anticoagulants, including vitamin K antagonists (VKA) are administered in a greeat majority of patients who are in need of prophylaxis and treatment of thromboembolic events allover the world. Many patients benefit from anticoagulant effects of VKA in acute and chronic venous and arterial thromboembolic diseases, although nowadays they have been partly replaced by newly generated direct oral anticoagulants. Treatment with VKA therapy necessitates great caution because of its narrow therapeutic window. These drugs also mandate frequent monitoring and dose adjustments. In brief, these agents are not free of adverse effects. The most important and deadly untoward effect is bleeding. The incidence of bleeding in anticoagulated patients is 15–20% in a year [1] and among these, around one-sixth are major bleeding complications (1.7–3.4%) [2]. Although there have been many different treatment modalities in the management of these patients, PCC, FFP and vitamin K are the most commonly used treatment modalities, sometimes in combinations, to mitigate the effects of chronic or acute overdose of VKA. This article is a review and critical analysis of the most recent literature to analyse treatment with Prothrombin Complex Concentrate (PCC) in gastrointestinal hemorrhage **(**GIH) in patients on warfarin.

Clinical implications of GIH and major bleeding while taking VKA

The bleeding events associated with VKA use typically involve the gastrointestinal system, central nervous system, and/or soft tissues [2]. In 1996, Palerati et al. showed that GIH is the most common major bleeding complication of VKA therapy [3]. Recent publication by the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) emphasized that GIH comprised more than one-third (38%) of major bleeding episodes in those on warfarin [4]. A number of studies reported that the annual incidence rate of major bleeding episodes in VKA treated patients is between 1% and 3% [5-7]. Every year, life-threatening bleeding occurs in approximately 0.25% of this group of patients [3]. In a Dutch study, Brekelmans et al. analyzed the patients presented with bleeding while on VKA therapy [8]. Mean age was 74 years, 54% were male and 79% received VKA for atrial fibrillation. Most patients presented with ICH (41%) or GI bleeding (36%) (Table 1). Mortality rates are quite variable, in accord with the severity of the patients in the sample. Brekelmans et al. reported a rate as 22% in 2017, while in other studies three out of every five patients have died [8]. Chai-Adisaksopha recorded a rate of 25% in their meta-analyic study in 2016 [9]. More optimistic numbers were given by Sarode in 2013 and Johansen in 2015, as 5.8-7.8%, respectively [10]. Some authors classified the bleeding episodes during VKA treeatment into four classes. A severe clinical presentation (mostly category 3) was observed in almost two-thirds of the patients [11]. Category 4 describes immediately fatal or near-fatal events on presentation and includes around 1% to 5% of the patients.

Table 1: Characteristics of the patients referred to EDs with major bleeding while on VKA therapy.

Patient Characteristic with Major Bleeding on VKA	Values
Mean age	74 (years)
M/F ratio	Nearly 1
Main reason of using VKA	Atrial fibrillation (80%)
Bleeding site	ICH and GIH nearly 80%
Pre-treatment INR	Nearly 4
One-month mortality	5.8% to 60% (very high in those with ICH)

Assessment of bleeding severity

If >=1 of the following factors are identified in a given patient, the bleeding is classified as a major bleeding.

a) Bleeding in a Critical Site: Intracranial hemorrhage, pericardial tamponade, airway, including posterior epistaxis, hemothorax, intra-abdominal bleeding and retroperitoneal hemorrhage, extremity bleeds

b) Hemodynamic instability: mean arterial pressure<65 mm Hg in invasive monitoring; urine output <0.5 mL/kg/h

c) Overt bleeding with hemoglobin drop >=2 g/dL or administration of >=2 U of packed RBCs

Laboratory thresholds and features (INR and others)

High INR levels are commonly encountered in these patients with warfarin use. This laboratory measurement is thought to be closely related to the risk of GIH. Nearly two decades ago, researchers noted that GIH is three times more common in patients with an INR >3 than in those with INR is found between 2 and 3 [12].

Can we guide PCC and other treatments via laboratory tests?

Yes. Thromboelastometric assays (e.g., ROTEM™ Assays) use citrated whole blood (300µL per assay), which is recalcified and activated by tissue factor (extrinsic pathway), ellagic acid (intrinsic pathway), or ecarin (direct prothrombin activation). Extrinsically activated assays (e.g., EXTEM), intrinsically activated assays (e.g., INTEM, HEPTEM), and ecarin-activated assays have been devised to utilize in this context [13-15]. Since coagulation is triggered via the extrinsic pathway, initial thrombin generation and hence initial clotting mainly depend on the activity of the coagulation factors VII, X, V, II, and fibrinogen in EXTEM test. EXTEM CT can be used to guide FFP and PCC administration in patients suffering from bleeding due to vitamin K-dependent factor deficiency, e.g., due to warfarin therapy [13-15].

EXTEM assay uses [$CaCl_2$ + recombinant tissue factor + polybrene] to evaluate the integrity of the extrinsic pathway. The test allows the clinician to yield objective comment on a probable deficiency of factors of the extrinsic pathway, for example, VKAs (coumadin/ warfarin) and also gives clues on indication for PCC administration.

The history and background of Prothrombin Complex Concentrate (PCC)

Nonactivated PCCs are either 3-factor-PCC, including factors II, IX, and X or 4F-PCC, containing factors II, IX, X, and clinically relevant amounts of factor VII [16]. These were initially developed for use in people with a congenital deficiency in vitamin K-dependent coagulation factors when purified specific coagulation factor is not available [17-19]. The agent is now used for the expedient reversal of untoward high levels of international normalized ratio (INR) [20]. Compared to the 3-factor PCC, the 4-factor PCC has higher concentrations of factor VII in addition to some anticoagulant proteins (Protein C, Protein C, Antithrombin, and heparin) [21].

Treatment principles:

Patients with major bleeding while taking VKA therapy eventually diagnosed with acute overdose of VKA require rapid reversal of life-threatening coagulopathy. Among non-activated agents, four-factor PCC (4 F- PCC) was suggested as the backbone

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of the treatment strategy of VKA-induced major bleeding from any bodily region by the current guidelines [22,23]. PCC products are purified and concentrated solutions containing primarily the vitamin-K-dependent clotting factors. The preferred PCC is now the 4-factor PCC solution, which contains factors II, VII, IX, and X, as well as the anti-thrombotic factors proteins C and S [24]. For example, activated PCCs are indicated for treatment of hemophilia A or B with inhibitors. The clinical course of VKA-associated major bleeding events treated with PCC was categorized as 3 or 4 in terms of severity with above mentioned criteria, in 50% of patients [8]. Animal and human studies implicated that 4F-PCC demonstrated similar efficacy in relieving coagulopathy associated with the factor Xa inhibitors apixaban and rivaroxaban [25,26]. Indeed, PCC also represents an anticoagulation reversal strategy for patients treated with direct FXa inhibitors, as an alternative to dabigatran and andexanate. Karaca et al. compared the efficacy of PCC and FFP at lowering the INR level, decreasing active hemorrhages visible by endoscopy, and shortening the length of stay at the ED [27]. They noted that patients receiving PCC had INR levels reversed more quickly, less active bleeding on endoscopy, and shorter ED length of stay than in the FFP group. More recently, Refaai et al. focused on shortening the time period spent till the necessary procedure to stop bleeding in those with GIH using four-factor PCC and FFP in an UCLA study [28]. They reported that acute/severe GIH in need of urgent VKA reversal before an invasive procedure, 4F-PCC was linked with lesser infusion volumes, shorter infusion times, and reduced time to procedure, when compared to FFP. Lim et al. enrolled 934 patients with nonvariceal upper GIH in a prospective analysis, which identified the lone independent risk factor associated with all-cause mortality in high risk patients (Glasgow-Blatchford Score≥12) to be the time lapse between presentation and endoscopy [29]. This conclusion can not be extrapolated to low-risk patients (Glasgow-Blatchford Score<12). Only 4-factor PCCs are licensed for rapid warfarin reversal. The agent has the advantage of not requiring blood type testing. Also, it can be stored at room temperature (as lyophilized powder) PCC is dosed based on INR and body weight [9,30]. Administration of PCC was associated with effective haemostasis in 68% to 72% of patients with VKA-associated major bleeding [8,10]. This finding is in line with recommendations on PCC cited in current guidelines [22,31]. If a patient is actively bleeding or requires an urgent invasive procedure, infusion with a plasma-derived coagulation factor concentrate containing the four vitamin K-dependent factors, for example, PCC, plus IV vitamin K 1 (5–10mg), would be appropriate. FFP would be the least efficient replacement therapy due to the large transfusion volume (10–20mL/kg) required to partially and temporarily replenish deficient vitamin K-dependent factor levels [32] (Figure 1).

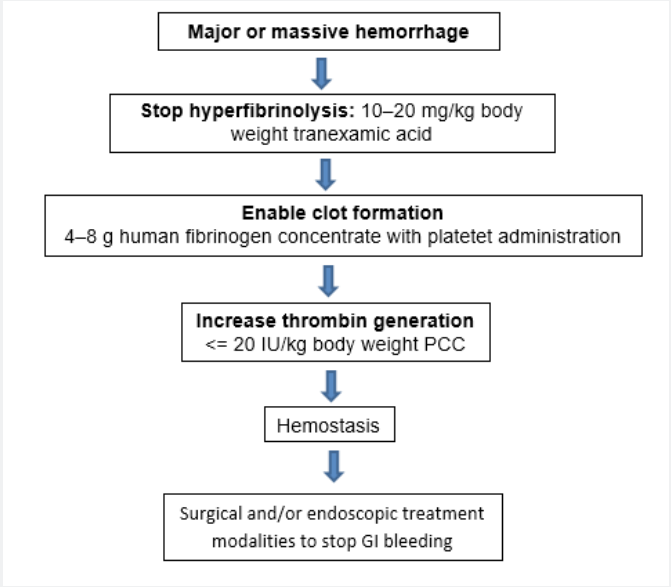

Figure 1: Proposed algorithm for major GI bleeding in patients on anticoagulant therapy.

Alternative agents in the treatment of GIH

FFP is widely used to replace volume and coagulation factors in those with bleeding in order to reverse warfarin. FFP contains all coagulation factors, including fibrinogen. An initial dose of 15-20ml/kg is deemed suitable [33]. It possesses the advantage of being at hand easily and a lower cost than most other treatment options. On the other hand, being a human product, it can trigger allergic reactions, transmit infections or cause a transfusion related lung injury (TRALI). An ABO compatibility test should be undertaken, which can take a long time to defrost. In addition, a high infusion volume (>1.5L) and a protracted infusion time could be needed to increase coagulation factor concentration [34]. These factors can limit usability of FFP in the emergency setting. Furthermore, high infusion volume can represent a

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drawback for patients with renal failure or cardiac insufficiency. Any deficiencies of "extrinsic" coagulation factors can be treated with direct supplementation of vitamin K. The agent can be given per oral or parenteral (IV), while 5 to 10 mg of IV vitamin K is preferred with its more rapid onset than oral administration in high-acuity situations [23]. However, the practitioner should keep in mind that it does *not* result in immediate correction of coagulopathy and thus must be accompanied by PCC or FFP in the management of major bleeds. In addition, a number of well-designed multicentric controlled studies such as CRASH have pointed out that tranexamic acid can be used with considerable success in traumatic hemorrhages including most fatal ones, i.e., intracranial hemorrhages and shocky states without a defined source of bleeding. In these grave circumstances, tranexamic acid is recommended to be administered within first 3 hours following trauma [35]. However, tranexamic acid has not proven to decrease blood loss or improve clinical outcomes in patients presenting with GI hemorrhage to date [36].

Comparison of PCC with FFP

In a meta-analytic comparison pf PCC and FFP, Brekelmans et al. included 19 studies and 2878 patients with VKA associated bleeding between 1945 and 2015 [8]. Baseline INR values ranged from 2.2 to >20. The INR within 1 h after PCC administration ranged from 1.4 to 1.9, and after FFP administration from 2.2 to 12. The mortality rate ranged from 0 to 43% (mean 17%) in the PCC, 4.8-54% (mean 16%) in the FFP and 23-69% (mean 51%) in the no treatment group. The mean mortality rates of patients treated with PCC and FFP were not statistically different (p = 0.73). In a Cochrane review and meta-analysis published in 2015, Johansen et al. concluded that PCC had demonstrated the possibility of reversal of VKA-induced coagulopathy without the need for transfusion of FFP, although there had been no proven mortality benefit [37] (Figure 2) (Table 2).

Table 2: Main differences among FFP and PCC derived from published data so far.

	FFP	PCC
When is it given?	After thawing and compatibility tests	Immediate
Feasibility-ease of use	+	++
Cost-effectiveness	+	++
Onset of efficacy	Later	Sooner
INR reversal	Slow	More rapid
How long does it take to infuse?	Hours	<20 minutes
How much to infuse?	Large	Small
Risk of infection	Considerable	Minimal
Risk of transfusion-related acute lung injury (TRALI)	Higher	Low
Risk of fluid overload	Significant	Absent
Risk of thrombotic events	Minimal	Low

FFP indicates fresh frozen plasma; PCC, Prothrombin Complex Concentrate

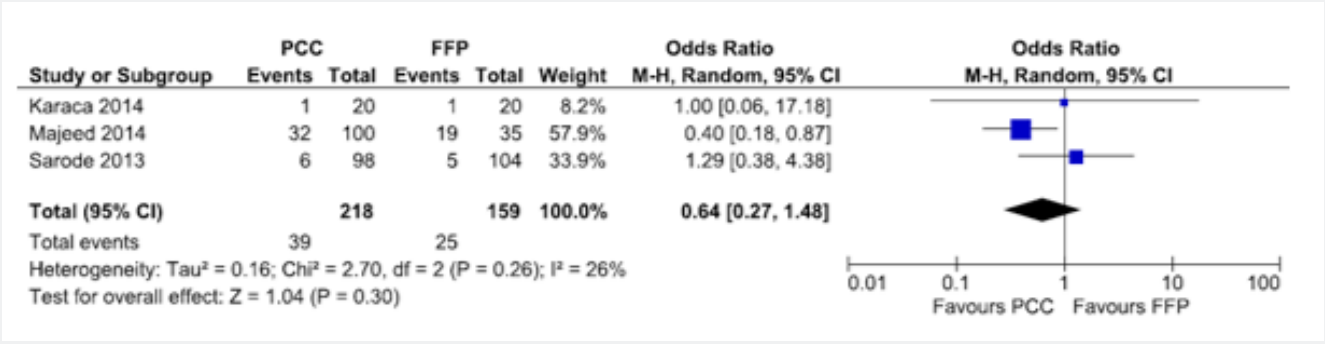

Figure 2: In the meta-analytic study of Brekelmans et al, 2017, three studies performed mortality analyses and compared PCC and FFP [8]. The mean mortality rates of patients treated with PCC and FFP were not statistically different (p = 0.73).

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Adverse effects and safety issues

The safety of PCC has been studied by many researchers in the recent decades. Thrombotic events are recognized as the main adverse effects of the treatment and have been postulated to increase in patients treated with higher doses PCC [38]. In many studies, the thrombotic complication rates were reported to fall in the range between 4% and 6.2% [8-10,39,40]. In a meta-analysis, 9 studies (incl. 2262 patents) reported on thrombotic complications. These complications were noted in 0-18% (mean 2.5%) of PCC and in 6.4% of those receiving FFP (BMPA 8). The thrombotic complication rate did not differ between the treatment arms (PCC or FFP) (p = 0.54). The authors concluded that 4-factor PCC is a safe option in reversal of VKA bleeding events in terms of adverse effects.

Dosing issues

One of the main disadvantages of PCC formulations used by different brands may be its non-standardized nature. Different sources of PCC are standardized based on factor IX levels. A main concern is their compositional differences whose effect on the outcomes are not established clearly [41]. Some sources of PCC supply a low level of factor VII, which are called 3 F-PCC. These 3 F-PCC are thought to be less efficacious in the treatment of VKA-induced coagulopathy [42]. One of the main dosing principles for PCC is using basal PCC as a guide for treatment. Table 3 depicts this rule for three different INR groups. Maximum dose for warfarin reversal is 5,000 units (calculated for 100 kg body weight). PCC is generally administered with vitamin K 10 mg IV [30,43].

Table 3: Dosing principles of 4F-PCC according to basal INR.

INR	Dose (U per kg body weight)
2 to 4	25 units/kg
4 to 6	35 units/kg
>6	50 units/kg

Conclusion:

PCC compounds has long been used to reverse coagulopathy following use of VKA. In selected cases with major bleeding, vitamin K can be used in conjunction with more rapidly-acting reversal agents such as PCCs. PCC has practical and theoretical advantages to FFP, as it can be used more rapidly and it does not warrant to be thawed or cross-match of blood groups. In patients bleeding on VKA, PCC dosage is established based on patient weight and target INR.

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