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Tolerability and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) for warfarin and non-warfarin reversals

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ABSTRACT

Purpose: Current guidelines favor 4F-PCC over plasma for warfarin reversal. Uncertainty remains on its thrombotic risk and hemostatic effectiveness when used for direct-acting oral anticoagulants (DOACs), transplants, massive transfusion protocols (MTP), and non-anticoagulated patients. This study sought to evaluate the tolerability and effectiveness of 4F-PCC in a real-world setting.
Materials and methods: This was a retrospective study of adults who received 4F-PCC from March 2014 to December 2015. The primary outcome was thromboembolic events within 14 days. The secondary outcome was hemostatic effectiveness within 24 h.
Results: The final analysis included 212 patients. Primary reversal indication was major bleed in 165 patients (77.8%) and emergent surgery in 47 patients (22.2%). Thromboembolism occurred in 22 patients (10.4%), more in emergent surgery than major bleed reversals (17% and 8.5%, respectively). MTP and heart transplant patients had the highest thromboembolic event rates (44.4% and 28.6%, respectively). Hemostatic effectiveness was 65.8% (68% in major bleed and 58.1% in emergent surgery). DOAC patients achieved hemostasis most often (78.9%). Administration of any reversal agent, major surgery within 14 days, and MTP activation were significant predictors of thromboembolism.
Conclusions: Use of 4F-PCC in this real-world setting was associated with variable thromboembolic and hemostatic effectiveness rates based on the indication for reversal.

1. Introduction

Prothrombin complex concentrates (PCCs), including the four-factor agent Kcentra® (4F-PCC), have become the mainstay of treatment over plasma for reversal of warfarin-related major bleeds [1,2]. Several studies have reported faster INR correction with 4F-PCC than plasma for warfarin reversal both for major bleeds and prior to emergent surgery [3-7]. Prospective, randomized controlled trials of 4F-PCC reported thrombosis rates of 7.8% for major bleed reversals and 7% for emergent surgery reversals; hemostasis rates were 72.4% for major bleed reversals and 90% for emergent surgery reversals [3,4].

Despite its superior INR-lowering effect compared to plasma, uncertainty remains on the risks and benefits of 4F-PCC related to its thrombotic potential and hemostatic effectiveness in a real-world setting. The pivotal prospective clinical trials with 4F-PCC excluded patients with thrombotic risk factors or a history of recent thromboembolic events [3,4]. Moreover, in clinical practice, 4F-PCC is frequently used for indications beyond warfarin reversal, including reversal of direct-acting oral anticoagulants (DOACs), bleeding or surgery not associated with anticoagulation, and as part of massive transfusion protocols (MTPs). Additionally, 4F-PCC is used for warfarin reversal during left ventricular assist device (LVAD) explant to heart transplant. The evidence for these additional reversal indications is derived primarily from retrospective data [8-13]. These exclusions and limitations prevent a thorough and robust characterization of the actual thrombotic risks and hemostatic benefits of 4F-PCC and do not reflect real-world practice.

Previous investigation of 4F-PCC at NewYork-Presbyterian Hospital from March 2014 to December 2014 in 93 patients showed an overall thromboembolic incidence of 11.8% and identified heparin-induced thrombocytopenia (HIT), major surgery within 14 days, and presence of >6 thrombotic risk factors as significant risk factors for development of subsequent thromboembolic events [12]. A robust multivariable

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analysis for independent risk factors associated with thromboembolic events was not performed given the small event size. Additionally, thromboembolic event rates were not assessed in all patient subgroups of interest (notably DOAC reversals, LVAD explant to heart transplants, and MTPs), and hemostatic effectiveness was not assessed for emergent surgery reversals. The small sample size and limitations of the previous study drove the design of this current study to evaluate the tolerability and effectiveness of 4F-PCC in a real-world setting, through the assessment of thromboembolic event rates and hemostatic effectiveness rates.

2. Materials and methods

2.1. Data collection

This retrospective study evaluated patients who received 4F-PCC (Kcentra®) between March 1, 2014 and December 31, 2015 at NewYork-Presbyterian Hospital's Columbia University Irving Medical Center and Weill Cornell Medical Center, both tertiary-care institutions. The study was approved by institutional review boards at both medical centers. All patient data was extracted from the electronic medical record.

Adult patients who were 18 years of age or older and received at least one dose of 4F-PCC were included in this analysis. Patients who received 4F-PCC at an outside hospital were excluded given the inherent challenges of ascertaining the exact timing and dose of 4F-PCC as well as concomitant reversal agents or blood products administered. Patients diagnosed with coagulopathy, defined as those patients not on baseline anticoagulation who were reversed for documented or suspected coagulopathy (e.g., INR elevation secondary to liver disease) while neither actively bleeding nor undergoing emergent surgery, were also excluded.

Additional reversal agents given within 4 h of 4F-PCC administration (e.g., desmopressin, protamine, vitamin K, 3F-PCC, and activated 4F-PCC) and blood products administered within 6 h prior and 24 h after 4F-PCC administration (e.g., packed red blood cells [PRBCs], plasma, platelets, cryoprecipitate, and fibrinogen concentrate) were recorded.

Patients were classified based on the primary indication for 4F-PCC administration: major bleed or emergent surgery. Major bleeds were classified as anticoagulation-associated bleeds or non-anticoagulated bleeds. Anticoagulation-associated bleeds were further defined as warfarin- or DOAC-related bleeds. Non-anticoagulated bleeds included MTP activation. Although there is a guideline for use of concentrated factors in MTP at our institution, the decision to give 4F-PCC is left to clinician discretion. Patients with multiple intracranial hemorrhages (ICHs) were classified by the type/location of the primary bleed using neurosurgical documentation and radiographic imaging results, consistent with prospective studies in ICH [5,14]. Emergent surgery patients were defined as patients who were not bleeding and received 4F-PCC prior to a surgical procedure or other intervention.

2.2. Outcomes

The primary outcome was the cumulative incidence of thromboembolic events occurring in the 14 days following 4F-PCC administration. Thromboembolic events included upper and lower extremity deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, myocardial infarction (MI), line-associated thrombosis, and any other documented thrombosis. Daily physician progress notes in the 14 days following 4F-PCC administration were assessed and thromboembolic events were confirmed with reliable radiological imaging techniques and laboratory markers as appropriate. DVT was confirmed by Doppler ultrasound, PE by computed tomography pulmonary angiography, ischemic stroke by neuroimaging, MI by electrocardiogram and troponin elevation, line-associated thrombosis by Doppler ultrasound with documentation of indwelling venous catheters or evidence of upper extremity catheter at the site of thrombosis within 7 days of thrombosis detection, and other thromboses by reliable radiographic imaging modalities.

The secondary outcome was hemostatic effectiveness within 24 h of 4F-PCC administration for patients reversed for major bleeds or emergent surgery. For major bleeds with ICH, hemostatic effectiveness was achieved if the first neuroimaging result within 24 h of 4F-PCC administration showed no change or an improvement in hematoma volume. For patients experiencing any other type of major bleed, hemostatic effectiveness was achieved if hemoglobin did not decrease by >20% from baseline within 24 h of 4F-PCC administration. In patients reversed for a surgical intervention, hemostatic effectiveness was achieved if hemoglobin did not decrease >20% from baseline within 24 h and if no supplemental blood products containing coagulation factors (e.g., plasma, cryoprecipitate, fibrinogen concentrates, 3F-PCC, activated PCC) were given intraoperatively after 4F-PCC administration. For emergent surgery patients undergoing LVAD explant to heart transplant, hemostatic effectiveness was achieved with a score of “moderate” or better based on a multidisciplinary international consensus 9-point scoring system developed for perioperative bleeding in cardiac surgery [15]. For each LVAD patient, the following were assessed to determine the final overall risk score: chest tube output, delayed sternal wound closure, need for re-exploration, post-operative administration of blood products (specifically PRBCs, plasma, platelets, and cryoprecipitate), administration of recombinant factor VII concentrate, and intraoperative administration of 4F-PCC [15].

Additional secondary outcomes assessed for patients reversed for warfarin included INR correction and INR rebound. INR correction was defined as attaining an INR <1.5 on the first blood draw following 4F-PCC administration for patients with an INR of 1.5 or greater at baseline. The incidence of INR rebound, which occurred if the INR was corrected but thereafter increased to 1.5 or greater within 24 h, was also examined.

2.3. Statistical analysis

Descriptive statistics were used to assess for significant risk factors for thromboembolic events and hemostatic effectiveness. Categorical variables were evaluated with the χ^2 or Fisher's exact test. Continuous variables were evaluated with the independent *t*-test. A univariable analysis comparing patients who experienced thromboembolic events with those who did not was conducted using established thrombotic risk factors. All variables with $p \leq 0.2$ in the univariable analysis were included in a multivariable analysis to determine independent factors associated with thromboembolic events. Statistical significance was considered as any $p \leq 0.05$ in the multivariable analysis. All statistical analyses were performed using STATA Statistics/Data Analytics software (version 14.2, StataCorp LP, College Station, TX).

3. Results

3.1. Baseline characteristics

Two hundred and sixteen patients received 4F-PCC between March 2014 and December 2015. Four patients were excluded for coagulopathy, and a total of 212 patients were included in the final analysis. 4F-PCC was administered for reversal of a major bleed in 165 patients (77.8%) and for reversal prior to emergent surgery in 47 patients (22.2%). Fig. 1 shows the breakdown of included patients based on primary indication for 4F-PCC.

Overall, 59.9% of patients were male with a median age of 71 years. The most common indication for anticoagulation was atrial fibrillation (53.3%). The indication for 4F-PCC was warfarin reversal in 61.8% of patients and DOAC reversal in 19.8% (59.5% rivaroxaban, 31% apixaban, and 9.5% dabigatran). Non-anticoagulated patients comprised 18.4% of all patients. MTP patients comprised 4.2% of all reversals. Table 1