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Original Contribution

Evaluation of fixed dose 4-factor prothrombin complex concentrate for emergent warfarin reversal

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ABSTRACT

Objectives: Four-factor prothrombin complex concentrates (4FPCCs) are emerging as the standard of care for emergent warfarin reversal due to their ability to rapidly and effectively achieve hemostasis. The ideal dose of this medication is not known. Recently, our hospital instituted a protocol where all doses of 4FPCC were a fixed dose of 1500 IU. This protocol provides 4FPCC rapidly and precludes delay waiting for international normalized ratio (INR) values. The purpose of this study was to evaluate our experience with this fixed dose protocol.
Methods: This is a retrospective review of patients who received 1500 IU of 4FPCC for emergent warfarin reversal between March 2014 and January 2015. Demographic and clinical data regarding administration, efficacy, and safety were collected and analyzed.
Results: A total of 39 patients met inclusion criteria. The most common indication for treatment was intracranial hemorrhage (28, 71.8%). The median INR at presentation was 3.3, and the median INR after a single dose of 1500 IU was 1.4 ($P < .001$). A total of 36 patients (92.3%) achieved successful reversal with a target INR of less than 2.0, and 28 patients (71.8%) achieved successful reversal with a target INR of 1.5 or less. There were no thrombotic adverse events within 7 days.
Conclusions: Administration of a fixed dose of 1500 IU of 4FPCC leads to high rates of successful INR reversal and no related thrombotic adverse events within 7 days, and there was no need to wait for INR at presentation. These findings suggest good efficacy and safety when using 1500 IU of 4FPCC for emergent warfarin reversal.

1. Introduction

Warfarin is an oral anticoagulant commonly prescribed for treatment and prevention of thrombotic and thromboembolic diseases. The major complication associated with warfarin is hemorrhage, which accounts for thousands of emergency department (ED) visits annually and can cause significant patient morbidity and mortality [1,2]. When patients on warfarin present to the hospital with major, life-threatening hemorrhage, it is imperative to reverse the pharmacologic effects of this medication and achieve rapid hemostasis. Several different options exist to reverse warfarin, including fresh frozen plasma (FFP); vitamin K; recombinant vitamin K–dependent factors (such as recombinant factor VIIa); and prothrombin complex concentrates (PCCs), including 3- and 4-factor formulations.

Historically, FFP has been the mainstay of treatment for warfarin reversal due to its widespread availability, clinician familiarity, and low cost. There are, however, several disadvantages to FFP—a large volume of plasma is often necessary to fully reverse warfarin (up to 10-15 mL/kg), it is a human blood product so providers must either provide universal AB plasma or wait for ABO compatibility testing before administration, and there is a prolonged time to thaw [3,4].

For these reasons, newer agents such as PCCs have gained popularity when emergent warfarin reversal is indicated. For several years, 4-factor PCC (4FPCC) has been used extensively in the international setting, but 4FPCC was first approved for use in the United States in 2013 [5]. Four-factor PCC is a plasma concentrate that contains vitamin K–dependent coagulation factors (II, VII, IX, and X, in addition to protein C, protein S, antithrombin III, and human albumin). The primary advantage of 4FPCC over FFP is its significantly faster time to international normalized ratio (INR) reversal and achievement of clinical hemostasis with a similar safety profile [6-9]. Four-factor PCC is now recommended for use in emergent oral anticoagulation reversal by multiple national and international guidelines [10-12].

Despite increasing popularity of 4FPCC, the ideal dose of this medication is not known. The dose of 4FPCC that is approved for use on the package insert is based on the patient's INR at presentation and body weight. This dose of 4FPCC ranges from 25 to 50 U of factor IX per kilogram of body weight (international units per kilogram), with a maximum dose specified for each presenting INR range based on a 100-kg maximum. This particular dosing regimen has been studied extensively [6,13]. Other dosing regimens have been studied as well; these include regimens based just on body weight [14] and based on indication for

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administration [15] as well as lower fixed doses [16-18]. Despite all of these studies, including those that have directly compared dosing regimens [19,20], no regimen has been proven to be superior or has emerged as the standardized optimal dose.

In 2014, our hospital instituted a protocol where the initial dose of 4FPCC administered was targeted as a fixed dose of 1500 IU. This dose was given to all adults regardless of presenting INR, patient weight, or indication for administration. This protocol provides 4FPCC as rapidly as possible and precludes delay waiting for INR values. In addition, lower doses result in lower costs. The decision to use this dosing regimen was approved after extensive review by the hospital's Pharmacy and Therapeutics Committee and the Transfusion Service. This was the dose chosen by these clinical committees based on the success of prior Canadian literature using 1000 IU [16]. Our hospital chose to modify this to 1500 IU to account for higher expected patient weights in our region and increase the likelihood of successful reversal after a single dose (as we are a high-acuity level 1 trauma center).

This study documents our hospital's experience to date with this fixed dose protocol. To our knowledge, no prior studies have looked exclusively at 1500 IU fixed doses of 4FPCC in the setting of emergent warfarin reversal.

2. Methods

2.1. Study design

This study is a retrospective review of all patients who received 1500 IU of 4FPCC for emergent warfarin reversal after the institution of a recently approved fixed dose protocol. All consecutive cases from March 2014 to January 2015 were reviewed. Retrospective cohort design was used, as the study intervention had been previously implemented. The institutional review board approved the study. Informed consent was waived.

2.2. Study setting and population

The setting for this study was an urban level I trauma center with more than 95 000 ED visits annually. The decision to administer 4FPCC was at the discretion of the ordering physician. The 4FPCC used was Kcentra (CSL Behring, Marburg, Germany). Patients were included in the study if they were administered 1500 IU of 4FPCC per the fixed dose protocol for the purpose of emergent oral anticoagulation reversal for any clinical indication. Any oral anticoagulant that antagonizes vitamin K–dependent coagulation factors was included. Patients were included regardless of their initial INR at presentation, even if the INR later returned as normal (or subtherapeutic) after the 4FPCC was administered. These patients were included because this is an inevitable occurrence when giving 4FPCC before obtaining an INR at presentation.

Patients were excluded from the cohort if there was no post-4FPCC administration INR value available (due to death or transfer to other facility). This decision was made before data collection, and the rationale was that without these data, there would be no way to determine efficacy in these cases. Only patients on chronic oral anticoagulation were eligible for inclusion; acute overdoses were excluded. Other exclusion criteria included age younger than 18 years.

2.3. Study protocol

All cases were identified using the transfusion service's records for 4FPCC authorization. All data were collected using the hospital electronic medical record (Epic) and the laboratory information system (Cerner Millennium). Data were collected by 2 of the authors and entered directly into an electronic database. Data points collected included age, weight, diagnosis/indication for treatment, hospital location of administration, type of chronic oral anticoagulant, dose administered (which differed slightly from 1500 IU based on vial size), cost of dose, other reversal agents given (FFP and vitamin K), and patient outcome.

Data on the incidence of thrombotic events within 7 days of 4FPCC administration were also collected. For patients who died before 7 days, these data were collected until the time of death. Thrombotic events of interest included deep vein thrombosis, pulmonary embolism, acute coronary syndrome, limb ischemia (due to a venous or arterial process), and nonhemorrhagic stroke or transient ischemic attack. The providers of the transfusion service monitored for thrombotic events prospectively after 4FPCC administration as part of their clinical protocol. To ensure that no events were missed, the authors reviewed all documentation during the patient's hospitalization, documentation from any subsequent clinic or ED visits within 7 days, and any imaging studies performed (such as ultrasound for deep vein thrombosis or computed tomographic scan for pulmonary embolism).

Pre-4FPCC administration INR values (presenting INR) as well as the times they were obtained were recorded. The value used was the most recent INR collected before the administration time. Post-4FPCC administration INR values (post-INR) and the times they were obtained were also recorded. This was defined as the next INR collected after the administration time. Because of the nature of retrospective data collection and systematic issues related to electronic documentation during emergency resuscitations (particularly blood draw timing and labeling), there were some discrepancies between the electronic medical record and the laboratory information system records for INR values and times. If these discrepancies existed between the 2 records, the INR and time used for data analyses were the one closest chronologically to the medication administration time. In 2 cases, additional clinician and nursing documentation was necessary to determine correct presenting and post-INR values and times.

All cases with discrepancies underwent consensus review by the authors. Rates of successful INR reversal were then determined using 2 different targets, both of which were determined a priori. The first target used was a post-INR less than 2.0; the second target used was a post-INR of 1.5 or less. Two cutoffs were used because the definition of successful INR reversal varies greatly in the literature, regionally, and within different scopes of clinical practice (surgical vs nonsurgical patients). Finally, cost data were obtained. This was cost for the hospital pharmacy, not cost incurred by the patient. The cost per administered dose was calculated based on the known cost per international unit available to the hospital's pharmacy. Then, the potential cost if dosing was based on the package insert was calculated using presenting INR, patient weight, and the formulas provided in the package insert.

2.4. Data analysis

Statistical analysis was performed using SPSS 22.0 (2013; IBM Corp, Armonk, NY) after the completion of data collection. Confidence intervals, interquartile ranges (IQRs), and medians were calculated when appropriate. For the purpose of calculation, INR values greater than 10 (which is the upper limit detected on the hospital laboratory equipment) were included as INR equal to 10. Presenting INR and post-INR medians were compared by Wilcoxon signed rank test.

Next, comparisons were made between the group with post-INR of 1.5 or less and post-INR greater than 1.5 to attempt to determine factors associated with successful INR reversal. Data points compared included age, weight, median presenting INR, and percentage of INR values greater than 10. Comparisons were made by Mann-Whitney *U* test and Fisher exact test.

3. Results

There were 41 patients who received 4FPCC during the study period. Two patients were excluded due to having no available post-INR values (as previously described), leaving 39 total patients for analyses. All patients included were on chronic oral anticoagulation. There were