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Brief Report

Four-factor prothrombin complex concentrate dose response relationship with INR for warfarin reversal

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ABSTRACT

Introduction: For reversal of warfarin-induced coagulopathy, FDA labeling of four-factor prothrombin complex concentrate (4F-PCC) endorses a dosing strategy based on body weight and baseline INR. Recent literature suggests lower, fixed doses of 4F-PCC may be equally efficacious. The present evaluation aims to characterize the relationship between 4F-PCC dose and degree of reduction in INR.
Methods: This is a retrospective, single-center review of 4F-PCC administrations for warfarin reversal between May 2014 and August 2017. The primary endpoint evaluates the relationship between doses of 4F-PCC and INR measurement after reversal, represented as a linear regression. Exploratory endpoints characterize the relationships of both body weight and baseline INR, the components determining initial 4F-PCC dose, with INR after reversal. Additionally, for records presenting with an INR of 2–3.9, mean INR after reversal was characterized as a function of two 4F-PCC dose cohorts (< 30 and ≥30 IU fIX/kg).
Results: A significant linear relationship between 4F-PCC dose and INR after reversal (INR after 4F-PCC = 1.3651–0.00004(4F-PCC Dose), $p = 0.0071$, $R^2 = 0.0630$) was observed. Body weight and baseline INR were not correlated with INR after reversal. The subgroup analysis of records with presenting INR of 2–3.9 demonstrated no difference in mean INR after reversal with 4F-PCC for those receiving <30 IU fIX/kg and those receiving ≥30 IU fIX/kg.
Conclusion: This evaluation found no clinically relevant relationship with 4F-PCC doses and degree of INR reversal. Further prospective study is required to determine optimal dosing schemes of 4F-PCC for warfarin reversal.

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1. Introduction

Oral anticoagulants, including warfarin, are commonly used for primary and secondary prevention of arterial and venous thromboembolism [1]. Use of warfarin, independent of the indication, is associated with increased risks of bleeding [2]. Rapid and complete reversal of the pharmacologic effects of warfarin is necessary to manage patients experiencing more severe, and even life-threatening, bleeding episodes.

Reversal of warfarin-induced coagulopathy can be achieved with phytonadione administration, although the slow onset of action is problematic in the setting of a life-threatening bleeding episode. Clotting factor-based agents provide options for more rapid correction of warfarin-induced coagulopathy [3]. The most recently approved agent is 4F-PCC, a non-activated, blood coagulation factor replacement product containing coagulation factors II, VII, IX, and X as well as proteins C and S and heparin. If used concomitantly, phytonadione and 4F-PCC

can achieve rapid and sustained reversal of warfarin-induced coagulopathy [3]. FDA labeling for 4F-PCC utilizes a dosing scheme based on the total body weight and presenting INR [4]; however, dose finding studies have not been performed and the optimal dose remains unknown [5,6].

There is emerging evidence evaluating the efficacy and safety of alternative dosing strategies for 4F-PCC. Various studies have evaluated outcomes with fixed doses of 4F-PCC ranging from 1000 to 1500 IU fIX [7-9]. Despite marked variability in the methods and definitions for successful warfarin-induced coagulopathy reversal across these studies, each suggests that fixed 4F-PCC doses, especially those that evaluated doses of 1500 IU fIX [8,10], were comparable to variable dosing schemes. A recently conducted systematic review aimed to present efficacy outcomes across a variety of 4F-PCC dosing strategies, but was ultimately unable support or refute the use of body weight and presenting INR for 4F-PCC dosing [11]. The present study sought to characterize the relationship between dose of 4F-PCC and the degree of reduction in INR.

2. Methods

This is a retrospective review of 4F-PCC dose-effect for reversal of warfarin-induced coagulopathy, approved by our Institutional Review

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Records meeting
Inclusion Criteria:
310

Exclusions:
196

Transfers: 7
INR Exclusion: 137
Other Blood Factor: 42
Phytonadione Exclusion: 10
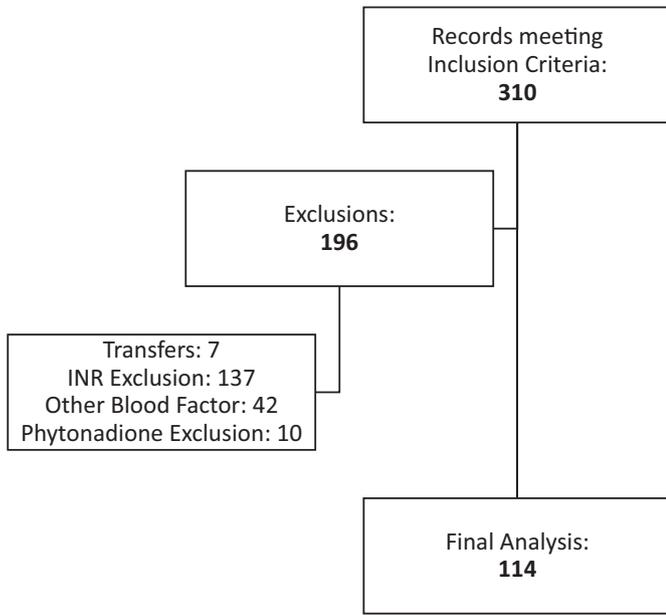
Final Analysis:
114

Fig. 1. Records included in final analysis and reasons for exclusion.

Board. The setting for this study was a level I trauma, tertiary care facility. Electronic medical records were queried for 4F-PCC administrations from May 21, 2014 to August 25, 2017. Records were included if they were 18 years of age or older, had an INR of 2 or more during admission, and did not have a diagnosis of liver disease, hemophilia A, hemophilia B, or Von Willebrand disease based on ICD10 codes. All data abstraction was completed by a single, non-blinded abstractor.

Records were excluded if they did not have a history of warfarin use at baseline. Further exclusions aimed to identify confounding variables that could have altered the characterization of INR reversal from a single 4F-PCC administration. These consisted of transfers from outside hospitals, other sources of blood factor administered prior to the post-reversal INR measurement, and phytonadione administered >6 h prior to the post-reversal INR measurement. Patients were also excluded for absent INR measurements, if the baseline INR was >24 h prior to 4F-PCC administration or if the post-reversal INR was >6 h after 4F-PCC administration. In the event of multiple 4F-PCC administrations during the encounter, only the first administration and subsequent INR were included, if eligible. All data were collected and managed using REDCap electronic data capture tools [12].

The primary endpoint evaluates the relationship between doses of 4F-PCC and INR measurement after reversal, represented as a linear regression. Secondary, descriptive endpoints consist of rates of thromboembolic events within 10 days of 4F-PCC administration and all cause in-hospital mortality; both are reported across four dose cohorts.

Exploratory endpoints characterize the linear relationships between body weight with INR after reversal as well as presenting INR with INR after reversal. Additionally, for the subgroup of patients presenting with INRs of 2–3.9, the mean INR after reversal was compared for two 4F-PCC dose cohorts (<30 and ≥30 IU fIX/kg). This evaluation was performed as an analysis of covariance (ANCOVA), controlling for differences in baseline INR across the subgroup. The data analysis for this paper was generated using SAS software. Copyright © 2017 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA [13].

3. Results

A total of 310 records were identified for inclusion into the evaluation, of which 196 were excluded and final analyses were performed with the remaining 114 records (Fig. 1). The study population had a median age of 74.5 (IQR 65–83) years and the median INR prior to reversal was 2.74 (IQR 2.3–3.4). Of the total population, 42.1% were being treated for an intracranial bleed (Table 1).

The linear regression model for the primary endpoint (Fig. 2) demonstrates a statistically significant relationship between 4F-PCC dose and INR measurement after reversal (INR after 4F-PCC = 1.3651–0.00004(4F-PCC Dose), $p = 0.0071$, $R^2 = 0.0630$). All doses of 4F-PCC were based on total body weight and baseline INR, except in situations of life-threatening bleeding where the provider could elect to give 50 IU fIX/kg regardless of baseline INR. As a consequence, this linear regression model could not be controlled for body weight or baseline INR.

Secondary endpoints (Table 2) across the four dosing cohorts as defined by FDA labeled dosing demonstrate a low number of thromboembolic events ($n = 7$) in the ten days after 4F-PCC administration. As 4F-PCC dose increased, so did the incidence of in-hospital mortality.

In an attempt to characterize the individual factors that determined a given 4F-PCC dose, a post-hoc exploratory analysis was conducted to compare these components to INR after reversal. The linear regression models demonstrate no relationship for total body weight ($p = 0.8555$) (Fig. 3) or baseline INR ($p = 0.7615$) (Fig. 4) with INR after reversal.

An additional post-hoc subgroup analysis was conducted for the 96 records with baseline INR values of 2–3.9 in an attempt to further elucidate the relationship between dose and INR after reversal as this subgroup comprised the majority of our cohort. Records were divided into two groups: those that received <30 IU fIX/kg of 4F-PCC ($n = 71$) and those that received greater than or equal to 30 IU fIX/kg ($n = 25$). An ANCOVA, controlled for variability among baseline INR, demonstrates no significant difference ($p = 0.055$) when comparing INR after reversal for these two groups (Table 3). Of note, all records in this subgroup obtained a post-reversal INR of <2 and 92.7% achieved an INR <1.5.

Table 1
Population demographics.

|			
Age (y), median (IQR)	74.5 (65–83)	Baseline INR, median (IQR)	2.74 (2.3–3.4)
Race, n (%)		Warfarin reversal indication, n (%)	
White	106 (92.9)	Intracranial bleed	48 (42.1)
Black	6 (5.3)	Trauma	25 (21.9)
Asian	1 (0.9)	Procedure	19 (16.7)
Not Reported	1 (0.9)	Gastrointestinal bleed	12 (10.5)
		Genitourinary bleed	2 (1.8)
		Other	8 (7.0)
Weight (kg), median (IQR)	87.6 (69.8–106)	Vitamin K administration, n (%)	
		Yes	94 (82.5)
		No	20 (17.5)
Gender, n (%)		Time from 4F-PCC to INR after reversal (min), median (IQR)	
Male	62 (54.4)		104 (52–185)
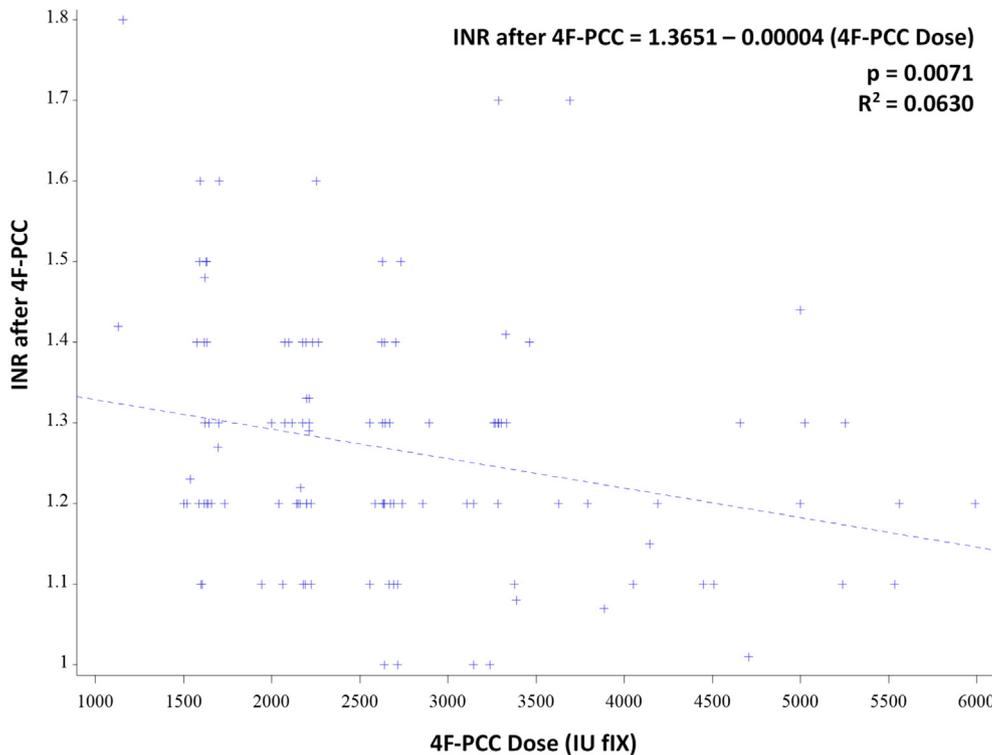
Fig. 2. Linear regression for 4F-PCC dose with INR after reversal.

4. Discussion

This retrospective review adds to the body of evidence evaluating alternative 4F-PCC dosing schemes for warfarin reversal. The primary endpoint (Fig. 2), while significant, may have minimal clinical implications. It accounts for a small proportion of the variation from the linear relationship ($R^2 = 0.0630$) and demonstrates that for every additional 500 IU fIX increase in the 4F-PCC dose, the INR minimally decreases by 0.02. When looking at the two components that comprise 4F-PCC doses in this population, both total body weight (Fig. 3) and baseline INR (Fig. 4) do not have a significant linear relationship with INR after reversal. Ultimately, the above analyses suggest that alternative 4F-PCC dosing schemes, independent of total body weight and baseline INR (contrary to present FDA labeling), may be valid and requires further research to elucidate optimal dosing for warfarin reversal.

In regards to the incidence for in-hospital mortality (Table 2), we observed that as mortality increased, so did 4F-PCC doses. This was likely because our institution-specific protocol allows for more aggressive 4F-PCC dosing as the severity of the clinical situation dictates.

When analyzing the results of the primary endpoint, it was observed that the majority of the population presented with baseline INRs in the range of 2–3.9. Given this, an additional exploratory analysis was conducted on this subgroup to 1) verify the findings of the total population and 2) remove any influence the outliers with severely elevated INRs may have had. In the post-hoc subgroup analysis (Table 3), patients receiving <30 IU fIX/kg were considered to be receiving doses representative of FDA-labeled dosing (our institution allows for ±10% dose

variance, targeting the nearest vial size) while patients receiving doses greater than or equal to 30 IU fIX/kg were considered to be receiving supratherapeutic doses with respect to FDA-labeled dosing with greater potential to lower INR. The difference between the INR after reversal between the two groups was not significant, suggesting that patients with an INR <3.9 at presentation do not experience additional benefit in terms of INR reversal from higher doses.

Our findings complement recent literature supporting the study of alternative dosing strategies for 4F-PCC. Dose finding studies were not performed as part of the FDA approval process for 4F-PCC in the United States [5,6,14]. Adding to the uncertainty of how to optimally dose 4F-PCC, there is debate as to what INR value constitutes successful warfarin reversal. The impetus for FDA approval of 4F-PCC for warfarin reversal was a phase III trial by Sarode et al., in which they defined successful reversal as an INR of less than or equal to 1.3 [15]. The Joint Commission, however, states that for hemorrhagic stroke in the setting of warfarin-induced coagulopathy, reversal should be initiated for INR values >1.4, favoring PCC for reversal, yet lacks guidance on dosing for 4F-PCC [16]. Other studies evaluating 4F-PCC for warfarin reversal have defined success as an INR of 1.5 or less [8-10].

Previously, a systematic review aimed to present efficacy outcomes across a variety of 4F-PCC dosing strategies. The authors found much heterogeneity between studies and were unable to perform a meta-analysis, but did conclude that the use of several different 4F-PCC treatment protocols produced relatively good outcomes. They also noted that future studies should evaluate the necessity of including total body weight and presenting INR into 4F-PCC dosing schema [11]. Our results also call into question the need for total body weight and presenting INR when determining 4F-PCC dose.

The majority of our included population had an INR of <4 at baseline and, as such, our results need to be interpreted with some caution. Khorsand et al. observed that patients presenting with INRs >7.5 were less likely to achieve INRs <2 in a fixed dose arm (1000 IU fIX) as compared to the variable (FDA labeling) dose arm [7]. Similarly, in a post-hoc analysis, Klein et al. suggested that patients were ten times as likely to not achieve INR reversal when the presenting INR was >10 (27.3%

Table 2
Comparison of thromboembolic event rates and mortality to 4F-PCC dose.

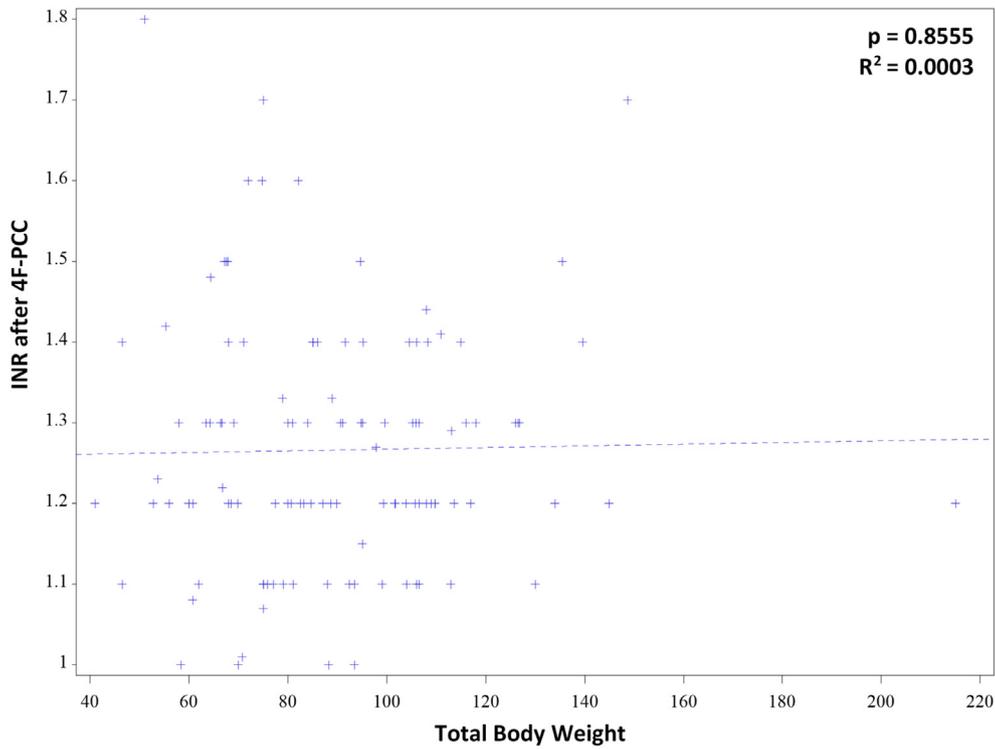| IU fIX/kg group (n)	TE Events (n)	Mortality (n)
<20 (5)	–	20% (1)
20–29.9 (73)	8.2% (6)	9.6% (7)
30–39.9 (13)	–	30.8% (4)
≥40 (23)	4.3% (1)	52.2% (12)

Fig. 3. Linear regression for weight with INR after reversal.

versus 3.6%) [8]. While our findings suggest that weight could be left out of 4F-PCC dosing schemes, the above studies suggest dose escalation may be necessary based on INR and needs further study.

Another limitation for the present study is the retrospective, single center design. Furthermore, while the inclusion and exclusion criteria were restrictive to closely analyze the effect of a single 4F-PCC

administration, this limits external validity. Lastly, because a majority of records presented with a baseline INR of 4 or less, most received 25 IU fIX/kg, limiting the analysis at the upper ends of 4F-PCC dose and baseline INR spectra.

In conclusion, while this evaluation was not designed to find or compare fixed doses of 4F-PCC, it does call into question the utility of current
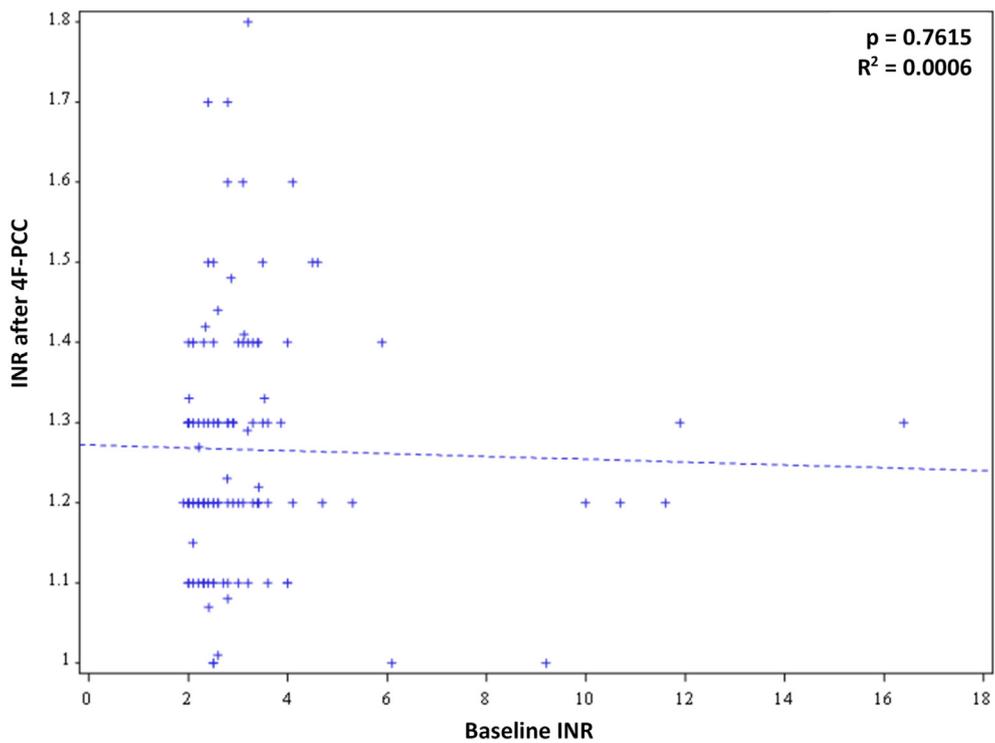

Fig. 4. Linear regression for baseline INR with INR after reversal.

Table 3
Comparison of 4F-PCC IU fIX/kg group to mean INR after reversal (Subgroup: Baseline INR 2–3.9).

IU fIX/kg group (n)	Mean INR after reversal (SD)	p-Value
<30 (71)	1.28 ± 0.15	0.055
≥30 (25)	1.22 ± 0.15	

dosing schemes utilizing total body weight and initial INR. Further prospective study is required to determine optimal dosing schemes of 4F-PCC for warfarin reversal.

Acknowledgements

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