The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–6, 2019

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2019.10.013

ELSEVIER

Pharmacology in Emergency Medicine

PROSPECTIVE EVALUATION OF A FIXED-DOSE 4-FACTOR PROTHROMBIN COMPLEX CONCENTRATE PROTOCOL FOR URGENT VITAMIN K ANTAGONIST REVERSAL

Michael T. Bitonti, PHARMD, BCPS,* Rachel L. Rumbarger, PHARMD, BCPS,* Randall K. Absher, PHARMD, BCPS,† and Lisa M. Curran, PHARMD, BCPS, CPP, BCCP*

*Department of Pharmacy, Moses H. Cone Memorial Hospital, Greensboro, North Carolina and †Department of Pharmacy, Wesley Long Hospital, Greensboro, North Carolina

Corresponding Address: Michael T. Bitonti, PHARMD, BCPS, Department of Pharmacy, Moses H. Cone Memorial Hospital, 1200 N. Elm St., Greensboro, NC, 27401

☐ **Abstract—Background: Four-factor prothrombin complex concentrate (4F-PCC) is the standard of care for reversal of vitamin K antagonists (VKAs). Research has demonstrated noninferior efficacy with the use of lower, fixed-dose strategies for 4F-PCC dosing. Objectives: We compared a fixed-dose 4F-PCC protocol to weight-based dosing at our institution. Methods: This was a multicenter, noninferiority, interventional, quasiexperimental cohort study including subjects who were administered 4F-PCC for VKA reversal. The retrospective cohort consisted of subjects given a weight-based dose of 4F-PCC dependent on international normalized ratio (INR). The prospective cohort was managed with a fixed-dose protocol. The fixed dose was 1500 units of factor IX unless subjects weighed >100 kg or had a baseline INR >7.5, in which case the dose was 2000 units of factor IX. The primary endpoint was achievement of a postinfusion INR of <2. Secondary endpoints included achievement postinfusion INR <1.5, mean 24-h INR, 7-day mortality, and 7-day venous thromboembolic events. Results: Twenty-four subjects were enrolled in the prospective cohort and 30 in the retrospective cohort. A postinfusion INR <2 was achieved in 96% of subjects in the retrospective cohort and 95% in the prospective cohort ($p = 0.0035$ for noninferiority). A postinfusion INR <1.5 occurred in 90% of subjects in the retrospective cohort and 75% in the prospective cohort ($p > 0.4$ for noninferiority). There were no significant differences in 24-h postinfusion INRs, mortality, or venous thromboembolic events. Conclusion: The use of a fixed-dose 4F-PCC protocol is safe and effective for the rapid reversal of VKA-associated anticoagulation.** © **2019 Elsevier Inc. All rights reserved.**

☐ **Keywords—anticoagulation; bleed; prothrombin complex concentrate; warfarin**

INTRODUCTION

Four-factor prothrombin complex concentrate (4F-PCC) (Kcentra; CSL Behring LLC, Marlburg, Germany) was approved by the U.S. Food and Drug Administration (FDA) in 2013 for the urgent reversal of vitamin K antagonists (VKAs). It has become the standard of care in patients requiring rapid VKA reversal because of major bleeding complications or the urgent need for an invasive surgery, and guidelines recommend it as the first-line reversal agent in conjunction with intravenous vitamin K (1,2). More specifically, 4F-PCC is preferred over fresh frozen plasma (FFP) in the majority of patients because of lower volume requirements, faster preparation times, and reduced immunogenicity risks (3). In addition, studies have demonstrated superior efficacy outcomes and similar safety risks when comparing 4F-PCC with FFP (4,5).

Preliminary findings from this research were presented at the American College of Cardiology Scientific Sessions, New Orleans, LA, March 17, 2019.

Reprints are not available from the authors.

RECEIVED: 1 August 2019; FINAL SUBMISSION RECEIVED: 24 September 2019;
ACCEPTED: 13 October 2019

Current FDA labeling for 4F-PCC dosing depends upon the patient's baseline international normalized ratio (INR) and weight, with doses ranging from 25–50 units/kg. However, the optimal dosing strategy for 4F-PCC remains unknown, and formal dose-finding studies have never been published (6). Emerging research has focused on the use of low, fixed-dose strategies for 4F-PCC products. Initial studies showed mostly positive results, but the dosing protocols varied, and they were performed primarily in Europe (7–10). In addition, the trial by Abdoellakhan et al. showed lower rates of achieving target INR with a fixed-dose regimen (10).

Several recent studies performed in the United States have shown successful results with implementation of fixed-dose 4F-PCC protocols (11–13). However, these trials were all retrospective, and 2 did not include comparator cohorts. The purpose of this study was to prospectively evaluate a fixed-dose 4F-PCC protocol at our institution.

METHODS

This was a multicenter, noninferiority, interventional, quasiexperimental (before and after) cohort study comparing a prospective, fixed-dose 4F-PCC cohort with a historically controlled, weight-based dose 4F-PCC cohort. This study was conducted across 4 hospitals and 1 stand-alone emergency department within our health care system. The primary study site was a 517-bed tertiary care teaching hospital, and the other sites were community hospitals. The prospective cohort included patients admitted between November 2018 and May 2019. The retrospective cohort included patients admitted between October 2017 and June 2018. All subjects were >18 years of age and were administered 4F-PCC for rapid reversal of warfarin because of severe bleeding or the need for an invasive surgery or procedure. Subjects were excluded if they were given 4F-PCC for reversal of a direct-acting oral anticoagulant (i.e., apixaban, rivaroxaban, dabigatran, and edoxaban), reversal of a parenteral anticoagulant (i.e., unfractionated heparin, enoxaparin, bivalirudin, argatroban, and fondaparinux), or reversal of a coagulopathy not caused by an anticoagulant. Subjects without postinfusion INR data were excluded as well, and subjects within the prospective cohort who received a weight-based 4F-PCC dose were excluded.

The study was approved by the health care system's institutional review board in September 2018. The retrospective cohort was administered 4F-PCC with weight-based dosing that is dependent on initial INR according to the package insert (14). Subjects received 25 units/kg if the baseline INR was 1.5–3.9, 35 units/kg if the baseline INR was 4–6, or 50 units/kg if the baseline INR was >6. The prospective cohort was administered a fixed dose of 4F-PCC via a protocol approved by the Pharmacy and Therapeutics Committee in August 2018. As approved by the committee, this dosing became the preferred formulary dosing for reversal of warfarin across the health care system; however, weight-based dosing was allowed at the discretion of the treating physician. The fixed-dose protocol involved giving a single dose of 4F-PCC 1500 units factor IX (FIX) as an intravenous (IV) infusion over 25 min. This dose could be administered without needing to assess the patient's baseline INR or weight. If baseline INR or weight information was already available and the subject weighed >100 kg or had an INR >7.5, the fixed dose was increased to 4F-PCC 2000 units FIX over 25 min. All subjects received IV vitamin K 10 mg, and a postinfusion INR was collected 1 h after the 4F-PCC infusion was completed. Additional doses of vitamin K or 4F-PCC or the use of additional reversal agents (i.e., FFP) were administered at the discretion of the treating physician.

Demographic information and baseline characteristics were collected for all subjects, as well as information related to use of FFP and additional doses of 4F-PCC or vitamin K. The primary outcome was achievement of a postinfusion INR <2. Secondary outcomes included achievement of a postinfusion INR <1.5, mean 24-h INR, 7-day mortality, and 7-day venous thromboembolic events (VTEs). INR-based outcomes were chosen because hemostasis would be difficult to retrospectively assess in the historical cohort. These INR targets were chosen to be consistent with previous fixed-dose 4F-PCC trials. All data were collected via the health care system's electronic medical record.

Statistical Analysis

Descriptive statistics were used for all baseline demographic information. The primary and secondary outcomes were compared using a hierarchical testing approach. Noninferiority was tested first, and if confirmed, was followed by a test for superiority. The noninferiority margin was set a priori at 15% using the relevant boundary of a 1-sided 95% confidence interval for difference in proportions. Superiority was tested using the chi-square, Fisher exact, or Mann–Whitney *U* tests as appropriate, using a 2-sided test with alpha set at 0.05. Power calculations completed before study enrollment based upon a fixed sample size in the retrospective cohort demonstrated that a sample size of 24 was needed in the prospective cohort to provide 80% power. All statistics were analyzed electronically using Stata software (version 15.1; StataCorp, College Station, TX).

RESULTS

Thirty subjects were included for analysis in the retrospective cohort. The prospective cohort consisted of 24 subjects based on a priori power calculations. Baseline characteristics are noted in Table 1 and were statistically similar between the 2 cohorts. Most patients were taking warfarin because of a history of atrial fibrillation, and baseline INR upon presentation was 3.83 in the weight-based group and 4.58 in the fixed-dose group ($p = 0.34$). The indication for 4F-PCC was an intracranial hemorrhage in 63% of subjects in the weight-based group and 37% in the fixed-dose group ($p = 0.27$). Gastrointestinal bleeding was the indication in 26% and 50% of patients ($p = 0.27$), respectively, and urgent surgical indications were only present in 1 subject in each cohort.

Intravenous vitamin K was administered to all but 1 subject in the prospective cohort ($p = 0.44$), and FFP was administered to 3 subjects in each cohort ($p = 0.55$) (Table 2). Rescue use of additional vitamin K or FFP after administration of 4F-PCC was used in 20% of subjects in the retrospective cohort and 12% of subjects in the prospective cohort ($p = 0.133$). No additional doses of 4F-PCC were administered to any patients. The average doses of 4F-PCC in units FIX were 2591 and 1725, respectively ($p = 0.001$). Within the fixed-dose group, 6 subjects received the 2000-unit FIX dose because of baseline weight or INR information, whereas the other 18 received the 1500-unit FIX dose.

Safety and efficacy outcomes are shown in Table 3. A postinfusion INR of <2 was achieved in 96% of subjects in the weight-based group and 95% in the fixed-dose group ($p = 0.0035$ for noninferiority; the p value was not significant [NS] for superiority). The postinfusion INR was <1.5 in 90% of subjects in the weight-based group and 75% of subjects in the fixed-dose group (p = NS for noninferiority). There were no differences in mean INR values postinfusion or 24 h later between the 2 cohorts (Table 2). There were no VTEs within 7 days of administration of 4F-PCC, and mortality was similar among the cohorts ($p < 0.009$ for noninferiority).

Table 1. Baseline Characteristics

	Retrospective (n = 30)	Prospective (n = 24)
Mean age, y	74	77
Gender, n (%)		
Male	19 (63.3)	11 (45.8)
Female	11 (36.7)	13 (54.2)
Race, n (%)		
White	21 (70)	17 (70.8)
African American	7 (23.3)	7 (29.2)
Hispanic	2 (6.7)	—
Mean weight, kg	87.9	80.2
Mean baseline INR	3.83	4.58
VKA indication, n (%)		
Atrial fibrillation	20 (66.7)	18 (75)
Venous thromboembolism	6 (16.2)	6 (25)
Valvular disease	3 (10)	—
Other	2 (6.7)	—
4F-PCC indication, n (%)		
Surgery	1 (3.3)	1 (4.2)
Intracranial hemorrhage	19 (63.3)	9 (37.5)
Gastrointestinal bleed	8 (26.7)	12 (50)
Abdominal bleed	2 (6.7)	1 (4.2)
Other major bleed	—	1 (4.2)

4F-PCC = 4-factor prothrombin complex concentrate; INR = international normalized ratio; VKA = vitamin K antagonists.

DISCUSSION

Our study compared INR outcomes of a low, fixed-dose 4F-PCC strategy with traditional package insert–based dosing of 4F-PCC dependent on baseline INR and weight. To our knowledge this is the first prospective comparison involving fixed-dose 4F-PCC carried out within the United States. When looking at the primary outcome of achievement of a postinfusion INR <2, the fixed-dose strategy was found to be noninferior to weight-based dosing, with 95% and 96%, respectively, reaching the INR target of <2. Although the secondary outcome of postinfusion INR <1.5 did not reach statistical significance for 1-sided noninferiority, the proportion of subjects in each cohort reaching this target were similar (90% and 75%). The totality of this evidence suggests that use of a low, fixed dose of 4F-PCC provides rapid reversal of VKA activity in the setting of a major bleed. The INR values 24 h after administration of 4F-PCC were nearly identical between groups as well, suggesting sustained anticoagulation reversal with lower doses of 4F-PCC.

The results of our prospective analysis are similar to recent retrospective studies evaluating a fixed-dose 4F-PCC protocol. Klein et al. used a 1500-unit FIX dose

Table 2. Numerical International Normalized Ratio Outcomes and Reversal Agent Characteristics

	Retrospective (n = 30)	Prospective (n = 24)
Mean postinfusion INR	1.328	1.38
Mean 24-h postinfusion INR	1.32	1.31
Mean 4F-PCC dose, units FIX*	2591	1725
Other reversal agents, n (%)		
Vitamin K	30 (100)	23 (95.8)
Plasma	3 (10)	3 (12.5)
Rescue reversal agents, n (%)		
Vitamin K	3 (10)	—
Plasma	3 (10)	1 (4.2)
Vitamin K and plasma	—	2 (8.33)

4F-PCC = 4-factor prothrombin complex concentrate; FIX = factor IX; INR = international normalized ratio.
* $p < 0.0001$.

Table 3. Target International Normalized Ratio Achievement and Clinical Outcomes

	Retrospective (n = 30)	Prospective (n = 24)	*p* Value for Noninferiority
Postinfusion INR <2, n (%)	29 (96.7)	23 (95.8)	0.0035
Postinfusion INR <1.5, n (%)	27 (90)	18 (75)	>0.45
7-day mortality, n (%)	4 (13.3)	2 (8.3)	0.009
7-day VTE events, n (%)	0 (0)	0 (0)	0.021

INR = international normalized ratio; VTE = venous thromboembolism.

for all subjects and found rates of a postinfusion INR <2 in 92.3% of subjects and an INR of <1.5 in 71.8% of subjects (11). Similarly, Astrup et al. found rates of 100% and 74.3%, respectively, with a 1500-unit FIX dose (12). Scott et al. found lower rates of achievement of an INR <1.5 (53%), but this study used a lower fixed dose of 1000 units of FIX, which likely explains the discrepancy (13).

Importantly, clinical outcomes were similar in this study as well, with no increased risk of mortality with a lower dose. The overall mortality rate was higher in each cohort compared with earlier studies comparing 4F-PCC to plasma but lower than more recent studies involving fixed-dose 4F-PCC (4,5,11–13). The mortality difference compared with more recent studies is likely related to the fact that mortality was only recorded in this trial during the initial 7 days after administration of 4F-PCC to avoid confounding with other events that may occur during the hospital stay that could invoke mortality, whereas the other analyses included all death from presentation through discharge. Notably, no VTEs occurred within either cohort of this study. Previous trials of fixed-dose 4F-PCC have also demonstrated a lack of VTEs with smaller total doses, but trials with higher weight-based dosing showed a VTE rate around 7% (4,5,11,12).

There are some notable differences from our study compared with the other recent fixed-dose 4F-PCC trials. First, the use of FFP was much lower in our trial compared with the studies by Klein et al. and Astrup et al. (11,12). Only 12.5% of our subjects in the fixed-dose group received concomitant FFP, and all but 1 subject received concomitant vitamin K because of a prescribing error. The lower use of FFP limits the potential confounding of the true INR-lowering effect of fixed-dose 4F-PCC alone. In addition, the baseline INR in our fixed-dose cohort was 4.58, whereas in the aforementioned studies the baseline INR was no higher than 3.3 (11–13). Finally, the dosing regimens differed slightly among the studies. A 1500-unit FIX dose was chosen for the majority of patients, given the successful results of the trial by Klein et al. (11). A slightly higher dose of 2000 units FIX was given to subjects with a baseline weight >100 kg or a baseline INR >7.5. This is partly because a post hoc analysis completed by Khorshand et al. suggested that a baseline INR >7.5 was suggestive of a fixed-dose regimen being less effective (8). In addition, the trial by Klein et al. noted weight to be a baseline characteristic that trended toward significantly altering the effectiveness of a fixed-dose regimen ($p = 0.054$) (11). Because of this, the mean unit FIX per kilogram dose was slightly higher in the current study at 21.5 compared with 20.4 and 20.1 in the trials by Klein et al. and Astrup et al. (11,12). In contrast, Scott et al. used the lowest dose among these trials as noted above (13).

Limitations

There are several limitations to this study. First, although this study included a prospective cohort, it was not randomized. The ongoing PROPER3 trial will help address this question (15). Second, this study was conducted across multiple emergency departments within the health care system, but a true multicenter study across multiple health care systems would increase external validity. In addition, while there were no statistically significant differences amongst baseline characteristics between the 2 cohorts, numerical differences in baseline INR and bleeding type were present. Finally, while INR-based outcomes are objective, they do not always accurately reflect hemostasis and clinical outcomes. Our noninferiority margin of 15% was chosen at the investigators' discretion and driven by the use of an INR-based endpoint as the primary outcome measure. We acknowledge that for the clinical endpoints a more conservative margin could have value and support exploration of this by future investigations using larger sample sizes. Our study did not assess hemostasis because it was pharmacist-driven, and likely outside their scope of practice to accurately determine achievement of hemostasis.

CONCLUSION

This trial shows the noninferiority of a fixed-dose 4F-PCC dosing protocol for urgent reversal of VKA compared with the weight- and INR-based dosing present within the package insert. A dose of 1500 units of FIX for the majority of patients was safe and efficacious, with a dose of 2000 units of FIX being effective for the subgroup of patients with a higher baseline weight or INR.

Additional randomized studies with hemostatic outcome measures are needed to further elucidate the efficacy of low, fixed-dose 4F-PCC regimens for the emergent reversal of VKA-associated major bleeding.

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ARTICLE SUMMARY

1. Why is this topic important?

Life-threatening bleeding is the most concerning adverse event associated with vitamin K antagonist (VKA) use, but optimal dosing of 4-factor prothrombin complex concentrate (4F-PCC) remains unclear. Lower, fixed-dose 4F-PCC dosing protocols have the potential to provide more rapid administration of product, significant cost savings, and lower thromboembolic risk.

2. What does this study attempt to show?

This study shows that the fixed-dose 4F-PCC protocol used in our health care system is noninferior to standard-dose 4F-PCC in VKA reversal, This study shows that the fixed-dose 4F-PCC protocol used in our health care system is noninferior to standard-dose 4F-PCC in VKA reversal.

3. What are the key findings?

Fixed-dose 4F-PCC provides rapid international normalized ratio reversal and does not lead to worse clinical outcomes.

4. How is patient care impacted?

Lower doses of 4F-PCC can be used to safely and effectively reverse VKAs.