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Four-factor prothrombin complex concentrate for life-threatening bleeds or emergent surgery: A retrospective evaluation

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ABSTRACT

Purpose: Previous trials investigating usage of four-factor prothrombin complex concentrate (4F-PCC) excluded patients with various thrombotic risk factors. The objective of this study was to evaluate the safety and effectiveness of 4F-PCC in a real-world setting based on an institutional protocol that does not have strict exclusion criteria.
Methods: This was a retrospective study of adult patients who received 4F-PCC. The primary outcome was a confirmed thromboembolism within 14 days after 4F-PCC administration. Secondary outcomes included international normalized ratio (INR) correction to <1.5 at first draw and incidence of INR rebound for patients undergoing reversal of warfarin and hemostatic effectiveness for patients experiencing a bleed.
Results: Ninety-three patients received 4F-PCC. Sixty-three (67.7%) were reversed for bleeding and 30 (32.3%) for surgery. Eleven patients (11.8%) developed a thromboembolism within 14 days. The median (interquartile range) time to event was 5 (2-7) days. Significant risk factors were heparin-induced thrombocytopenia (P= .01) and major surgery within 14 days (P= .02), as well as the presence of >6 thrombotic risk factors (P= .01). For patients post-warfarin reversal, 45/63 (71.4%) achieved INR correction at first draw, 55/63 (87.3%) achieved INR correction within 24 hours, and 14/55 (25.5%) experienced INR rebound. Of these 14 patients, 8 (57.1%) did not receive concomitant vitamin K.
Conclusions: 4F-PCC was associated with a notable thromboembolic risk. All patient-specific risk factors should be considered prior to administration. 4F-PCC remains a useful agent for warfarin reversal. Lack of concomitant vitamin K may contribute to INR rebound.

1. Introduction

In April 2013, the Food and Drug Administration approved four-factor prothrombin complex concentrate (4F-PCC) in the United States under the proprietary name Kcentra [1]. 4F-PCC has been available outside of the United States for many years, being first approved in Germany in 1996 under the tradename Beriplex [2]. Kcentra is a concentrated mixture of inactivated vitamin K-dependent coagulation factors (factors II, VII, IX, and X) derived from human plasma, as well as protein C and protein S. Excipients in the formulation include heparin and antithrombin III. It currently has two labeled indications: warfarin reversal in patients with acute major bleeds and in patients requiring urgent surgeries or invasive procedures [1]. Other concentrated coagulation factor products are available on the market including three-factor prothrombin complex concentrate (3F-PCC), activated prothrombin complex concentrate and recombinant activated factor VII, but none are approved for the reversal of anticoagulation.

Recent international guidelines recommend the use of 4F-PCC over fresh frozen plasma (FFP) for reversal of warfarin in life-threatening bleeds [3-7]. Traditionally, FFP is infused at doses of 10 to 15 mL/kg to provide a bleeding patient with enough exogenous factors to promote hemostasis [8]. Limitations of FFP include risk of transfusion-related acute lung injury, hypocalcemia, disease transmission, prolonged time required for infusion, and potential for fluid overload, particularly in patients with heart failure, liver cirrhosis, or renal insufficiency. Kcentra is available as a lyophilized powder, allowing for easy reconstitution and rapid intravenous administration in small volumes [9-12]. For example, a 70 kg patient would receive 70 to 140 mL of 4F-PCC depending on the pre-treatment international normalized ratio (INR), as opposed to 700 to 1050 mL of FFP. In clinical studies, 4F-PCC has been demonstrated to provide a faster time to INR reversal compared to FFP [13-20]. In randomized clinical trials (RCT) comparing 4F-PCC and FFP for warfarin reversal in patients with major bleeding and patients requiring urgent procedures, significantly more patients achieved

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rapid INR reduction with 4F-PCC. A 7.8% and 6.8% incidence of thromboembolism was reported with 4F-PCC in the trials, respectively. Of note, patients with various thrombotic risk factors were excluded from both trials (e.g., history of a thromboembolic event within 3 months of enrollment, heparin-induced thrombocytopenia (HIT), inherited or acquired prothrombotic conditions, disseminated intravascular coagulation) [19,20].

Off-label use of 4F-PCC has also been investigated for reversal of the direct-acting oral anticoagulants. 4F-PCC normalized both prothrombin time and endogenous thrombin potential after administration of rivaroxaban in young, healthy volunteers [21-23]. In vivo and in vitro studies showed 4F-PCC partially restored endogenous thrombin potential and prothrombin time in healthy volunteers treated with apixaban [24,25]. Results from a study in healthy volunteers showed that 4F-PCC increased endogenous thrombin potential after dabigatran administration, but had no effect on activated partial thromboplastin time, ecarin clotting time, or thrombin time [21,26].

NewYork–Presbyterian Hospital's institutional protocol recommends 4F-PCC for reversal of coagulation deficiencies induced by warfarin, rivaroxaban, or apixaban in adult patients with life-threatening major bleeding or who require emergent surgery. It may also be used in patients with uncontrolled perioperative bleeding as part of a massive transfusion protocol (MTP). For reversal of warfarin, we follow the 4F-PCC dosing recommendations provided by the manufacturer (25-50 IU/kg depending on the INR). If administering 4F-PCC for reversal of direct-acting anti-Xa inhibitors, or as part of a MTP, we recommend a dose of 25 IU/kg with a maximum of 2500 IU. Additional indications are evaluated on a case-by-case basis and require approval from a hematologist. The protocol does not have strict exclusion criteria and all patients are eligible to receive 4F-PCC, regardless of the presence of various thrombotic risk factors. The aim of this study was to investigate the safety and effectiveness of 4F-PCC in a real-world setting without strict exclusion criteria.

2. Materials and methods

This was a retrospective study performed at NewYork–Presbyterian Hospital, Columbia University Medical Center and Weill Cornell Medical Center, both of which are tertiary-care institutions. Institutional Review Board approval was obtained from both medical centers and informed consent was waived given the retrospective study design.

All patients 18 years of age and older who received at least one dose of 4F-PCC between March 1, 2014 and December 31, 2014, were included in the analysis. There were no exclusion criteria applied. Demographic information, medical history, laboratory values, medication administration records, daily physician progress notes, and results of diagnostic imaging and tests were extracted from each patient's electronic medical record. All patients were retrospectively analyzed for 14 days after administration of 4F-PCC, until hospital discharge, or until death, depending on whichever came sooner.

The primary safety outcome was any confirmed thromboembolic event within 14 days after administration of 4F-PCC based on diagnostic imaging or tests and physician notes. Myocardial infarction was confirmed by electrocardiogram, ischemic stroke by neuroimaging, lower or upper extremity deep vein thrombosis (DVT) by Doppler ultrasound, pulmonary embolism by computed tomography pulmonary angiography, and other venous or arterial thromboembolisms were confirmed by reliable imaging techniques showing presence of the obstruction.

Secondary outcomes included hemostatic effectiveness for patients experiencing a bleed, as well as INR correction and INR rebound for patients undergoing reversal of warfarin. For patients with intracranial hemorrhages (ICH), hemostatic effectiveness was achieved if the first neuroimaging result within 24 hours showed an unchanged or improved bleed. For all other hemorrhages, including gastrointestinal bleeds (GIB), hemostatic effectiveness was achieved if hemoglobin levels did not drop more than 20% from baseline within 24 hours. For patients being reversed for warfarin, INR correction was achieved if the first INR draw after 4F-PCC administration was <1.5. Rebound occurred if INR correction was achieved and subsequently increased to ≥1.5 within the same 24 hour period.

The presence of the following thrombotic risk factors in each patient was assessed: age ≥75 years, body mass index ≥30 kg/m^2, active smoking, history of cardiovascular disease states, active cancer, history of thromboembolism, major trauma, major surgery within 14 days, 4F-PCC dose ≥35 IU/kg, concomitant blood products (ie, FFP, cryoprecipitate, platelets), and concomitant pharmacologic reversal agents (ie, aminocaproic acid, desmopressin acetate, protamine sulfate). In addition, we also identified patients with thrombotic risk factors that were excluded from the RCTs including a recent thromboembolism within the prior 3 months, HIT, and inherited or acquired prothrombotic conditions. The aforementioned 14 variables were collected to determine potential correlation with the risk of thromboembolism.

Descriptive statistics were utilized and compared with the chi-squared test or the Fisher's exact test as appropriate (STATA Data Analysis and Statistical Software, version 13, StatCorp LP, College Station, TX). A $P < .05$ was deemed to be statistically significant.

3. Results

3.1. Patient demographics

A total of 93 patients received 4F-PCC during the pre-specified time period. Patient demographics are summarized in Table 1. Sixty-three (67.8%) were reversed for acute bleeding and 30 (32.3%) were reversed for an invasive procedure. The most common type of bleed was ICH (66.7%), followed by GIB (11.1%). The most common type of surgery was cardiothoracic (56.7%), followed by exploratory laparotomy (20%).

Seventy-nine patients (84.9%) were on oral anticoagulation prior to 4F-PCC administration: 63 (79.7%) were reversed for warfarin, 11 (13.9%) for rivaroxaban, 3 (3.8%) for apixaban, and 2 (2.5%) for dabigatran. Fourteen patients (15.1%) were not on anticoagulation prior to 4F-PCC administration: 11 were reversed for an elevated INR and 3 as part of a MTP. All 14 of these patients were still included in our primary analysis.

3.2. Incidence of thromboembolism

Thromboembolic events were reported in 11 patients (11.8%) within 14 days after 4F-PCC administration. Of these events, 6 (54.5%) were upper extremity DVTs, 2 (18.2%) were myocardial infarctions, 1 (9.1%) was an ischemic stroke, 1 (9.1%) was a pulmonary embolism, and 1 (9.1%) was a dorsalis pedis arterial thrombosis. The median (interquartile range [IQR]) time to thrombosis was 5 (2 to 7) days. Additional information regarding these 11 patients is provided in Table 2.

Since the institutional protocol did not have strict exclusion criteria, our study included 15 patients with thrombotic risk factors that were excluded from the RCTs: 9 patients with a recent history of thromboembolism, 4 patients with inherited or acquired prothrombotic conditions, and 2 patients with HIT. Of these 15 patients, 4 (26.7%) developed a thromboembolic event. When comparing the 11 patients who developed a thromboembolic event versus the 82 patients who did not, 4/11 (36.4%) versus 11/82 (13.4%) had thrombotic risk factors that were excluded from the RCTs. This comparison did not reach statistical significance ($P = .07$).

The prevalence of notable thrombotic risk factors in all 93 patients is outlined in Table 3. A univariate comparison of risk factors was performed between the 11 patients who developed a thromboembolism and the 82 patients who did not. Significant differences were seen in major surgery within 14 days ($P = .02$) as well as heparin-induced thrombocytopenia ($P = .01$). Any history of thromboembolism seemed to trend towards a difference, but did not reach statistical significance ($P = .06$). Patients were also grouped by the number of prevalent risk factors. Individuals with 7 thrombotic risk factors were more likely to