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Original Contributions

PHARMACIST PRESENCE DECREASES TIME TO PROTHROMBIN COMPLEX CONCENTRATE IN EMERGENCY DEPARTMENT PATIENTS WITH LIFE-THREATENING BLEEDING AND URGENT PROCEDURES

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☐ **Abstract—Background: Reversal of anticoagulation with four-factor prothrombin complex concentrate (4F-PCC) is critical, yet the optimal timing to 4F-PCC administration and whether quicker administration improves hemostasis remains unknown. Objective: The objective of this study was to determine if pharmacist presence is predictive of faster time to 4F-PCC. Methods: This retrospective cohort study included patients receiving 4F-PCC for life-threatening bleeding or urgent procedure in the emergency department (ED) from 2014 to 2018. Patients with pharmacists at bedside (PharmD group) were compared with physician teams alone (control group). The primary outcome was time from ED presentation to 4F-PCC administration. Results: Of 252 patients evaluated, 116 patients (46%) were included (n = 50 PharmD group; n = 66 control group). Most patients presented on warfarin (68.1%), and of the life-threatening bleeds (94%), intracranial hemorrhage was most common (67.2%). The median time to 4F-PCC administration was significantly shorter in the PharmD group (66.5 vs. 206.5 min, $p < 0.001$). Pharmacist at bedside was the only factor independently associated with reduction in time to 4F-PCC (β coefficient −163.5 min, 95% confidence interval −249.4 to −77.7). Although there was no difference in hemostasis or mortality, patients in the PharmD group had a shorter intensive care unit length of stay (LOS) (2 vs. 5 days, $p < 0.01$) and hospital LOS (5.5 vs. 8 days, $p = 0.02$). Conclusion: A pharmacist at the bedside of patients who present to the ED with life-threatening bleeding or need for emergent procedure decreased time to 4F-PCC administration by 140 min, even after accounting for confounders. Faster time to 4F-PCC was associated with significantly shorter intensive care unit and hospital LOS.** © 2019 Elsevier Inc. All rights reserved.

☐ **Keywords—prothrombin complex concentrate; intracranial hemorrhage; gastrointestinal bleed; pharmacist; anticoagulant reversal; anticoagulation**

INTRODUCTION

Four-factor prothrombin complex concentrate (4F-PCC) is indicated for the treatment of acute major bleeding in patients with acquired deficiency of vitamin K-dependent clotting factors from the use of vitamin K antagonists (VKA), such as warfarin (1). It has also been routinely administered off-label for life-threatening hemorrhage associated with non-VKA anticoagulation, including dabigatran, rivaroxaban, apixaban, and edoxaban (2). The American College of Chest Physicians, the Neurocritical Care Society, and the Society of Critical Care Medicine guidelines recommend the use of 4F-PCC for anticoagulation reversal in patients experiencing VKA-associated major bleeding or necessitating urgent surgical intervention (3,4).

In patients with VKA-associated intracranial hemorrhage (ICH), 4F-PCC showed a reduction in hematoma expansion rates, as compared with fresh frozen plasma

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(FFP), due to faster normalization of the international normalized ratio (INR) (5). Although time to anticoagulation reversal can be critical, available literature lacks definitive evidence regarding the optimal timing of administration of 4F-PCC to maximize clinical outcomes. In a small retrospective study of 45 patients who presented to the emergency department (ED) with a VKA-associated ICH, 4F-PCC administration of fewer than 200 min of patient presentation was associated with less hemorrhagic expansion of ICH on repeat imaging, as compared with patients who received 4F-PCC after 200 min of presentation (6). Presently, no study has examined the effect of faster 4F-PCC administration on life-threatening bleeding due non-VKA anticoagulation and clinical outcomes, such as length of stay (LOS), hemostasis, and mortality.

The decision to reverse anticoagulation, as well as the complex dosing and preparation requirements of 4F-PCC, may delay time to administration (7). Clinical pharmacists work alongside physicians and nurses at the bedside to optimize pharmacotherapy, increase efficiency and cost-effectiveness of care, and ultimately improve patient safety outcomes (8,9). Interventions targeting a faster time to administration of 4F-PCC, including pharmacists at the bedside, have not been evaluated. Therefore, the purpose of this study is to evaluate the impact of a clinical pharmacist in the treatment of life-threatening bleeding or urgent procedure requiring anticoagulant reversal.

MATERIALS AND METHODS

Methods

We conducted a retrospective cohort study of patients who presented to the Loyola University Medical Center ED with a life-threatening bleed or requiring an urgent procedure necessitating anticoagulation reversal with 4F-PCC. We reviewed the electronic medical records of consecutive patients for whom an order for 4F-PCC was placed from January 2014 to November 2018. Patients over the age of 18 years on oral anticoagulation (including warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) necessitating rapid reversal given life-threatening bleeding or need for emergent procedural or surgical intervention were included. The following patients were excluded: age less than 18 years, receipt of 4F-PCC outside of the ED setting (e.g., in the intensive care unit [ICU] or operating room), 4F-PCC administration at an outside hospital prior to arrival at our ED, receipt of 4F-PCC for any indication aside from life-threatening bleeding or urgent procedure, concurrent factor VII use, history of heparin-induced thrombocytopenia, known disseminated intravascular coagulation, and receipt for idarucizumab for dabigatran-associated bleeding. The research protocol was approved by the Loyola University Medical Center Institutional Review Board.

We compared patients with a pharmacist at the bedside (PharmD group) to a physician team alone (control group). At our institution, clinical pharmacists obtained medication histories regarding anticoagulant and time of last dose, assessed the appropriateness of 4F-PCC use and contraindications to 4F-PCC, facilitated appropriate order entry, ensured co-administration of phytonadione for warfarin-associated bleeding, and recommended appropriate post-administration laboratory follow-up. Although 4F-PCC is reconstituted at the central pharmacy of our institution, clinical pharmacists communicated with the intravenous preparatory area in central pharmacy to ensure timely bedside delivery of 4F-PCC. Moreover, a clinical pharmacist was *typically* present in the ED during weekdays and *not typically* present during nights and weekends. Specifically, an emergency medicine clinical pharmacist was present in the ED from 9:30 AM to 10:00 PM on Mondays and Fridays and from 9:30 AM to 6:00 PM on Tuesdays, Wednesdays, and Thursdays. The ICU clinical pharmacist responded to stroke/ICH codes from 6:00 PM to 10:00 PM on Tuesdays, Wednesdays, and Thursdays, and on the weekends. Pharmacist presence was confirmed through a review of the electronic medical record, where clinical pharmacist standard practice includes documentation of involvement in the form of medication interventions or progress notes. Epic (Verona, WI) was the electronic medical software that we utilized throughout the study period.

Endpoints

The primary endpoint was time to 4F-PCC administration, defined as the length of time from ED presentation to the recorded start of 4F-PCC administration. Secondary endpoints were achievement of hemostasis, number of transfusions (e.g., packed red blood cell, platelet, and FFP), appropriateness of clinical use, safety outcomes, discharge disposition, ICU LOS, hospital LOS, and 30-day mortality. As hemorrhages on multiple oral anticoagulants were included, the achievement of hemostasis was determined using the definition by the International Society of Thrombosis and Hemostasis Scientific and Standardization Subcommittee criteria for the assessment of the effectiveness of major bleeding management to ensure assessments were objective and consistent (10). Hemostasis for ICH was defined as stabilization or a $< 35\%$ increase in hematoma volume on imaging. Hemostasis for visible bleeding was defined as the cessation of visible bleeding within 4 hours of 4F-PCC administration. Hemostasis for nonvisible bleeding was defined as stable hemoglobin at 48 hours after 4F-PCC administration. Incidence of adverse events during hospitalization

was collected, including deep vein thrombosis, pulmonary embolism, ischemic stroke, arterial thrombus, hypersensitivity reaction, transfusion-related acute lung injury, and transfusion-associated circulatory overload.

Data Collection

The baseline characteristics that we collected included: age, gender, race, weight, body mass index, past medical history, indication for anticoagulation, sequential organ failure assessment score on admission, Glasgow Coma Scale (GCS) score on admission, anticoagulant therapy, and concomitant antiplatelet therapy. Initial laboratory data included baseline INR for warfarin-associated bleeds, and baseline hemoglobin and platelets for the entire study cohort. The type and location of hemorrhage were recorded for patients who presented with life-threatening bleeding. The type of surgery or procedure was recorded for patients on oral anticoagulation who required emergent reversal for the urgent surgery or procedure. Using the electronic medical record, the timestamp of first provider contact and timestamp of 4F-PCC administration were obtained and used to calculate time to 4F-PCC administration. We also collected the timestamp of 4F-PCC order entry in the electronic medical record to 1) calculate the time from ED patient presentation to 4F-PCC order entry and 2) calculate the time of 4F-PCC order entry to the time of 4F-PCC administration. Moreover, the appropriateness of 4F-PCC dosing (units/kg), as well as the timing and route of phytonadione co-administration, were obtained. We also collected the day of the week (weekday vs. weekend) and time of shift (morning [7:01 AM to 7:00 PM] vs. evening [7:01 PM to 7:00 AM]) that 4F-PCC was administered. All study data were collected and managed using Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN) electronic data capture tools (11).

Statistical Analyses

Descriptive statistics including mean ($\pm$ standard deviation) or median (interquartile range), as appropriate, and proportions were used to characterize baseline demographics. The Shapiro-Wilk test was used to determine the normality of data. Continuous data that were normally distributed were analyzed using a *t*-test. Nonparametric continuous data were analyzed using a Mann-Whitney *U* test. Chi-squared and Fisher's exact tests were used to analyze categorical data. We also conducted a multivariable linear regression analysis to determine predictors of faster time to 4F-PCC administration and account for confounders. Variables based on prior literature and from the univariate analyses with a p-value ≤ 0.2 were evaluated for inclusion into the regression analysis (12). Based on previous literature, a 19-min difference was anticipated, which warranted at least 48 patients in each group to meet a power of 80% (13). We analyzed the data using Microsoft Excel (Microsoft Corporation, Redmond, WA) and SPSS (Version 21.0; IBM Corp, Armonk, NY).

RESULTS

Of the 252 patients that received 4F-PCC during the study period, 116 patients (46%) were included in the study. The most common reason for exclusion was 4F-PCC administration outside of the ED (e.g., in the ICU or the operating room; Figure 1). Of the 116 patients included, 50 patients had a clinical pharmacist at the bedside (PharmD group), and 66 patients had a physician team alone (control group). Baseline characteristics were well matched across both treatment groups (Table 1). The most common indication for anticoagulation was atrial fibrillation (70% vs. 75.8%, $p = 0.49$), and the most common anticoagulant prescribed in the cohort was warfarin (64% vs. 71.3%, $p = 0.41$). The PharmD group had a lower, albeit nonsignificant, median GCS score on admission, as compared with the control group (12.5 vs. 15, $p = 0.19$).

4F-PCC administration data were similar between groups. The majority of 4F-PCC administration was due to life-threatening bleeding (98% vs. 90.1%, $p = 0.84$), with the most common type of bleed presenting as an ICH (67.3% vs. 75%, $p = 0.80$). The median time to 4F-PCC administration was significantly shorter in the PharmD group as compared with the control group (66.5 min vs 206.5 min, $p < 0.01$; Figure 2). Furthermore, the median times from ED patient presentation to 4F-PCC order entry, as well as from 4F-PCC order entry to 4F-PCC administration, were significantly shorter in the PharmD group (Table 2). Although there were no differences in the median number of packed red blood cell or platelet transfusions, patients in the PharmD group

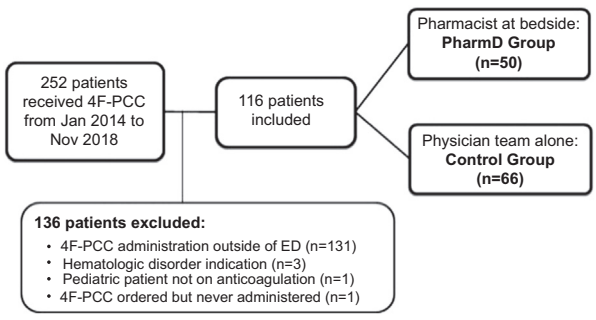

Figure 1. Patient enrollment. 4F-PCC = four-factor prothrombin complex concentrate. ED = emergency department.

Table 1. Baseline Characteristics

Baseline Characteristic	PharmD (n = 50)	Control (n = 66)	*p*-Value
Male sex, n (%)	35 (70%)	37 (56%)	0.13
Age at bleed (years), median (IQR)	77.6 (69.2–86)	71.8 (60–83.7)	0.89
Weight (kg), median (IQR)	89.9 (79.1–100.7)	80.7 (66–95.4)	0.08
BMI (kg/m^2), median (IQR)	29.9 (24–35.8)	27.9 (23.4–32.4)	0.26
Race, n (%)			
Caucasian	33 (66%)	42 (63.4%)	0.53
African American	12 (24%)	16 (24.2%)	0.93
Hispanic	4 (8%)	3 (4.6%)	0.44
Asian	1 (2%)	2 (3.1%)	0.73
Other	0 (0%)	3 (4.6%)	0.13
Indication for anticoagulation, n (%)			
Atrial fibrillation	35 (70%)	50 (75.8%)	0.49
Deep vein thrombosis	8 (16%)	6 (9%)	0.26
Pulmonary embolism	5 (10%)	6 (9%)	0.87
Cancer with VTE	1 (2%)	0 (0%)	0.25
Mechanical mitral valve	6 (12%)	13 (19.7%)	0.27
Ventricular assist device	1 (2%)	1 (1.5%)	0.84
History of VTE	0 (0%)	2 (3%)	0.21
SOFA score on admission, median (IQR)	3.5 (0–7.5)	3 (1–5)	0.89
GCS score on admission, median (IQR)	12.5 (8.5–15)	15 (14–15)	0.19
Anticoagulant prescribed, n (%)			
Warfarin	32 (64%)	47 (71.3%)	0.41
Rivaroxaban	9 (18%)	9 (13.6%)	0.52
Apixaban	8 (16%)	9 (13.6%)	0.72
Edoxaban	1 (2%)	0 (0%)	0.25
Dabigatran	0 (0%)	1 (1.5%)	0.38
Concomitant antiplatelet, n (%)			
Aspirin	9 (18%)	10 (15.2%)	0.68
Clopidogrel	12 (24%)	17 (25.8%)	0.83
Prasugrel	0 (0%)	3 (4.5%)	0.13
None	29 (58%)	36 (54.5%)	0.71

IQR = interquartile range; BMI = body mass index; VTE = venous thromboembolism; SOFA = sequential organ failure assessment; GCS = Glasgow Coma Scale.

receive a fewer mean number of FFP transfusions as compared with the control group (0.20 vs. 0.56, $p = 0.04$; Table 3). Yet, significantly more patients in the PharmD group presented on weekdays and during the AM shift (Table 2).

There were 79 patients (68.1%) in the cohort that presented with a warfarin-associated hemorrhage. The median INR on admission (2.7 vs. 2.8, $p = 0.65$) and the median INR up to 24 hours post 4F-PCC (1.2 vs. 1.2, $p = 0.65$) were similar among groups. No differences were seen in regards to the i.v. route of phytonadione administration (96.9% vs. 85.1%, $p = 0.88$) among groups. However, more patients in the PharmD group received phytonadione co-administration, as compared with the control group (32 [100%] vs 43 [91.4%], $p = 0.09$).

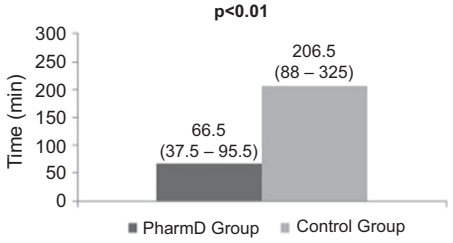

Figure 2. Median (interquartile range) time to four-factor prothrombin complex concentrate (4F-PCC) administration among study groups.

There were no differences in hemostasis or safety outcomes between the two groups (Table 3). Patients in the PharmD group were found to have a significantly shorter ICU LOS and hospital LOS (Figure 3). More patients in the PharmD group were discharged to home (19 [38%] vs. 13 [19.7%], $p = 0.03$), whereas more patients in the control group were discharged to a long-term care facility or nursing home (21 [42%] vs. 40 [60.6%], $p = 0.06$). Finally, there were no differences seen in-hospital mortality (10 [20%] vs. 13 [19.7%], $p = 0.57$) or death within 30 days of 4F-PCC administration (11 [22%] vs. 14 [21.2%], $p = 0.55$) among groups.

A planned multivariable linear regression was conducted to explore predictive factors associated with reduced time to 4F-PCC and to account for confounding variables. The following variables were included in the analysis: weight, pharmacist at the bedside, baseline INR, GCS on admission, weekday presentation, and day-shift presentation. A clinical pharmacist at the bedside was the only factor independently associated with a

Table 2. 4F-PCC Administration Characteristics

Characteristic	PharmD (n = 50)	Control (n = 66)	*p*-Value
4F-PCC indication, n (%)			
Life-threatening bleed	49 (98%)	60 (90.1%)	0.84
Urgent surgery or procedure	1 (2%)	6 (9.9%)	0.65
Type of bleed, n (%)*			
Intracranial bleeding	33 (67.3%)	45 (75%)	0.80
Visible bleeding	13 (26.6%)	13 (21.7%)	0.42
Nonvisible bleeding	3 (6.1%)	2 (3.3%)	0.44
4F-PCC day of the week, n (%)			
Weekday (Monday, Tuesday, Wednesday, Thursday, Friday)	47 (94%)	42 (63.4%)	< 0.01
Weekend (Saturday, Sunday)	3 (6%)	24 (36.6%)	< 0.01
4F-PCC shift, n (%)			
Morning (0701 to 1900)	40 (80%)	28 (42.4%)	< 0.01
Evening (1901 to 0700)	10 (20%)	38 (57.6%)	< 0.01
Time (minutes) from patient presentation to ED to 4F-PCC order entry, median (IQR)	22.5 (10–50)	123 (60.7–225.3)	< 0.01
Time (minutes) from 4F-PCC order entry to 4F-PCC administration, median (IQR)	34.5 (24.3–41)	43.5 (32–60.8)	0.02
4F-PCC dose (units/kg), median (IQR)	25.2 (22.6–27.8)	27.2 (22.4–32)	0.50
Appropriate 4F-PCC dose, n (%)	48 (96%)	61 (92.4%)	0.42

4F-PCC = four-factor prothrombin complex concentrate; ED = emergency department; IQR = interquartile range.
* Denominator for PharmD group is 49 and for control group is 60 based on the life-threatening bleeding patient cohort.

reduction in time to 4F-PCC administration (β coefficient −163.5 min, 95% confidence interval −249.4 to −77.7; Table 4). Multicollinearity was evaluated and the variance inflation factor for each variable was 1.55 or less, indicating that the benefit of pharmacist presence is not confounded by other factors in the model (e.g., weekend or overnight presentation).

DISCUSSION

This study demonstrates the benefit of a clinical pharmacist at the bedside during 4F-PCC administration for patients who present to the ED with life-threatening bleeding or need for emergent procedure. Clinical pharmacist presence reduced time to 4F-PCC by 140 min,

Table 3. Hemostasis and Safety Outcomes

Intracranial Bleeding Hemostasis	PharmD (n = 33)	Control (n = 45)	*p*-Value
Hematoma volume stable or increased by < 35% as compared with baseline, n (%)	29 (87.8%)	38 (84.4%)	0.67
Deterioration in GCS at 24 h, n (%)	1 (3%)	6 (9.1%)	0.11
Need for further hemostatic agents or coagulation factors at 48 h, n (%)	0 (100%)	0 (100%)	> 0.99
Visible bleeding hemostasis	**PharmD (n = 12)**	**Control (n = 13)**	
Cessation of visible bleeding within 4 h of 4F-PCC administration, n (%)	12 (100%)	12 (92.3%)	0.38
Need for further hemostatic agents or coagulation factors at 48 h, n (%)	0 (100%)	0 (100%)	> 0.99
Nonvisible bleeding hemostasis	**PharmD (n = 3)**	**Control (n = 2)**	
Stable hemoglobin at 48 h after 4F-PCC, n (%)	3 (100%)	2 (100%)	> 0.99
Need for further hemostatic agents or coagulation factors at 48 h, n (%)	0 (100%)	0 (100%)	> 0.99
Additional outcomes	**PharmD (n = 50)**	**Control (n = 66)**	
Adverse event during hospitalization, n (%)	0 (0%)	0 (0%)	> 0.99
Packed red blood cells within 24 h of 4F-PCC, mean (SD)	0.11 (0.4)	0.06 (0.3)	0.53
Platelet transfusions within 24 h of 4F-PCC, mean (SD)	0.15 (0.5)	0.38 (0.7)	0.25
Fresh frozen plasma within 24 h of 4F-PCC, mean (SD)	0.20 (0.6)	0.56 (1)	0.04

GCS = Glasgow Coma Scale; 4F-PCC = Four-Factor Prothrombin Complex Concentrate.

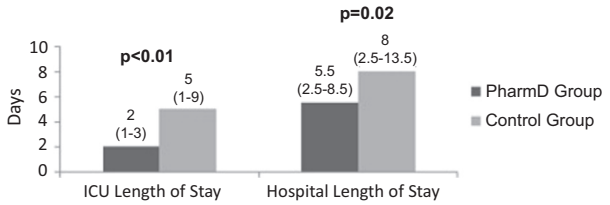

Figure 3. Median (interquartile range) intensive care unit (ICU) and hospital length of stay among study groups.

even after accounting for confounding factors such as time of presentation and day of the week. The reduction in time to 4F-PCC in the PharmD group may have impacted ICU and hospital LOS due to the faster achievement of hemostasis. These findings suggest that a clinical pharmacist at bedside provides significant value and optimizes time to receipt of life-saving pharmacotherapy.

The clinical pharmacists at our institution ensure timely and appropriate administration of 4F-PCC by obtaining medication histories to determine anticoagulant use and time of last dose, advocating for accurate weight, and recommending necessary laboratory parameters (e.g., INR) on patient presentation to reduce delay in administration if 4F-PCC may be indicated. When the administration of 4F-PCC is indicated, the clinical pharmacist facilitates 4F-PCC order entry in conjunction with the attending physician and recommends an appropriate dose based on the type of anticoagulant on presentation or INR value. The clinical pharmacist also ensures phytonadione co-administration for warfarin-associated bleeds, recommends against concomitant FFP administration due to the increased thrombotic risk, and communicates with the intravenous preparatory area in the central pharmacy to ensure timely bedside delivery. As the median time from patient presentation to 4F-PCC order entry in the PharmD group was shorter in our study, the data suggests that pharmacists at our institution assisted emergency physicians in clinical decision-making and appropriate order entry. Also, we found that the median time from 4F-PCC order entry to 4F-PCC administration was shorter in the PharmD group. These data suggest that pharmacists actively communicated with the central pharmacy intravenous preparatory area to ensure that the life-saving medication was delivered to the patient in a timelier manner. Although 4F-PCC is reconstituted in the central pharmacy at our institution, the storage of 4F-PCC in the ED and bedside reconstitution by the clinical pharmacist may be a means to further decrease time to 4F-PCC administration.

Table 4. Multivariable Linear Regression

Factor	β Coefficient	p-Value	95% Confidence Interval
Weight (kg)	1.37	0.07	−0.09 to 2.84
PharmD at bedside	−163.57	< 0.01	−249.44 to −77.71
Baseline INR	5.50	0.28	−4.55 to 15.54
GCS score on admission	2.46	0.64	−7.93 to 12.84
Weekday presentation	−36.37	0.39	−120.11 to 47.35
Day shift presentation	−1.83	0.96	−77.68 to 74.02

INR = International Normalized Ratio; GCS = Glasgow Coma Scale.

Two studies have attempted to target faster time to 4F-PCC administration, in which a pharmacist-driven protocol was compared with a blood bank-driven protocol. The first single-center, retrospective study analyzed pharmacy vs. blood bank management on the turnaround time of 4F-PCC.[14] The pharmacist was responsible for peripheral clinical evaluation, dose rounding, preparation, and distribution of 4F-PCC. The median turnaround time of 4F-PCC was lower in the pharmacy group (43 min) as compared with the blood bank group (62 min), $p = 0.03$. The second single-center, retrospective study analyzed the impact of a pharmacist-driven protocol vs. a blood bank-driven protocol on time to administration of 4F-PCC in patients with warfarin-associated ICH (14). The pharmacist was responsible for determining the appropriate dose, preparation, bedside delivery, and order entry into the electronic medical record. Prior to implementation of the pharmacist-protocol, the blood bank was responsible for approval of 4F-PCC, dosing, product preparation, and arranging delivery with ED staff. The median time to administration of 4F-PCC was significantly shorter in the pharmacist-driven protocol group (35 min) vs. the preprotocol group (70 min) for warfarin-associated ICH, $p = 0.034$. Notably, both studies assessed only the effect of 4F-PCC on warfarin-associated ICH, and both studies were not powered to detect differences in LOS, hemostasis, or mortality. Although these studies have several limitations, particularly their retrospective design and small sample size, they demonstrate that pharmacists can play a role in the preparation and dispensing of 4F-PCC for patients with VKA-associated life-threatening hemorrhage. Our study builds on these findings by examining the impact that a clinical pharmacist has on multidisciplinary team-based decision-making and bedside patient care.

Of the patients in our study who presented to the ED with a life-threatening bleed, ICH was the most common type of bleed. Anticoagulant-associated ICH has a poor prognosis, with a mortality rate approaching 65% (15). In our study, patients with a pharmacist at the bedside had a lower median GCS score on admission (12.5 vs. 15, $p = 0.19$), as compared with the control group. Although this difference was not statistically significant, a lower GCS score on admission was shown to be a strong

predictor for higher 30-day mortality in ICH patients (16). Despite a lower GCS on admission, patients in the PharmD group had less deterioration in GCS at 24 hours as compared with the control group (3% vs. 9.1%, $p = 0.11$) and a shorter ICU and hospital LOS. Although both groups who presented with a warfarin-associated hemorrhage had a similar median INR on admission, more patients in the PharmD group received phytonadione co-administration. 4F-PCC replacement affords rapid correction by supplementation of absent coagulation factors, whereas phytonadione replaces vitamin K and allows for ongoing factor synthesis (17). Less deterioration in GCS at 24 hours may be due to the earlier achievement of hemostasis owing to faster 4F-PCC administration as well as phytonadione co-administration in the PharmD group.

Although there is no literature evaluating the impact of a pharmacist at the bedside during a hemorrhagic stroke, current American Stroke Association guidelines recommend initiating intravenous thrombolysis for acute ischemic stroke within 60 min of patient arrival, given that the benefits are time-dependent (18). Multiple studies have evaluated the impact of a pharmacist at the bedside in reducing door-to-needle time to thrombolysis in acute ischemic strokes (19–21). Based on the data that anticoagulation reversal time of fewer than 200 min was associated with significantly less hemorrhagic expansion of ICH and the results of our study, it can be argued that the benefits of 4F-PCC may also be time dependent (6).

Although this study was not powered to detect differences in hemostasis or mortality, a shorter ICU and hospital LOS in patients who received faster 4F-PCC administration may have been due to a faster cessation of bleeding and achievement of hemostasis. Previous literature has demonstrated that a shorter LOS results in better functional outcomes for patients, while also decreasing health care-associated expenses (22). Additionally, a prolonged ICU LOS was a significant predictor of decreased long-term survival and higher overall mortality in multiple critically ill patient populations (23–25). Strategies to reduce LOS may pose functional benefits to the patient and financial benefits to the institution.

Limitations

There are several limitations to our study that deserve consideration. First, the single-center retrospective design limits the ability to control for all potential confounders and affects the generalizability of the study. Furthermore, there is limited availability of clinical pharmacists during nights and weekends at our institution. Weekend presentation of intracranial and gastrointestinal hemorrhages has been associated with worse outcomes (12). Additionally, patients in the PharmD group had a numerically lower GCS score on admission as compared with the control group (12.5 vs. 15, respectively). Although this would seem to bias the results toward worse outcomes in the PharmD group, these patients experienced a shorter LOS. Furthermore, to control the effects of GCS score on admission as well as the time and day of patient presentation, a multivariable linear regression analysis was conducted. Given the retrospective nature of the study, the presence of a pharmacist and the study outcomes rely on accurate documentation in the electronic medical record. Lastly, the study was not powered to detect differences in hemostasis, ICU and hospital LOS, and mortality. Larger, prospective trials are warranted to assess the effect of faster time to 4F-PCC on hemostasis and mortality.

CONCLUSIONS

A clinical pharmacist at the bedside of patients who present to the ED with life-threatening bleeding or need for emergent surgery or procedure decreased time to 4F-PCC administration by 140 min after accounting for confounders. Faster time to 4F-PCC was associated with a significantly shorter ICU LOS (−3 days) and hospital LOS (−2.5 days). Although the impact of clinical pharmacists has historically been hard to capture, these findings demonstrate that a clinical pharmacist provides valuable therapeutic recommendations and optimizes time to receipt of life-saving pharmacotherapy. Large, prospective trials that are appropriately powered to determine whether faster time to 4F-PCC administration improves hemostasis and decreases mortality in patients with a life-threatening bleed or need for urgent surgery or procedure are warranted.

REFERENCES

1. Quinlan DJ, Eikelboom JW, Weitz JI. Four-factor prothrombin complex concentrate for urgent reversal of vitamin K antagonists in patients with major bleeding. Circulation 2013;128:1179–81.
2. Tao J, Bukanova EN, Akhtar S. Safety of 4-factor prothrombin complex concentrate (4F-PCC) for emergent reversal of factor Xa inhibitors. J Intensive Care 2018;6:34.
3. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: American College of Chest Physicians Evidence Based Clinical Practice Guidelines (9th ed.). Chest 2012;141(2 suppl):e152S–84.
4. Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 2016;24:6–46.
5. Huttner HB, Schellinger PD, Hartmann M, et al. Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. Stroke 2006;37:1465–70.

6. Mehta C, Jones M, Cuero MR, et al. Intracranial hemorrhage on warfarin: time to reversal is of the essence. Poster presented at the 68th Annual Meeting of the American Academy of Neurology. Vancouver, BC, Canada; 2016 Apr 17.
7. Bordeleau S, Poitras J, Marceau D, Breton C, Beaupré P, Archambault PM. Use of prothrombin complex concentrate in warfarin anticoagulation reversal in the emergency department: a quality improvement study of administration delays. BMC Health Serv Res 2015;15:106.
8. Eppert H, Reznek A. ASHP guidelines on emergency medicine pharmacist services. Am J Health Syst Pharm 2011;68:e81–95.
9. Brown JN, Barnes CL, Beasley B, et al. Effect of pharmacists on medication errors in an emergency department. Am J Health Syst Pharm 2008;65:330–3.
10. Khorsand N, Majeed A, Sarode R, et al. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. J Thromb Haemost 2016;14:211–4.
11. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
12. Crowley RW, Yeoh HK, Stukenborg GJ, et al. Influence of weekend hospital admission on short-term mortality after intracerebral hemorrhage. Stroke 2009;40:2387–92.
13. Langstraat E, Martinelli A, Spoelhof B, et al. Effect of pharmacy management on turnaround time of 4-factor prothrombin complex concentrate. Am J Health Syst Pharm 2017;74(17 suppl 3):S61–6.
14. Corio JL, Sin JH, Hayes BD, et al. Impact of a pharmacist-driven prothrombin complex concentrate protocol on time to administration in patients with warfarin-associated intracranial hemorrhage. West J Emerg Med 2018;19:849–54.
15. Steiner T, Weitz JI, Veltkamp R. Anticoagulant-associated intracranial hemorrhage in the era of reversal agents. Stroke 2017;48:1432–7.
16. Safatli DA, Gunther A, Schlattmann P, et al. Predictors of 30-day mortality in patients with spontaneous primary intracerebral hemorrhage. Surg Neurol Int 2016;7(suppl 18):S510–7.
17. Taberner DA, Thomson JM, Poller L. Comparison of prothrombin complex concentrate and vitamin K1 in oral anticoagulant reversal. Br Med J 1976;2:83–5.
18. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2018;49:e46–110.
19. Rech MA, Bennett S, Donahey E. Pharmacist participation in acute ischemic stroke decreases door-to-needle time to recombinant tissue plasminogen activator. Ann Pharmacother 2017;51:1084–9.
20. Jacoby JS, Draper HM, Dumkow LE, et al. Emergency medicine pharmacist impact on door-to-needle time in patients with acute ischemic stroke. Neurohospitalist 2018;8:60–5.
21. Montgomery K, Hall AB, Keriazes G. Impact of an emergency medicine pharmacist on time to thrombolysis in acute ischemic stroke. Am J Emerg Med 2016;34:1997–9.
22. van Vliet M, Huisman M, Deeg DJH. Decreasing hospital length of stay: effects on daily functioning in older adults. J Am Geriatr Soc 2017;65:1214–21.
23. Moitra VK, Guerra C, Linde-Zwirble WT, et al. Relationship between ICU length of stay and long-term mortality for elderly ICU survivors. Crit Care Med 2016;44:655–62.
24. Williams TA, Ho KM, Dobb GJ, et al. Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients. Br J Anaesth 2010;104:459–64.
25. Naidech AM, Beaumont JL, Rosenberg NF, et al. Intracerebral hemorrhage and delirium symptoms – length of stay, function, and quality of life in a 114-patient cohort. Am J Respir Crit Care Med 2013;188:1331–7.

ARTICLE SUMMARY

1. Why is this topic important?

There is currently a paucity of evidence regarding the importance of the timing of anticoagulation reversal in patients with life-threatening bleeding or those necessitating urgent reversal for surgery or procedures.

2. What does this study attempt to show?

Clinical pharmacists work alongside physicians and nurses at the bedside to optimize pharmacotherapy, increase efficiency and cost-effectiveness of care, and ultimately improve patient safety. At our institution, a pharmacist at the bedside obtains medication histories regarding anticoagulant and time of last dose, assesses the appropriateness of four-factor prothrombin complex concentrate (4F-PCC) use and contraindications to 4F-PCC, facilitates correct order entry and timely preparation of 4F-PCC, ensures co-administration of phytonadione for warfarin-induced bleeding, and recommends appropriate pre- and postadministration laboratory follow-up. This study attempts to demonstrate the benefit of clinical pharmacist presence in shortening the time between presentation to the emergency department and 4F-PCC administration.

3. What are the key findings?

When 4F-PCC administration is indicated for anticoagulation reversal in life-threatening bleeding or urgent procedure, clinical pharmacist involvement resulted in a 140-min reduction in time to administration, even after accounting for confounders via a multivariable linear regression. Patients in the PharmD group had a significantly shorter intensive care unit (ICU) and hospital length of stay (LOS) and were more likely to be discharged to home.

4. How is patient care impacted?

A clinical pharmacist at the bedside of patients in need of 4F-PCC in the ED translated to improved patient care, as demonstrated by a reduction in both ICU and hospital LOS. Although this study was not powered to detect differences in achievement of hemostasis, a shorter ICU and hospital length of stay in patients who received faster 4F-PCC administration may have been due to a faster cessation of bleeding. Previous literature has demonstrated that a shorter length of stay results in better functional outcomes for patients, while also decreasing health-care associated expenses (22).