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EVALUATION OF FIXED-DOSE FOUR-FACTOR PROTHROMBIN COMPLEX CONCENTRATE FOR EMERGENT WARFARIN REVERSAL IN PATIENTS WITH INTRACRANIAL HEMORRHAGE

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□ **Abstract—Background: Different strategies exist for dosing four-factor prothrombin complex concentrate (PCC4) for international normalized ratio (INR) reversal in the setting of life-threatening bleeding. Fixed doses ranging from 1000 IU to 1750 IU have demonstrated efficacy similar to weight-based dosing, however, few studies look exclusively at intracranial hemorrhage (ICH). Objective: Our aim was to evaluate whether a fixed dose of 1000 IU of PCC4 achieves INR reversal similar to weight-based dosing in patients with ICH who were anticoagulated with warfarin. Methods: We compared a weight-based dose vs. 1000 IU PCC4 between January 2014 and January 2017. The primary end point was achieving an INR < 1.5. Secondary end points included in-hospital mortality, patient disposition, and reversal defined by INR < 1.6. Results: A total of 31 patients were included in the weight-based group and 30 were included in the fixed-dose group, with baseline INRs of 2.98 and 2.84, respectively (p = 0.39). Twenty-two patients (71%) achieved an INR < 1.5 in the weight-based group vs. 16 (53%) in the fixed-dose group (p = 0.15), while 25 (81%) achieved an INR < 1.6 in the weight-based group vs. 22 (73%) in the fixed-dose group (p = 0.49). There was no difference in the number of patients discharged to home (19% vs. 20%; p = 0.95) or in-hospital mortality (26% vs. 27%; p = 0.93). Conclusions: We found a non–statistically significant difference in warfarin reversal to an INR goal of < 1.5 when comparing a fixed dose of 1000 IU PCC4 and a weight-based dose for ICH. Further studies correlating clinical outcomes with INR reversal are needed.**

□ **Keywords—warfarin; anticoagulant; hemostasis; intracranial hemorrhages; pharmacology**

INTRODUCTION

Warfarin-related hemorrhages result in thousands of emergency department (ED) visits and hospital admissions annually. These are associated with high morbidity and mortality, particularly in the setting of intracranial hemorrhage (ICH), which carries a mortality rate of 40–60% (1–4). The number of patients who require anticoagulation has increased steadily in recent years, likely due to increased rates of atrial fibrillation and recommendations for antithrombotic therapy. Warfarin remains the most common agent prescribed due to factors including cost, familiarity, and available evidence in various comorbidities (2–6). An estimated 1.3% of patients anticoagulated with warfarin will experience major bleeding events, despite adequate monitoring of the international normalized ratio (INR) (1–3).

Rapid reversal of the INR has been demonstrated to reduce the risk of hematoma expansion and associated poor outcomes for patients presenting with ICH (7,8). Currently, four-factor prothrombin complex

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concentrate (PCC4) is considered the gold standard for rapid INR reversal over fresh frozen plasma (FFP) (9,10). While both contain vitamin K−dependent clotting factors II, VII, IX, and X, PCC4 eliminates the need for blood typing, reduces adverse events associated with transfusing large volumes and decreases the time to administration.

Most guidelines now recommend PCC4 for emergent INR reversal in the setting of major bleeding, however, the optimal dose remains an area of active investigation (9,10). Dosing regimens based on patient's actual body weight, indication, and INR on presentation have been studied with no regimen proving superior to another (5,6,11–14). Several articles have examined the efficacy and safety of fixed doses of PCC4 for rapid INR reversal, though few have looked exclusively at intracranial hemorrhage. The available studies vary in the fixed dose administered and range from 1000 IU to 1500 IU (11–17).

Available data from fixed-dose PCC4 administration suggests that this is an effective strategy to rapidly reverse warfarin anticoagulation though INR reversal has not been correlated with reduced mortality. PCC4 has been shown to be superior to FFP in faster INR reversal with fewer adverse events (1,2). Utilization of a fixed-dose protocol may shorten time to administration and potentially further improve outcomes and decrease costs.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective cohort study conducted at a 450-bed academic medical center. In April 2015, the Pharmacy and Therapeutics committee approved a protocol change from a weight-based dose of PCC4 to a 1000-U fixed dose, repeated as necessary to reach goal INR. The weight-based therapy followed the package labeled dose of 25, 35, and 50 U/kg as indicated by pretreatment INR. This retrospective review looks at pre- and post-protocol dosing changes to evaluate if there was a difference in achieving goal INR or clinical outcomes.

Selection of Participants

A list of PCC4 administrations was generated from electronic medical system records beginning in January 2014 until January 2017. Patients were eligible for inclusion if they were at least 18 years of age and received PCC4 in the ED for ICH while on chronic warfarin therapy. Patients were excluded if their INR was < 2 on presentation or if repeat laboratory values were unavailable, such as instances where withdrawal of care was pursued. This study was approved by the Institutional Review Board at the (The University at Buffalo).

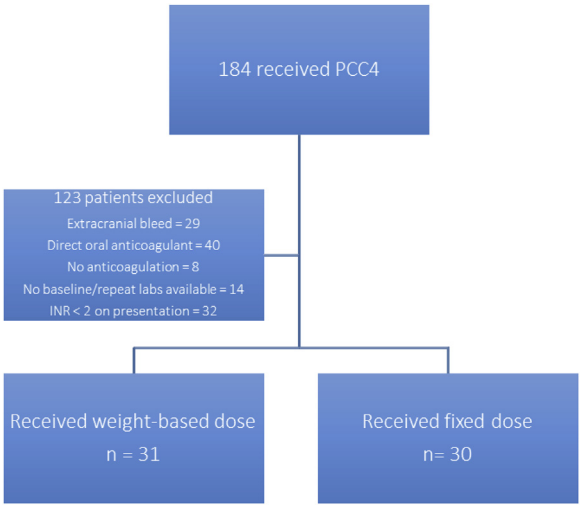

Figure 1. Flowchart of study inclusion. PCC4 = four-factor prothrombin complex concentrate; INR = international normalized ratio.

Interventions

Patients were included in either the fixed-dose or the weight-based group based on the initial dose of PCC4 administered as documented in their electronic medical record. The weight-based dose was administered from January 2014 until April 2015, thereafter the 1000-U fixed dose was utilized.

Methods and Measurements

Doses of PCC4 were taken directly from each patient's medication administration records in the electronic chart. Doses recorded as administered within 20 min of each other were collected as one dose, which is standard practice in our institution. It was also noted whether or not a patient received a second dose of PCC4 at any time after the initial dose. The laboratory values closest to the recorded time of administration of the first dose were recorded for the pre- and post-administration values. Details regarding mortality and patient disposition were obtained from discharge summaries.

Outcomes

The primary end point was INR reversal defined by achieving an INR < 1.5. Secondary end points included in-hospital mortality, disposition on discharge, INR reversal to < 1.6 and necessity of additional doses of PCC4 to meet the INR goal. Further evaluating INR