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INTRACRANIAL HEMORRHAGE WHILE ON WARFARIN: MANAGEMENT PRINCIPLES

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ABSTRACT

Introduction: Physicians prescribe vitamin K antagonists (VKA) with many different indications to induce coagulopathy which protect the patients from thrombotic processes and embolism thereof. On the other hand, these agents are not innocent and a substantial number of patients experience serious bleeding. This article is a review and critical analysis of the recent literature to analyse treatment with the agents used to treat intracranial hemorrhage (ICH) in patients on treatment with warfarin. **Methods:** Currently available literature on the use of vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCC) in ICH was identified by searches of available databases. Usage of these agents was addressed in the literature data found by searches of databases. The indications, efficacy and outcomes associated with the use of PCC (3 vs 4-factors) were abstracted from the manuscripts. **Results:** VKA–induced ICH represents a challenge for the healthcare system with a high mortality rate and long-term socioeconomical burden. Comparisons of results following treatment with PCC and vitamin K, Fresh frozen plasma (FFP) are summarized. PCC appears to be the first-line treatment for reduction of prothrombin time and

INR values to normal limits and restoration of hemodynamic status in patients with VKA-ICH. Dosing rules are also discussed. **Conclusion:** VKA–ICH can be viewed as a catastrophic event in the vulnerable group of anticoagulated patients. Although many reasonable options are available, PCC in conjunction with vitamin K administration appear to be the most fruitful strategy for resuscitation in VKA-ICH associated with high INR values. Adverse and untoward effects of the agents do not outweigh the benefits of usage in patients with VKA-ICH.

KEYWORDS: Prothrombin complex concentrates; vitamin K antagonists; warfarin; coagulopathy; intracranial hemorrhage.

INTRODUCTION

Many patients benefit from anticoagulant effects of vitamin K antagonists (VKA) in acute and chronic venous and arterial thromboembolic diseases, although nowadays they have been partly replaced by newly generated direct /new oral anticoagulants (NOACs).

Treatment with VKA therapy necessitates great caution because of its narrow therapeutic window, which is maintained by adjusting the dose to an international normalized ratio (INR) of 2.0 to 3.0 for most conditions.[1]

Up to one-fifth of the patients receiving anticoagulant agents experience bleeding every year.[2] Furthermore, major bleeding complications constitute an annual rate of 1.7 to 3.4%.[3] Annually 0.2–1% of all VKA users develops an ICH.[4,5] From another point of view, approximately 20% of all ICH is associated with use of anticoagulants.[4-6] Parry-Jones et al. culminated all patients' data on ICH from 16 stroke registries in 9 countries (n=10 282), of whom 17% were on VKA.[7]

Liver disease is another major factor which cause coagulation disorder worldwide. In a JACC review published in 2018, Qamar et al. depicted the mechanisms driving increased thrombosis and bleeding in patients with liver disease in various stages (8). In this group of patients, many different mechanisms contribute in deficient coagulation cascade and resultant clinically appparent bleeding diathesis. **Table 1** summarizes these factors in an average patient with cirrhosis or chronic liver disease.

Patients on anticoagulation therapy can experience any type of ICH—i.e., subdural / epidural hematoma, subarachnoid hemorrhage, and intracerebral hemorrhage. In a recent study,

Tsivgoulis et al. compared bleeding characteristics of NOACs and VKAs and showed that although functional outcome in the first three months was comparable after NOAC-ICH and VKA-ICH, patients with NOAC-ICH had smaller baseline hematoma volumes and less severe acute stroke syndromes.[9] Gerner et al. wrote that PCC administration was not associated with a reduced rate of hematoma enlargement in NOAC-related ICH, in contrast to blood pressure control.[10] They noted that these findings indicated the need of further investigations exploring new hemostatic reversal strategies for patients with factor Xa inhibitor-related ICH.

Use of anticoagulant therapy causes a boost in the risk of an ICH by almost 10-fold.[11] Another point is, up to one-fifth of all ICH cases are found to be anticoagulation-associated cerebrovascular accidents.[12,13]

Freeman has pointed out that ICH had a high mortality rate between 40 and 60%.[14] Other authors, also cited that the mortality rate of VKA-ICH have not declined despite PCC and other anticoagulant therapies.[15,16] The high mortality rates may be affected by hemorrhage expansion, as ICH triggered by VKA or NOACs is associated with greater expansion than spontaneous ICH.

Patients diagnosed with VKA-ICH require urgent correction of their coagulopathy to prevent hemorrhage expansion, limit tissue damage, and facilitate surgical intervention as necessary. Although there have been many different treatment modalities in the management of these patients, vitamin K, PCC and FFP are among the most commonly used treatment modalities, sometimes in combinations, to mitigate the effects of chronic or acute overdose of VKA.

The use of 3-factor PCC (activated and inactivated) and rFVIIa are off-label options in the treatment of VKA-ICH in the US.[11] Nonetheless, 4-factor PCC has been approved for the emergent reversal of VKA-ICH in acute major bleeding since 2013. FFP is the only other product approved for this indication in the US.[17]

This paper aims to review and analyse recent literature to highlight clinical characteristics along with treatment principles of VKA-ICH in patients on warfarin.

Pathophysiology and clinical characteristics of ICH while taking VKA

Brekelmans et al. analyzed all consecutive patients presented with bleeding while on VKA therapy in Netherlands.[18] Mean age of the patients in the sample was 74 years of age, 54%

were male and 79% received VKA for atrial fibrillation. Most patients presented with ICH (41%) followed by GI bleeding (36%) (Table 2).

Compared to general ICH cohorts, patients with OAC-ICH are older, exhibit larger ICH-volumes, have more frequent intraventricular hemorrhage, and importantly have a greater frequency of hematoma expansion (HE), all of which are significant outcome predictors determining an even poorer prognosis.[19-21] In VKA-ICH, on the other hand, HE may occur protractedly even exceeding 24h, if anticoagulation status is not reversed.

Hematoma expansion is a major cause of mortality in patients with VKA-ICH. In general, every third patients with ICH experience significant "early" hematoma expansion, and this risk is doubled in VKA-ICH.[22]

Management encompasses normalization of the INR, although optimum haemostatic management is controversial.[23]

Bleeding episodes during VKA treatment have been classified into four classes. A severe clinical presentation (mostly category 3) was observed in almost two-thirds of the patients (24). Category 4 describes immediately fatal or near-fatal events on presentation and includes around 1% to 5% of the patients.

How severe is the patient's bleeding?

If one or more of these factors are found in a patient, the bleeding is deemed a 'major hemorrhage'.

- Bleeding in a critical site: ICH, pericardial tamponade, airway, epistaxis (posterior), hemothorax, intra-abdominal bleeding and retroperitoneal hemorrhage, extremity bleeds
- Hemodynamic instability: mean arterial pressure<65 mm Hg; urine output <0.5 mL/kg/h
- Overt bleeding with hemoglobin drop >=2 g/dL or administration of >=2 U of packed RBCs

The clinical course of VKA-associated major bleeding events treated with PCC was categorized as 3 or 4 in terms of severity with abovementioned criteria, in 50% of patients.[15]

Treatment principles

Expedient reversal of anticoagulant effect in the management of ICH plays a critical role in alleviating the risk of hematoma expansion[19,25,26], which is definitely associated with grave outcome.[27]

Vitamin K takes several hours to initiate sufficient endogenous clotting factor production. Therefore, PCC and FFP were widely employed as emergent treatments to rapidly replace vitamin K– dependent clotting factors (II, VII, IX, X), with practice varying between different centers and countries.[28]

The four-factor PCC (4 F- PCC) solution contains factors II, VII, IX, and X, as well as the anti-thrombotic factors proteins C and S. 4-F PCC is non-activated agent suggested as the main treatment strategy of VKA-induced major bleeding from any body part by the contemporary guidelines.[29-31]

Only 4-factor PCCs are licensed for rapid warfarin reversal. The agent has the advantage of not requiring blood type testing. It can be stored at room temperature as lyophilized powder. Its dose is based on INR and body weight.[32,33]

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 (5–10 mg), would be appropriate. (Figure 1).

Administration of PCC was associated with effective haemostasis in 68% to 72% of patients with VKA-associated major bleeding.[15,34] This finding is in accord with recommendations on PCC in current guidelines.[29,35]

Vitt et al. evaluated the impact of an electronic order set designed to standardize and facilitate more timely reversal of coagulopathy in VKA- ICH in a three-year period.[36] They reported that order set use was associated with an important decrease in the time from identification of ICH on imaging to the treatment with PCC (83 vs 45 minutes; $P = .02$), more accurate dosing (29.4% vs 92.9%; $P < .01$). In brief, an electronic order set for administering PCC for VKA-ICH was associated with significantly faster time to PCC administration and increased dosing accuracy.

Alternative agents in the treatment

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.[30] 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. **Table 3** demonstrates main differences among FFP and PCC abstracted from published literature.

FFP is mostly available easily and less costly 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 (>1.5 L) and a protracted infusion time could be needed to increase concentrations of coagulation factors.[37] Eby et al. also pointed out the disadvantage of FFP with its large transfusion volume (10–20 mL/kg) required to partially and temporarily replace vitamin K-dependent factor levels[38]

These factors can limit usability of FFP in the emergency setting. Furthermore, high infusion volume can represent a drawback for patients with renal failure or cardiac insufficiency.

Tranexamic acid (TXA) has sparked attention in the management of almost every kind of ICH. Recently, Lancet has published an international randomised, placebo-controlled, phase 3 superiority trial called 'Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2)' with 2325 participants.[39] They reported that functional status 90 days after intracerebral haemorrhage did not differ significantly between patients who received TXA and those who received placebo, despite a reduction in early deaths and serious adverse events. In brief, TXA has not proven to decrease blood loss or improve clinical outcomes in patients presenting with ICH so far.

In a meta-analytic comparison pf PCC and FFP, Brekelmans et al. included 19 studies and 2878 patients with VKA associated bleeding in a 70-year period.[18] The mean mortality rates of patients treated with PCC and FFP were not statistically different ($p = 0.73$).

In a Cochrane paper published in 2015, authors reported 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.[40] Similarly, in a multinational registry study Parry-Jones et al. concluded that the combination of FFP and PCC might be associated with the lowest case fatality in reversal of VKA-ICH.[7]

In 2010, Woo et al. compared the safety and effectiveness of three methods- FFP, activated factor VIIa, and PCC in reversal of coagulopathy of warfarin in patients with severe IC.[41] As an adjunct to Vit K for rapid warfarin reversal, FVIIa and PCC appear more effective than FFP. Either FVIIa or PCC are reasonable options for reversal, but FVIIa is considerably more expensive and may have greater risk of INR rebound.

Steiner et al. conducted a multicentric randomized prospective trial of PCC and FFP in treatment of VKA-ICH between 2009 and 2015.[23] In patients with VKA-ICH, 4-F PCC appears to be superior to FFP with respect to normalizing the INR, and more expedient INR normalization was associated with smaller haematoma expansion. In a post-hoc analysis, 30 min after the start of drug infusion, 17 (65%) of 26 patients in the PCC group and none of 19 in the FFP group had an INR of 1·2 or lower. Their data favored the use of PCC over FFP in VKA-ICH.

Adverse effects and safety problems: Thrombotic events are known as the main untoward effects of the treatment and reported to boost in patients treated with higher doses PCC (42). In many studies, the thrombotic complication rates were reported to fall in the range between 4% and 6.2%.[18,32,34,43,44]

In 2016, Steiner et al. compared FFP and PCC in terms of thromboembolic events and other untoward effects of reversal treatment.[23] Three thromboembolic events occurred within 3 days (one in the FFP group and two in the PCC group), and six after day 12. 43 serious adverse events (20 in the FFP group and 23 in the PCC group) occurred in 26 patients. Six serious adverse events were judged to be FFP related (four cases of haematoma expansion, one anaphylactic reaction, and one ischemic stroke) and two PCC related (ischemic stroke and pulmonary embolism).

In a meta-analytic study, thrombotic complications were noted between 0-18% (mean 2.5%) of PCC and in 6.4% of those receiving FFP.[18]

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.[45] Three-factor-PCC compounds are thought to be less efficacious in the treatment of VKA-induced coagulopathy.[46]

Dosing principles of 4F-PCC is adjusted according to basal INR. For example, if the patient's INR is between 2 and 4, 25 units/kg will probably be adequate to normalize INR. If the INR is above 6, 50 units/kg will be necessary. Maximum dose for warfarin reversal is 5,000 units (calculated for 100 kg body weight).

In a study on VKA-ICH published in 2016, Abdoellakhan et al. administered PCC treatment to reduce the INR below 1.5 in an attempt to limit hematoma growth.[47] In order to facilitate PCC dosing, their institution had recently changed from a variable dose based on body weight, baseline- and target-INR, to a fixed 1000 IU fIX PCC dosing protocol for ICH. In a before and after design, they compared successful achievement of an INR <= 1.5 with a fixed dosing strategy versus the variable dosing strategy of PCC in patients presenting with ICH while on VKA. They reported that the fixed dose protocol necessitates additional PCC infusions more frequently to achieve a target INR below 1.5.

CONCLUSION

PCC has long been used to reverse VKA-ICH following use of VKA. PCC has advantages to FFP, as it can be used more practically, without a need to be thawed or cross-matched. Management of VKA-ICH comprises expedient reversal of K vitamin antagonism via administration of vitamin K, PCC or FFP, which should be tailored to resources and patients' situation. Adverse and untoward effects of PCC do not outweigh the benefits of the agent in patients with VKA-ICH.

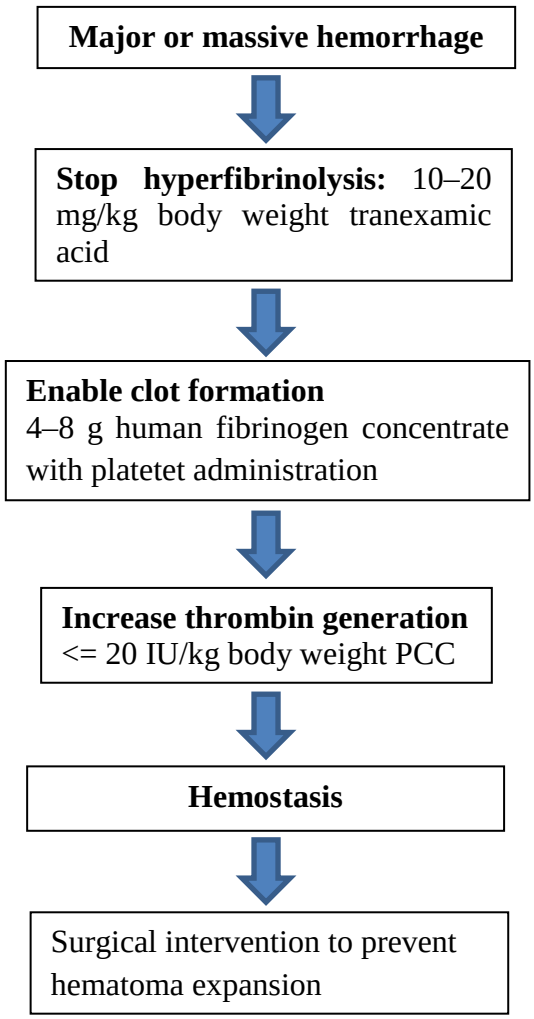

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Figure 1: Proposed algorithm for ICH in patients on anticoagulant therapy.

Table 1: Mechanisms paving the way to increased thrombosis and bleeding in patients with liver disease in various stages.

↑ Thrombosis	↑ Bleeding
Increased Platelet-Vessel Wall Interaction	**Reduced Platelet-Vessel Wall Interaction**
• ↑ von Willebrand factor	• ↓ Platelet count
• ↑ ADAMTS 13	• ↓ Platelet function
High Thrombin Generation	**Low Thrombin Generation**
• ↑ Factor VIII	• ↓ Fibrinogen
• ↓ Protein C, Protein S	• ↓ Factor II, V, VII, IX, X, XI
• ↓ Antithrombin	
• ↓ TFPI	
Low Fibrinolysis	**High Fibrinolysis**
• ↓ Plasminogen	• ↑ Tissue-plasminogen activator
• ↑ PAI	• ↓ Plasmin inhibitor
	• ↓ TAFI

ADAMTS 13: a disintegrin and metalloprotease with thrombospondin type 1 motif 13;

PAI: plasminogen activator inhibitor;

TAFI: thrombin-activatable fibrinolysis inhibitor;

TFPI: tissue factor pathway inhibitor.

Table 2: 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/or GIH constitute nearly 80%
Pre-treatment INR	Nearly 4
One-month mortality	5.8% to 60% (very high in those with ICH)

Table 3: 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.

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