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Activated prothrombin complex concentrate for warfarin reversal in traumatic intracranial hemorrhage

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ABSTRACT

Background: Patients with traumatic intracranial hemorrhage (TIH) anticoagulated with warfarin are at an increased risk of mortality. Fresh frozen plasma (FFP) and vitamin K have been the standard treatment for warfarin reversal; however, guidelines now recommend the use of prothrombin complex concentrate (PCC) for warfarin reversal in patients with life-threatening bleeding. Our protocol uses one vial (~1000 units) of activated PCC (aPCC) for warfarin reversal, regardless of the weight or presenting international normalized ratio (INR). The purpose of this study was to determine the safety and efficacy of using fixed, low-dose aPCC for warfarin reversal in patients with TIH.

Methods: This was a retrospective chart review that included patients with an Abbreviated Injury Scale Head score of ≥3, TIH, and initial INR ≥ 1.5 on warfarin. Patients aged <18 years and those with no repeat INR were excluded. The primary outcome was to compare the percentage of patients with INR ≤ 1.4 after receiving aPCC versus FFP within 24 hours.

Results: Eighty-nine patients were in the FFP group and 31 patients in the aPCC group. The INR was reversed more effectively in the aPCC group compared with the FFP group (90.3% versus 69.7%, $P = 0.029$). The median time (hours) to reversal was also significantly shorter in the aPCC group compared with the FFP group (3.75 versus 6.75, $P = 0.003$). However, there was no difference in mortality (35.5% aPCC versus 22.2% control, $P = 0.162$) or incidences of thrombosis.

Conclusion: Fixed, low-dose aPCC is safe and more effective at reversing the effects of warfarin than FFP in patients with TIH.

Introduction

Millions of patients in the US are prescribed warfarin each year, and multiple studies have shown the risk of death from traumatic intracranial hemorrhage (TIH) to be significantly higher in patients taking warfarin than those not on warfarin.[1-3]

Warfarin is a vitamin K antagonist that produces anticoagulation through the depletion of coagulation factors II, VII, IX, and X. Historically, in the setting of severe or life-threatening bleeding, the standard of care (SOC) for rapid reversal of warfarin was vitamin K in combination with fresh frozen plasma (FFP). FFP provides faster reversal of warfarin

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than vitamin K alone, but the volume required to reverse coagulopathy may lead to volume overload with subsequent sequelae.[4,5] In addition, the time necessary to complete multiple transfusions is not ideal for life-threatening bleeding, especially intracranial hemorrhage. Owing to these limitations, prothrombin complex concentrate (PCC) is now the recommended reversal agent when immediate reversal of warfarin is indicated.[6-8]

PCC is a solution of concentrated coagulation factors containing variable amounts of factors II, VII, IX, and X. PCC products are classified as either 3-factor PCC, which contain factors II, IX, and X with negligible amounts of factor VII or 4-factor PCC. In addition, there is a 4-factor PCC product that contains activated factor VII and is referred to as activated PCC (aPCC). Currently, dosing recommendations for the reversal of warfarin with PCC are highly variable with guidelines suggesting doses from 10-50 units/kg.[5-9] More recently, studies have shown that using smaller, fixed doses of 4-factor PCC and aPCC has been effective in reversing warfarin in the setting of life-threatening bleeding.[10-12]

Our institution adopted a fixed, low-dose aPCC–dosing regimen, and the purpose of this study was to determine the safety and efficacy of our aPCC-dosing protocol versus FFP and vitamin K only for the reversal of warfarin in patients with TIH.

Methods

This was an Institutional Review Board–approved, retrospective study from January 2010 to November 2015 comparing the safety and efficacy of FFP versus fixed, low-dose aPCC in patients with TIH, and a waiver of informed consent was obtained. The study was performed at a level I trauma center and community teaching hospital.

Patients were included in the study if they were admitted to the hospital with a traumatic brain injury (TBI), an Abbreviated Injury Scale (AIS) Head score $\geq$3, had evidence of intracranial hemorrhage on imaging, and were on warfarin with an international normalized ratio (INR) $\geq$ 1.5. Patients were excluded if they were aged <18 years or if there was no repeat INR available.

The patients were divided into two study groups. The control group consisted of all patients who received FFP $\pm$ vitamin K alone. Any patient who met the inclusion criteria and who received aPCC was included in the aPCC group. In 2012, Orlando Health made aPCC the preferred agent for reversal of warfarin in the setting of life-threatening bleeding including TBI, although the use of only FFP $\pm$ vitamin K was still permitted and left to the discretion of the physician. At that time, there were no US Food and Drug Administration–approved PCC products available in the US for warfarin reversal, and aPCC was the only 4-factor product commercially available. PCC products are pooled coagulation factors that range in actual units per vial based on lot number; therefore, dosing guidelines were created and recommend a standard, fixed dose of one vial (~1000 units) of aPCC for the reversal of warfarin, regardless of INR. For lot numbers with less than 750 units per vial, the dose was rounded to two vials. Administration of aPCC exceeding the recommended dose along with repeated dosing was allowed and left to the discretion of the physician. FEIBA (Baxter Healthcare Corporation, Westlake Village, CA) was the aPCC product used for the entire study period.

The primary efficacy outcome of the study was to compare the rate of warfarin reversal between the two groups, with successful reversal defined as an INR $\leq$ 1.4 within 24 hours of initial reversal agent administration. Secondary efficacy outcomes included time to INR $\leq$ 1.4 (up to 48 hours), need for neurosurgical intervention (defined as craniotomy/craniectomy, external ventricular drain placement, intracranial pressure bolt placement, or burr hole procedure), time to neurosurgical intervention (defined as time from first administration of FFP, vitamin K, or aPCC at our institution to either pre-procedure time-out or anesthesia induction), intensive care unit and hospital length of stay, mechanical ventilation days, incidence of acute respiratory distress syndrome, incidence of ventilator-associated pneumonia, adjunctive blood product and reversal agent usage, and mortality. The primary safety outcome was incidence of venous thromboembolism in each group.

Patients were identified through our institution's trauma registry database. Patient data included basic demographics (age, gender, race, height, and weight), dose and indication for warfarin, and type of intracranial hemorrhage. Laboratory and intervention data included pre- and postintervention INR(s), dose(s) of reversal agent(s) used, and type plus the number of blood products administered within the first 24 hours. Outcome data collected included time to surgical intervention intensive care unit and hospital length of stay, duration of mechanical ventilation, hospital mortality, discharge disposition, and diagnosis of thromboembolic events.

Statistical analysis was performed using SPSS, version 22.0 (IBM Corporation, Armonk, New York). Nominal data were assessed using chi-square and Fisher's exact test. Outcomes with continuous data were assessed with Student's t-test and the Mann–Whitney U test, where appropriate. A P-value of <0.05 was used to determine statistical significance.

Results

A total of 3043 patients with documented TBI and an AIS Head score $\geq$3 were screened for analysis, with 142 meeting the inclusion criteria. Furthermore, 22 patients were excluded from the analysis because of having no repeat INR available. A total of 120 patients were included in the study, with 89 patients in the control group and 31 patients in the aPCC group (Figure). There were no statistically significant differences in baseline characteristics observed between the groups (Table 1). The mean age for patients in both groups was 77 years, and atrial fibrillation was the most common indication for warfarin. The median Injury Severity Score, while numerically higher in the aPCC group (17 versus 10), was not statistically different ($P = 0.145$). There were two patients (one in each group) who presented with multisystem trauma and hemorrhagic shock. The median admission INR was similar between the groups (2.8 in the control group and 2.6 in the aPCC group; $P = 0.739$).

For the primary outcome, a significantly higher percentage of patients in the aPCC group achieved an INR $\leq$ 1.4 within