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Protocolized warfarin reversal with 4-factor prothrombin complex concentrate versus 3-factor prothrombin complex concentrate with recombinant factor VIIa

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ABSTRACT

Introduction: Life-threatening bleeding can complicate warfarin therapy. Rapid anticoagulant reversal via replacement of vitamin-K dependent clotting factors is essential for hemostasis. We compare two methods of rapid factor replacement for warfarin reversal.
Methods: A retrospective cohort study of warfarin-treated patients experiencing life-threatening bleeding who received a reversal protocol comprised of 4F PCC or 3F PCC and rFVIIa was performed. Demographic, clinical and anticoagulant reversal information, and all adverse events attributed to warfarin reversal were recorded.
Results: 195 patients were included in final analysis. While baseline demographics were similar between groups, the 3F-PCC group had a longer ICU LOS and higher in-hospital mortality ($p < .01$, .01). Pre-reversal INR was similar between both groups, but post-reversal INR was significantly lower in the 3F-PCC group, 0.8 versus 1.3 ($p < .01$). Significantly more patients experienced thromboembolic complications in the 3F-PCC group than the 4F-PCC group ($p < .01$). Receipt of rFVIIa was significantly associated with thromboembolic complications.
Discussion: A 4F PCC reversal strategy is efficacious in INR reversal and provides lower thromboembolic risk as compared to 3F PCC with rFVIIa.

1. Introduction

Warfarin is one of the most commonly prescribed oral anticoagulants and is associated with a major bleeding rate of 3–3.4% per year.[1–6] Patients presenting with major or life-threatening bleeding due to warfarin require rapid INR normalization. Current anticoagulation reversal guidelines recommend the use of four-factor prothrombin complex concentrate (4F PCC) over fresh frozen plasma (FFP), due to its superior ability to rapidly and completely reverse INR with lower volume and fewer adverse events, yet alternate reversal strategies combining vitamin K with other PCCs persist.[7–12] Three-factor prothrombin complex concentrate (3F PCC) contains inactivated factors II, IX, X, and small amounts of factor VII, whereas 4F PCC contains all four factors inhibited by warfarin. 3F PCC has been used off-label for warfarin reversal but may not be as effective at reversing international normalized ratio (INR) without supplementary factor VII provided in products such as FFP or rFVIIa.[13–15]

Recombinant factor VIIa (rFVIIa) is used off-label for warfarin reversal. While effective at INR normalization, rFVIIa use has been associated with high rates of thromboembolism and increased risk of arterial thrombus.[8]

Prior to the commercial availability of 4F PCC in the United States, a warfarin reversal protocol combining 3F PCC with rFVIIa was used to create a four-factor analogue. Once available in early 2014, 4F PCC was incorporated into the standard warfarin reversal protocol. It remains unclear how 3F PCC-based strategies compare

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with 4F PCC.[16–18] The present study compares the safety and efficacy of the combination of 3F PCC + rFVIIa versus 4F PCC for the emergent reversal of patients with warfarin-associated major or life-threatening bleeding.

2. Material and methods

An institutional review board-approved, single-site retrospective cohort study of all patients admitted for major warfarin-associated bleeding to a large academic medical center from March 2011 through August 2016 was conducted.

Patients were included if they were 18 years of age or older, hospitalized for greater than or equal to 72 h, admitted for major life-threatening warfarin-associated bleeding requiring emergent reversal with either 4F PCC or the combination of 3F PCC and rFVIIa, and had an INR greater than or equal to 1.5 on admission. Patients were excluded if they were pregnant, reversed for any indication other than active bleeding, died within 12 h of hospital admission, had an INR less than 1.5, or received PCC or other reversal agent prior to admission.

Patients were identified in the electronic health record (EHR) by an order for and receipt of either 4F PCC or 3F PCC and rFVIIa. Patients were further screened through application of the inclusion and exclusion criteria, including documented prior to admission warfarin usage combined with elevated INR. Data were collected from chart review of the EHR. Information on the following were documented: demographics, clinical data, hospital and ICU lengths of stay, receipt of reversal agents, bleed location, coagulation parameters prior to and post-reversal, receipt of blood products, surgical interventions, indication for anticoagulation, use of antiplatelet agents, and thromboembolic complications.

The 3F PCC group consisted of patients who received a combination of the following: 50 units/kg 3F PCC (maximum: 4000 units) and 1 mg fixed-dose rFVIIa. The 4F PCC group consisted of patients who received 4F PCC dosed as follows: 25 units/kg if INR 2 to <4 (maximum: 2500 units), 35 units/kg if INR 4 to 6 (maximum: 3500 units), and 50 units/kg if INR > 6 (maximum: 5000 units). Protocols in both groups included a onetime dose of 10 mg IV vitamin K. Repeat doses of the reversal agent were allowed at the discretion of the provider.

The primary outcome of the study was efficacy at reversing INR to <1.4 upon repeat INR check after PCC administration. Timing of first repeat INR is standardized to 30 min, but compliance with the standard is variable; the time from reversal was collected.

Secondary efficacy outcomes included rate of rebound INR, hematoma expansion on repeat imaging in those with intracranial hemorrhage as determined by radiologist impression and packed red blood cell (pRBC) transfusion requirements pre- and 48 h post-reversal in those with gastrointestinal (GI) or traumatic hemorrhage. Rebound INR was defined as having achieved an INR <1.4 after PCC administration and then having an INR $\geq$1.4 within 48 h of reversal.

Safety outcomes identified as complications post-reversal during the index hospitalization were gathered from extensive chart review of the EHR, including progress notes, discharge summaries, and imaging. Complications included venous thromboembolism, ischemic stroke, myocardial infarction, transfusion reactions, and death. Surveillance for thromboembolic complications was performed at provider discretion.

Data were analyzed using IBM SPSS Statistics 22 Software with statistical significance defined as $\alpha \leq 0.05$. The Shapiro-Wilk W test was used to test continuous variables for normality. All continuous variables were tested for normality by Kolmogorov–Smirnov statistic and Shapiro–Wilk statistic. Nonparametric continuous variables were analyzed using Mann-Whitney-U Test, and categorical variables were compared with Pearson chi-squared test, Fisher exact test, or likelihood ratio test. A Poisson log-linear regression used to model the counts of thrombotic complications associated with the receipt of rFVIIa, receipt of FFP, receipt of vitamin K, and post-reversal INR.

3. Results

A search of all medication orders for 3F PCC and rFVIIa between March 2011 and February 2014 identified 374 patients. The reversal protocol was not administered to 145 patients. A total of 111 patients were excluded, with 118 patients included for final analysis in the 3F PCC group. A search of all medication orders for 4F PCC between February 2014 and August 2016 identified 191 patients. A total of 114 patients were excluded, with 77 patients included for final analysis in the 4F PCC group.

Patient characteristics of the 3F and 4F PCC groups are displayed in Table 1. The median Sequential Organ Failure Assessment (SOFA) score and Glasgow Coma Scale were similar between both groups. While hospital length of stay (LOS) was similar, ICU LOS was significantly longer in the 3F PCC group. In-hospital mortality was significantly greater in the 3F PCC group.

The distribution of treatment versus prophylaxis indications for anticoagulation for both groups was similar (Table 1). The most common indications for anticoagulation in both groups were atrial fibrillation, venous thromboembolism, and the presence of a mechanical valve. Use of prior to admission antiplatelet agents was similar. There was no difference in bleed location between the groups. Intracranial hemorrhages comprised the majority of cases. The most common type of ICH in the 3F PCC group was intraparenchymal hemorrhage (IPH), followed by subdural hematoma (SDH) and subarachnoid hemorrhage (SAH). In the 4F PCC group, the most common was SDH, followed by IPH and SAH.

A description of reversal agents administered is displayed in Table 2. Significantly more patients received vitamin K and FFP in the 3F PCC group. The post-reversal INR was significantly lower in the 3F PCC group (see Table 3).

In patients with ICH, the incidence of expansion of bleed on repeat imaging was similar. In trauma patients, transfusion requirements in the first 48 h after reversal did not differ between the two groups.

Significantly more patients experienced thromboembolic complications in the 3F PCC group than the 4F PCC group (Table 4). The most common thromboembolic complication in both groups was deep venous thrombosis (DVT). Because a single patient could suffer from multiple thromboembolic complications, a Poisson log-linear regression was used to model the count of complications in relation to prothrombotic factors. Receipt of rFVIIa, FPP, vitamin K and post-reversal INR were independent variables in this model with significance assessed by Wald statistic. Only receipt of rFVIIa had statistically significant association with thromboembolic complications (Table 5).

4. Discussion

This study demonstrated similar INR normalization efficacy and rates of rebound INR between two reversal strategies. The combination of 3F PCC and rFVIIa presented a greater than four-fold risk for thromboembolic events as compared to 4F PCC.

The American College of Chest Physicians guidelines recommend 4F PCC in conjunction with vitamin K for the reversal of warfarin-associated bleeding, but depending upon the availability of factor products, other reversal strategies such as the use of 3F PCC persist.[7,9,11,12] There are no randomized controlled trials and few retrospective cohort analyses directly comparing 3F and 4F