Interhospital Transfer Delays Anticoagulation Reversal in Warfarin-Associated Intracranial Hemorrhage

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Introduction: Intracranial hemorrhage (ICH) is a complication of warfarin-associated anticoagulation resulting in significant morbidity and mortality. The purpose of this study was to assess whether interhospital transfer delays the administration of 4-factor prothrombin complex concentrate to patients with warfarin-associated ICH. *Materials and Methods:* This was a retrospective cohort study of all patients presenting to a 60,000 visit academic ED between August 2013 and July 2017 requiring emergent anticoagulation reversal for warfarin-associated ICH. Patients were divided into 2 cohorts: (1) transfer patients who arrived at the academic center after receiving care in a local community hospital and (2) control patients who presented directly to the academic center ED. The primary outcome was time to administration of 4-factor prothrombin complex concentrate. Secondary outcomes included hematoma expansion, guideline-adherent vitamin K administration (10 mg IV), intensive care unit and hospital length of stay, disposition at discharge, and in-hospital mortality. *Results:* This study included 203 patients (177 transfer patients, 26 control). The median time to arrival in transfer patients was 186 minutes (IQR 145-242). The median time to administration of guideline-adherent therapy in transfer patients was 296 minutes, compared to 119 minutes in patients who were not transferred (median difference= −176, 95% confidence interval −143 to −208, $P \leq .001$). Delay in anticoagulation reversal did not result in hematoma expansion, intensive care unit and hospital length of stay, discharge disposition, or in-hospital mortality. *Conclusions:* Patients requiring interhospital transfer experienced significant delays in guideline-adherent anticoagulation reversal for warfarin-associated ICH, but this delay was not associated with worse outcomes.

Key Words: 4-factor prothrombin complex concentrate—intracranial hemorrhage—warfarin—interhospital transfer

Introduction

Intracranial hemorrhage (ICH) is a serious complication of warfarin therapy resulting in significant morbidity and mortality. The guideline endorsed treatment for emergent reversal of warfarin-associated ICH is early administration of intravenous vitamin K and 4-factor prothrombin complex concentrate (4F-PCC).[1-3] 4F-PCCs are favorable over fresh frozen plasma (FFP) in the setting of emergent international normalized ratio (INR) reversal due to the small total volume administered, reduced risk of adverse reactions from pooled plasma products, and rapid onset of anticoagulation reversal, with no increased risk of thromboembolic events compared to FFP.[4,5]

Guidelines for the management of spontaneous and traumatic ICH do not provide a specific time frame goal

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for administration of anticoagulation reversal; however both emphasize rapid reversal of anticoagulation in the setting of ICH.[1,2] Rationale for early reversal of anticoagulation is derived from the frequency of early hematoma growth after hemorrhagic stroke and associated decline in neurological function with hematoma expansion.[6-8] The association of ICH-mortality with hematoma expansion has been repeatedly established.[7,9,10] Therefore, preventing hematoma expansion with the early administration of 4F-PCCs remains a top priority in patients presenting with anticoagulation associated ICH.

Although there is endorsement from multiple guidelines, 4F-PCCs are costly, making their availability limited to larger academic and community hospitals.[11] Marginal access to 4F-PCC in rural and community hospitals has been confirmed though surveys of factor product availability in hospitals in our region, but the impact on treatment metrics and patient outcomes is not known.[11] We hypothesized that this unavailability of guideline-recommended reversal agents would be associated with a significant delay in anticoagulation reversal in patients transferred to a tertiary referral center. The primary objective of this study was to quantify the delay of guideline-adherent reversal of warfarin-induced anticoagulation in patients transported from other facilities. Secondary objectives included time to any reversal agent administration, hospital and intensive care unit (ICU) length of stay (LOS), in-hospital mortality, and discharge disposition.

Materials and Methods

We conducted a single-center, retrospective review of all emergency department (ED) patients presenting to a Midwestern tertiary referral center ED with a warfarin-associated ICH who received 4F-PCC between August 2013 and July 2017. Warfarin-associated ICH was defined as patients diagnosed with ICH who had elevated INR at admission and warfarin reported on their home medication list. For patients who received 4F-PCC on multiple ED visits during the study period, only the first visit was included in the analysis. Data were abstracted from the electronic medical record by a trained research assistant who was blinded to study objectives. Approximately 25% of data entries were reviewed by study personnel to verify accuracy of data collection and documentation.

All variables were defined a priori and were available for abstraction from the electronic medical record (EMR). Variables collected from the EMR included: gender, age, weight, ICH location and mechanism, indication for warfarin therapy, concomitant medications, outside hospital treatment, time to 4F-PCC administration time and dose, Glasgow Coma Scale, ICH score, and National Institutes of Health Stroke Scale, ICU and hospital LOS, disposition at discharge, INR, midline shift, maximum thickness of lesion, as well as the presence of hydrocephalus, intraventricular hemorrhage, and epidural hematoma.

The primary outcome of interest was time to administration of 4F-PCC from initial hospital arrival. Time to administration of 4F-PCC was determined by calculating the difference between the time 4F-PCC was administered and time of initial presentation to the hospital. Due to the nonparametric distribution of time, median, and interquartile ranges (IQR) are reported. Secondary outcomes included time to any reversal agent administration, time to INR <1.5, in-hospital mortality, disposition at discharge, hospital and intensive care unit length of stay, National Institutes of Health Stroke Scale score at admission and discharge, in-hospital mortality, guideline adherence with vitamin K administration, and change in hematoma size. Guideline adherent administration of vitamin K was defined as a dose of 10 mg given via intravenous route.[1-3] Differences in continuous variables across transfer or control were examined using the Student's t test for means or the Wilcoxon test of medians. Categorical variables were compared using the Pearson chi-square test. Based on a small internal audit we found that the average time to 4F-PCC administration was approximately 120 minutes after arrival to our ED. To detect a difference of 30 minutes in time to administration of 4F-PCC between groups ($\alpha = .05$, 80% power), the estimated necessary sample size was 44 total patients.

The design and results reporting were completed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.[12] All analyses were completed using SAS software, Version 9.3 of the SAS System for Microsoft, SAS Institute Inc., Cary, NC. The study received local Institutional Review Board approval under waiver of informed consent.

Results

Two-hundred and three patients were included in the final study analysis (Figure 1). Of these patients, 177 were

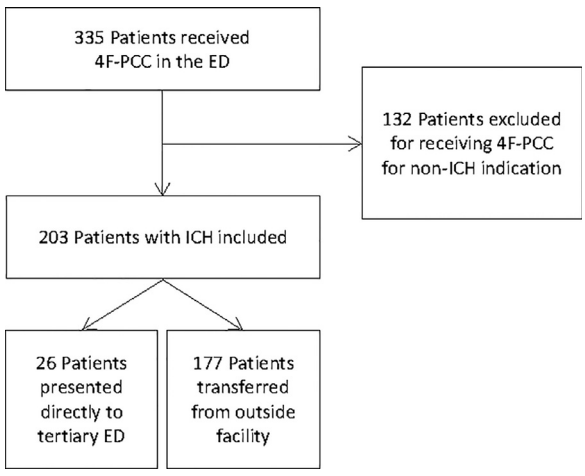

Figure 1. *Study subjects and design. Flow diagram of included controla and transfer patients for analysis*