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RISK OF VENOUS THROMBOEMBOLISM AFTER RECEIVING PROTHROMBIN COMPLEX CONCENTRATE FOR WARFARIN-ASSOCIATED INTRACRANIAL HEMORRHAGE

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☐ **Abstract—Background:** Prothrombin complex concentrates (PCCs) are commonly used to rapidly reverse warfarin-associated coagulopathy; however, venous thromboembolism (VTE) is an established adverse event. **Objective:** To determine risk factors for VTE AFTER administration of a three-factor prothrombin complex concentrate (3F-PCC) for warfarin-associated intracranial hemorrhage (ICH). **Methods:** Retrospective chart review of all patients with a warfarin-associated ICH who received a 3F-PCC at a single tertiary care hospital between 2008 and 2013. Outcomes were VTE events (defined as deep vein thrombosis [DVT], pulmonary embolism [PE], limb ischemia, transient ischemic attack, cerebrovascular accident, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction, and unexplained sudden death) occurring within 30 days of 3F-PCC administration. Risk factors in subjects with and without VTE complications were compared via Fisher's exact test, Student's *t*-test, Mann-Whitney *U* test, and univariate logistic regression as appropriate. **Results:** Two hundred nine subjects received 3F-PCC for warfarin-associated ICH. There were 22 VTE events in 19 subjects (9.1%). Baseline characteristics of subjects with and without VTE were similar. There was a significant increase in VTE events in 29 subjects who were taking warfarin for a previous PE or DVT (36.8% vs. 11.6%, *p* = 0.007; logistic regression odds ratio 4.455, *p* = 0.005). **Conclusions:** Patients with a prior history of PE or DVT who were given 3F-PCC for warfarin-associated ICH were 4.5 times more likely to sustain a VTE within 30 days. A careful analysis of risks and benefits of rapidly reversing anticoagulation must be made prior to the administration of 3F-PCC in this patient population. © 2016 Elsevier Inc.

☐ **Keywords**—warfarin; PCC; Profilnine; venous thromboembolism; intracranial hemorrhage

INTRODUCTION

Warfarin, a vitamin K antagonist, is used extensively to treat and prevent various types of venous thromboembolism (VTE), including cerebrovascular accident (CVA), pulmonary embolus (PE), deep vein thrombosis (DVT), and thrombus associated with atrial fibrillation. Among the bleeding complications of warfarin, intracranial hemorrhage (ICH) is associated with the worst morbidity and

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mortality (1,2). Prothrombin complex concentrates (PCCs) are commonly used as a means to rapidly reverse warfarin-associated coagulopathy in the setting of life-threatening bleeding. However, the use of PCCs has been associated with thromboembolic complications (3–6). Options to reverse warfarin-associated coagulopathy include vitamin K, fresh frozen plasma (FFP), and various PCC products, and depending on the nature and presentation of the ICH, not all patients require or receive a PCC.

There are multiple studies investigating the efficacy of PCCs on the reversal of INR, decrease in bleeding, and overall outcomes for warfarin-induced coagulopathy (1,3,4,7–10). In the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, the American College of Chest Physicians recommend PCC administration for vitamin K antagonist-associated major bleeding (11). However, rapidly reversing anticoagulation poses a risk of thromboembolism. Multiple studies report thromboembolic complication rates after PCC administration ranging from 1.4% to 10% (3–6,12).

Although overall VTE rates after PCC have been reported, there is sparse literature on the risk factors for developing a VTE after receiving PCC to reverse warfarin-associated coagulopathy. A recent review suggested a low incidence of VTE events in patients "without underlying risk" after modern PCC administration, although it did not clearly define the risk factors (13). A recent large meta-analysis of adverse events of PCCs did not elucidate risk factors for VTE (12). Of note, a safety and efficacy study for the first four-factor PCC approved for this indication in the United States (Kcentra®, CSL Behring, King of Prussia, PA) noted a VTE rate of 11.6% in subjects with a remote history of VTE, as compared to 2.9% without a history of VTE, although the overall number of subjects with VTE was low and this stratification is discussed in the Kcentra package insert and not the original article (14,15).

In the United States, three-factor PCCs (3F-PCC) have been used for rapid reversal of warfarin-associated hemorrhage since the 1970s; their use has accelerated since the mid-2000s. 3F-PCCs generally include factors II, IX, and X, with little or no factor VII. Our institution used a 3F-PCC (Profilnine® SD, Grifols Biologicals, Los Angeles, CA) to reverse warfarin-associated bleeding from 2008 to 2013. During 3F-PCC use, our institutional guidelines for life-threatening bleeding suggested intravenous administration of 30 units/kg of Profilnine, 10 mg of vitamin K, and 2 units of fresh frozen plasma.

Emergency physicians are often tasked with making the complex decisions regarding reversal of coagulopathy in patients with warfarin-associated ICH; they are required to weigh the benefits of rapid INR reversal against the risks of PCCs, such as VTE complications

and cost of the product. Therefore, determining risk factors for PCC-induced thromboembolic events would be of great benefit to the clinician. The goal of this study is to determine risk factors for developing VTE after administration of a 3F-PCC for warfarin-associated ICH.

MATERIALS AND METHODS

This study was a retrospective chart review at an academic tertiary care hospital. The project received expedited approval from the hospital's Institutional Review Board. The Emergency Department is an urban, Level I trauma center at a tertiary care referral center that sees 55,000 patients per year.

All patients who received a 3F-PCC at our hospital between January 1, 2008 and April 15, 2013 were identified from an inpatient pharmacy database. We excluded all patients who received 3F-PCC for indications other than ICH to limit heterogeneity in the subject population. A standardized data abstraction form was designed. For each subject, electronic medical records were reviewed for age, past medical history, medications, indication for taking warfarin, Glasgow Coma Scale score (GCS) on presentation, INR on presentation, and after receiving intervention (3F-PCC, usually with vitamin K and FFP), findings on head computed tomography (CT), surgical interventions, thromboembolic complications at 72 h and 30 days, neurologic outcomes, and disposition. VTE complications were defined as: DVT, PE, acute limb ischemia, myocardial infarction (both ST-segment elevation and troponin leak), transient ischemic attack, CVA, and unexplained sudden death (as a surrogate marker for PE or myocardial infarction).

Data were de-identified and stored in a Redcaps database. To ensure fidelity of data abstraction, a co-investigator analyzed 10% of included charts while blinded to initial data abstraction. Because inter-observer agreement with respect to medical history and VTE outcomes was high (99%), we included these data in our analysis. Because inter-observer agreement for GCS, INR values, head CT findings, and neurologic outcomes was lower (85%), likely owing to variations in laboratory values and imaging findings chosen at different times and to interpretation of medical notes, we present these data but did not rely on them for our conclusions.

A thrombophilic state was defined as active cancer receiving chemotherapy or radiation therapy, systemic lupus erythematosus, Factor V Leiden mutation, prothrombin gene mutation, anticardiolipin antibody, antiphospholipid antibody, protein C deficiency, protein S deficiency, antithrombin deficiency, dysfibrinogenemia, heparin cofactor II deficiency, plasminogen deficiency, plasminogen deficiency, Factor XII deficiency, or an idiopathic hypercoagulable state.