American Journal of Emergency Medicine 35 (2017) 871–874

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Comparison of the safety and efficacy between 3-factor and 4-factor prothrombin complex concentrates for the reversal of warfarin☆

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ARTICLE INFO

Article history:
Received 1 September 2016
Received in revised form 12 January 2017
Accepted 23 January 2017

Keywords:
Anticoagulation reversal
Prothrombin complex concentrate
Thromboembolic events
Warfarin

ABSTRACT

Purpose: Prior to the Food and Drug Administration approval of 4-factor prothrombin complex concentrate (4F-PCC), only 3-factor PCC (3F-PCC) products were available in the US. There is limited data comparing the safety and efficacy of 3F-PCC versus 4F-PCC. The purpose of our study, therefore, was to compare the safety and efficacy profiles of 3F-PCC versus 4F-PCC for the emergent reversal of warfarin.

Methods: A single-center, retrospective cohort analysis compared patients who received 3F-PCC or 4F-PCC for the emergent reversal of warfarin due to life-threating bleeding from January 2013 to September 2015. The primary objective of this study was the percentage of patients whose international normalized ratio (INR) reversed to ≤1.5 within 8 h of PCC administration. The secondary safety objective was incidence of thromboembolic events at 7 days post PCC.

Results: A total of 137 patients were included. The median baseline INR was 3.15 in the 3F-PCC group and 3.1 in the 4F-PCC group. The median post-PCC INR was 1.4 in the 3F-PCC group and 1.3 in the 4F-PCC group. INR ≤1.5 was achieved in 45/58 (78%) patients in the 3F-PCC group and 46/58 (79%) patients in the 4F-PCC group ($p = 0.61$). The thromboembolic event rate between the two groups at 7 days was similar, 4/68 (5.9%) for 3F-PCC versus 4/69 (5.8%) for 4F-PCC ($p = 1.0$).

Conclusions: There was no significant difference in the percentage of patients who achieved an INR ≤1.5 between the 3F-PCC and 4F-PCC groups for emergent reversal of warfarin.

1. Introduction

Patients presenting with life threating bleeding in the setting of the vitamin K antagonist (VKA) warfarin, may require emergent anticoagulation reversal. Therapeutic options for emergent warfarin reversal include administration of vitamin K, fresh frozen plasma (FFP), and prothrombin complex concentrates (PCC). There may be disadvantages, however, with the use of FFP and vitamin K, making PCC's a favorable option. For instance, FFP requires matching and thawing, which may delay therapy. Patients may also require large volumes of FFP for adequate reversal, with the potential to cause fluid overload and an increased risk for transfusion-related acute lung injury [1]. In regards to vitamin K, its delayed onset of action, despite its prolonged reversal, may make it a less favorable option for monotherapy compared to FFP and PCC.

The 9th edition of the American College of Chest Physicians practice guidelines for the use of oral anticoagulants recommends the use of 4-factor PCC (4F-PCC) in combination with intravenous vitamin K over the use of FFP for the rapid reversal of warfarin [1]. However, this recommendation for the use of 4F-PCC is based on limited data at the time of its publication. While 4F-PCC is recommended in the aforementioned clinical practice guidelines, multiple PCC products exist and are classified as either 3-factor PCC (3F-PCC) or 4F-PCC. Contents of each PCC product available in the United States are listed in Table 1 [2].

While, 4F-PCC was approved in 2013 by the Food and Drug Administration (FDA) for the urgent reversal of VKAs in acute major bleeding and has been available in Europe and Canada since 1996, none of the 3F-PCC products available in the US contain FDA approved labeling for this indication. Unfortunately, data is limited for recommending 4F-PCC over the use of 3F-PCC for this indication.

PCC products are not without their risk for adverse events. The most concerning adverse event associated with these products is the increased risk for thromboembolic events. The thromboembolic event rate in a phase III trial for 4F-PCC was 7.8% at 45 days compared to 6.4% in the FFP group [3]. The rate of thromboembolic events for 3F-PCC has been reported up to 8% [4-9].

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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http://dx.doi.org/10.1016/j.ajem.2017.01.049
0735-6757/

Table 1
Components of factor products [2].

Factor contents[a]	Factor II	Factor VII	Factor IX	Factor X	Protein C	Protein S	Protein Z	Anti-thrombin III	Heparin
Bebulin® VH	100	< 5	100	100	–	–	–	–	< 0.15
Profilnine® SD	150	35	100	100	–	–	–	–	–
Kcentra®	106	55.1	100	141.4	120.7	86.2	124.1	2.1	1.7

[a] IU per 100 IU of Factor IX.

The purpose of our study was to compare the safety and efficacy of 3F-PCC and 4F-PCC for the emergent reversal of warfarin for life-threating bleeding.

2. Methods

2.1. Data collection and study variables

This was a single-center, retrospective cohort study at a large tertiary care hospital. Patients greater than or equal to 18 years old, who received 3F-PCC from January 1, 2013 to May 31, 2014 or 4F-PCC from June 1, 2014 to September 15, 2015 for the emergent reversal of warfarin, were included. Only patients who received PCC at our hospital, either in the Emergency Department or during their inpatient stay were included. Prisoners, pregnant patients, or patients who received 4F-PCC prior to heart transplantation were excluded. This study was approved by the investigational review board of Allegheny-Singer Research Institute within Allegheny General Hospital in Pittsburgh, Pennsylvania.

Patients were identified through PCC dosing sheets that were completed by a pharmacist at the time of PCC dispensing and then filed after dispensing was complete. These sheets were required for all patients who were ordered either 3F-PCC or 4F-PCC.

The dose of 3F-PCC and 4F-PCC administered was based on our institutional PCC dosing protocols approved by the Pharmacy and Therapeutics Committee within the hospital (Table 2). During January 1, 2013 to May 31, 2014, 3F-PCC was the hospital's formulary approved PCC product. Starting from June 1, 2014 until present, 4F-PCC was the formulary PCC product that patients received. Patients in the 3F-PCC group received Bebulin® VH (Baxter Healthcare Corporation, Westlake Village, CA) [10]. Patients in the 4F-PCC group received Kcentra® (CSL Behring, Marburg, Germany) [11].

The PCC dosing strategy per our institutional protocols are listed in Table 2. Adherence to the institutional PCC dosing protocol was defined as patients meeting each of the following: baseline INR of ≥ 2.5, 2 units of FFP administered to patients who only received 3F-PCC with a baseline INR ≥ 4, received the correct PCC dose based on weight and baseline INR, received PCC for emergent bleeding only, follow-up INR drawn within 30 min after PCC administration, and received 10 mg of intravenous Vitamin K. Our institutional 3F-PCC dosing protocol recommended that FFP be administered in patients who were to receive 3F-PCC with an INR ≥ 4, as 3F-PCC has very low amounts of Factor VII.

The primary objective of this study was the percentage of patients achieving an INR reversed to ≤1.5 within 8 h of PCC administration. Secondary objectives included the incidence of thromboembolic events at 7 days post PCC, in-hospital all-cause mortality, percentage of patients who received additional blood products within 48 h of PCC administration, discharge disposition, and rate of adherence to PCC protocols.

Table 2
PCC dosing per protocol.

Baseline INR	2.5–4	4–6	>6
3F-PCC dosing[a]	25 units/kg	35 units/kg (actual body weight) PLUS 2 units of FFP	
4F-PCC dosing	25 units/kg	35 units/kg	50 units/kg

[a] 3F-PCC doses were rounded to nearest vial size; INR, international normalized ratio; PCC, prothrombin complex concentrate.

2.2. Statistical analysis

All analyses began with assessment of the normality of the data using the Shapiro-Wilk test. Patients' demographic, clinical and procedural data were reported as mean ± standard deviation if they were continuous variables and counts and percentages if they were categorical variables. Non-normally distributed data were reported as the median and range. The chi-square test or Fisher's exact test was used to determine the relationship between nominal variables. The independent samples *t*-test or the Mann-Whitney rank sum test was used to compare continuous variables between the 3F-PCC and 4F-PCC groups. The rates of all types of adverse events were summarized using counts and percentages. A value of $p < 0.05$ on two-tailed testing was considered statistically significant. Statistical analyses were performed using IBM-SPSS Statistics, version 20.0 (IBM-SPSS Inc., Armonk, NY).

3. Results

A total of 144 patients were screened. Seven patients were excluded and 137 patients were included in the final analysis (Fig. 1). Baseline characteristics are listed in Table 3. Patient weights were significantly higher in the 4F-PCC group. The most common indications for warfarin were atrial fibrillation and venous thromboembolism (VTE) in both groups, with significantly more patients with diagnosed VTE in the 3F-PCC group. The most common indication for PCC in each group was intracranial hemorrhage, 70.6% of the patients in the 3F-PCC group and 78.3% of patients in the 4F-PCC group. The median baseline INR was 3.15 and 3.1 ($p = 0.15$) for the 3F-PCC and 4F-PCC groups, respectively.

The results for the primary and secondary objectives are summarized in Tables 4 and 5. There were a total of 6 patients in each group who did not receive a repeat INR after PCC administration and 4 patients in the 3F-PCC group and 5 patients in the 4F-PCC group who did not receive their repeat INR within 8 h of PCC administration. Of the remainder analyzed patients, 45 of the 58 patients (78%) in the 3F-PCC group

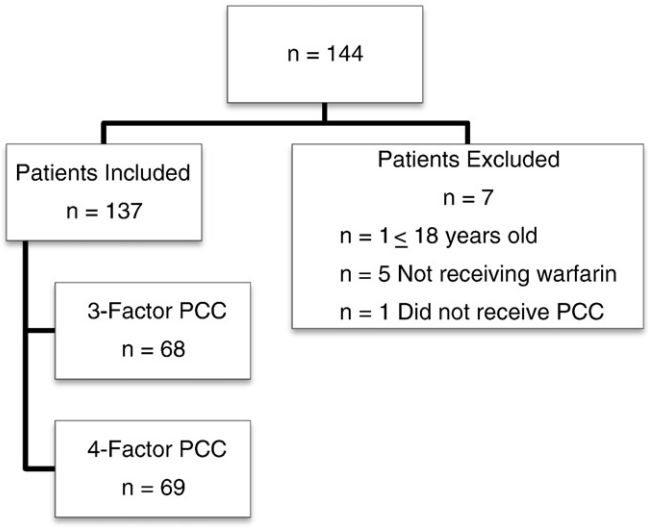

Fig. 1. Patient inclusion and exclusion.