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Original Article

A retrospective comparison of the emergent use of fixed-dose four-factor prothrombin complex versus weight-based dosing for intracranial hemorrhage assessing medication delivery time and cost

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Abstract: Objectives: The goal of this study was to evaluate a low fixed-dose versus weight-based dosing strategy for four-factor prothrombin complex (4F-PCC) time to administration in intracranial hemorrhage (ICH) patients. Methods: A retrospective analysis was conducted at a single rural Tertiary referral center in patients ≥18 years old on warfarin with ICH who received 4F-PCC. Continuous variables were summarized using mean (±95% CI) and compared using two-tailed tests; *p* values ≤0.05 were considered statistically significant. Results: A total of 46 ICH patients were reversed using 4F-PCC (Fixed, n = 27 and Weight, n = 19). Baseline characteristics were equivalent. Total units of 4F-PCC (mean dose units 2525.1 versus 1623.3) and dose per kg were significantly reduced in the fixed-dose group. Total time from order to delivery was significantly reduced with the fixed-dose strategy (mean time 43.0 versus 29.0 minutes). Hospital length of stay (LOS), intensive care unit LOS, and mortality were equivalent with a similar mechanism. International Normalized Ratio (INR) reversal success (≤1.5) and total INR change was comparable with no difference in adverse thromboses between groups. Conclusions: A fixed-dosed strategy reduced time to 4F-PCC administration for warfarin reversal in ICH, as compared to a weight-based strategy; with no increase in LOS, mortality, or need for additional dosing. This also resulted in significant cost savings.

Keywords: Warfarin, intracranial hemorrhage, four-factor prothrombin complex concentrate, international normalized ratio

Introduction

The indications for anticoagulation therapy include atrial fibrillation, venous thromboembolism, and post-heart valve replacement [1]. There are three predominant types of anticoagulatory medication [2]: (a) Low molecular weight heparins, (b) direct oral anticoagulants (DOACs), and (c) vitamin K antagonists (VKA), e.g., warfarin. Even though DOAC usage is the preferred medication for a multitude of reasons, including a lack of monitoring requirements [3], according to the United States Medicare patient pharmacy fill patterns, warfarin use remains higher in isolated and rural areas than in urban areas compared to DOACs [4].

Patients who suffer intracranial hemorrhage (ICH) while anticoagulated have a higher mortality than those who are not anticoagulated [5, 6]. Further, poor outcome in ICH is directly associated with expansion in hematoma size after admission [7], and historically, warfarin use has been correlated to larger intracerebral hemorrhage volume, especially at higher international normalized ratio (INR) values greater than three [8]. In addition, a more recent meta-analysis has shown warfarin patients with ICH have significantly larger hematoma volumes (mean difference of pooled volume of 9.7 ml) with more frequent hematoma expansions, compared to DOACs [9]. Thus, from symptom onset, time to reversal is key when treating anti-

coagulated patients due to temporal ICH hematoma expansion [10, 11].

Four-factor prothrombin complex (4F-PCC) is a United States Food and Drug Administration approved medication for reversal of VKAs in patients with acute major bleeding or requiring urgent surgery; it has become the standard therapy for emergent warfarin reversal with overall fewer adverse events when compared to fresh frozen plasma (FFP) [12, 13]. Four-factor prothrombin complex is traditionally dosed based on patient weight and INR, but this strategy can lead to an increased time before administration. This time difference, from baseline INR to factor product administration, represents a potential opportunity for process improvement in the management of warfarin-related ICH [14].

A 2017 retrospective study [15] found that implementation of 1000 units (U) 4F-PCC could not be recommended for VKA reversal in ICH, since additional dosing was required. The door to administration times were shorter in this cohort but not significant, and the effect on clinical outcomes was unknown [15]. Further, a study by Jansma, *et al.* [16] in 2020 demonstrated that a fixed dose regimen of 1500 U successfully achieved a target INR of ≤1.5 in the majority of patients and resulted in no adverse thrombotic events [16].

The goal of this study was to evaluate low fixed-dose versus weight-based dosing strategies for 4F-PCC time to administration in patients with an ICH. We hypothesized that a fixed-dose strategy would reduce time from the pharmacy order to administration, with no difference in achieving the target INR (≤1.5) reversal, and thus reduce overall dose requirements resulting in significant per patient cost saving.

Materials and methods

After approval from the Billings Clinic Institutional Review Board Privacy and Exemption Committee (Project approved 9/16/2020, identifier #20.016), non-randomized data was abstracted from the hospital registry between 2017 to 2021. Inclusion criteria: (a) patients ≥18 years old, (b) on warfarin, (c) intracranial hemorrhage observed on arrival computed tomography (CT) scan, (d) neurosurgical consultation obtained, and (e) received 4F-PCC to reverse the anticoagulation. Exclusions: non-emergent cases and patients <18 years old. Only patients meeting all criteria described above were included in the analysis.

Setting

This retrospective study was conducted at a single rural 305-bed American College of Surgeons (ACS) verified Level 2 Trauma center that serves as a four-state referral hub in the upper mountain west region of the United States.

Demographics and variables

All variables were abstracted from the electronic health record, however the following measurements were of particular note: (a) Glasgow coma scale (GCS) [17], used to measure patient level of consciousness after brain injury: Mild, GCS 15-13, moderate, GCS 12-9, and severe, GCS 8-3; (b) Charlson comorbidity index (Charlson score) [18], severity of patient comorbidity categorized into three grades: mild with scores of 1-2; moderate scores of 3-4; and severe scores ≥5; (c) LACE score [19], the risk for 30-day readmission and death, uses four variables (i) length of stay, (ii) acuity of the admission, (iii) comorbidity of the patient, and (iv) prior emergency department use 6 months before admission: scores range from 0-19, and those >10 are considered high readmission risk; (d) International normalized ratio (INR) [20], for evaluating blood coagulation: results of 1.0-1.5 are normal and desirable in an emergent ICH situation; in warfarin patients 2.0 to 3.0 is generally an effective therapeutic range, except with ICH; (e) Intracranial injury type and volume, determined by consulting neurosurgeon from head CT imaging upon arrival; and (f) The hemorrhage mechanism was defined as "traumatic" if a trauma activation (Level 1 or 2) or trauma consultation occurred upon patient arrival.

Four-factor prothrombin complex treatment

Introduction of fixed dosing occurred on April 1, 2019. Prior to this time, dosing was variable, and calculated based on weight and INR (following manufacturers guidelines). All weight-based dosing patients also received 10 mg intravenous (IV) vitamin K. This facility has a dose-rounding policy in which the dose is rounded to the nearest whole vial size. After

Table 1. Warfarin patient characteristics, pre-four-factor prothrombin complex

	Weight Based (*n* = 19)	Fixed Dose (*n* = 27)	*p* Value
Age, Mean [95% CI]	73.2 [68.6, 77.8]	78.2 [74.4, 82.0]	0.103
Sex Female, *n* (%)	11 (40.7%)	6 (31.6%)	0.746
Weight, Mean kg [95% CI]	89.4 [78.0, 100.8]	89.3 [79.3, 99.1]	0.987
Distance from Injury Site to Facility, Mean [95% CI]	43.5 [14.3, 72.6]	35.1 [12.9, 57.4]	0.660
Admission Glasgow Coma Scale (GCS), Mean [95% CI]	10.9 [8.3, 13.5]	12.9 [11.4, 14.4]	0.181
Charlson Score, Mean [95% CI]	4.6 [3.3, 5.9]	5.0 [4.5, 5.5]	0.553
LACE Score, Mean [95% CI]	7.9 [6.0, 9.8]	8.0 [6.7, 9.3]	0.963
Warfarin Indications, *n* (%)			0.641
Atrial Fibrillation	12 (63.2%)	20 (74.1%)	
Venous Thrombotic Events	7 (36.8%)	7 (25.9%)	

±95% confidence intervals (95% CI). *p values ≤0.05 were considered significant.

April 2019, the current fixed-dose rapid reversal pathway for patients with intracranial hemorrhage denotes administration of 1500 U 4F-PCC with 10 mg IV vitamin K. Coagulation labs including INR, thromboelastography (TEG), complete blood count (CBC), and fibrinogen were drawn 15 minutes post-infusion. One additional 500-unit dose of 4F-PCC could be given based on INR. The patient was admitted to the Intensive Care Unit (ICU) and repeat head CT scan performed 3 hours post-infusion or sooner if the patient developed neurologic changes.

Data analysis

A descriptive statistical analysis was performed using the statistical package R (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized using mean and ±95% confidence intervals (CI) and compared using Welch's two-tailed t-test. Categorical variables are reported as number and percentage and compared with Yates chi-squared test. All p values ≤0.05 were considered statistically significant.

Results

Patient demographics

A total of 46 patients with ICH on warfarin were reversed with 4F-PCC. This consisted of 21 patients with an initial INR ≥3 and 25 patients with an initial INR <3. The overall mean distance traveled for traumatically injured patients was 38.3 miles from injury to facility; however, 15% of patients travelled a mean of 157.9 miles (95% CI = 109.9, 206.0).

Table 1 presents the characteristics and demographics of the participants for the two groups (weight-based N = 19 and fixed-dose N = 27). The weight-based dose group was 59.3% male (mean age = 73.2), versus 68.4% male (mean age = 78.2) for the fixed dose group. All baseline characteristics between the groups were statistically equivalent (P>0.05).

Patient neurological overview upon arrival

A review of the head CT data, at hospital admission, is shown in **Table 2**. Specifically, the various types of intracranial hemorrhage, and the subsequent associated intracranial blood volume were similar between treatment methods.

Intracranial hemorrhage patients reversed by four-factor prothrombin complex

Table 3 describes the post 4F-PCC attributes. All INR values shown were statistically comparable between groups, specifically there was no difference between post-treatment INR in either group. Of note, the INR reversal success rate was >80% for both treatment methodologies (P = 1.000).

Dosing was reported as either units per patients (P<0.001) or per kg (P<0.001) and was significantly different between the two treatment groups. However, it should be noted that approximately 11% of patients from either treatment protocol required an additional dose of 4F-PCC (P = 0.951).

Table 2. Neurological presentation overview upon arrival

	Weight Based (*n* = 19)	Fixed Dose (*n* = 27)	*p* Value
Hemorrhage Mechanism, *n* (%)			1.000
Non-traumatic	7 (36.8%)	11 (40.7%)	
Traumatic	12 (63.2%)	16 (59.3%)	
Intracranial Injury Type, *n* (%)			
Subdural Hemorrhage (SDH)	14 (73.7%)	20 (74.1%)	0.776
Subarachnoid Hematoma (SAH)	3 (15.8%)	7 (29.6%)	0.464
Intraparenchymal Hemorrhage (IPH)	4 (21.1%)	7 (25.9%)	0.976
Blood Volume, *n* (%)			
SAH/IPH Hemorrhage, Small (<20 mm)	11 (57.9%)	15 (55.6%)	0.885
SAH/IPH Hemorrhage, Large (≥20 mm)	9 (47.4%)	12 (44.7%)	0.917
SDH Hematoma, Small (<20 mm)	6 (31.6%)	9 (33.3%)	0.846
SDH Hematoma, Large (≥20 mm)	8 (42.1%)	11 (40.7%)	0.833

±95% confidence intervals (95% CI). *p values ≤0.05 were considered significant.

Table 3. Intracranial hemorrhage patients reversed by four-factor prothrombin complex

	Weight Based (*n* = 19)	Fixed Dose (*n* = 27)	*p* Value
International Normalized Ratio (INR)			
INR Baseline, Mean [95% CI]	3.6 [2.8, 4.5]	3.7 [2.8, 4.7]	0.840
INR within 6 hrs, Mean [95% CI]	1.3 [1.1, 1.5]	1.3 [1.2, 1.4]	0.893
INR Change (6 hrs to Base), Mean [95% CI]	2.4 [1.5, 3.3]	2.1 [1.3, 2.9]	0.681
Rate Reversal Success (INR ≤1.5), *n* (%)	16 (84.2%)	23 (85.2%)	1.000
Four-Factor Prothrombin Complex Concentrate (4F-PPC) Dosing			
Dose Units, Mean [95% CI]	2525.1 [2091.8, 2958.4]	1623.3 [1515.1, 1731.5]	<0.001*
Dose/kg, Mean [95% CI]	28.9 [24.8, 33.0]	19.2 [17.2, 21.2]	<0.001*
Patients received >1 Dose, *n* (%)	2 (10.5%)	3 (11.1%)	0.951
Four-Factor Prothrombin Complex Concentrate (4F-PPC) Administration Timing			
Time from Basal INR to 4F-PCC dose, Mean (Hours:Minutes) [95% CI]	2:26 [0:52, 3:14]	0:43 [0:29, 0:57]	0.047*
Time from Pharmacy Order to Administration, Mean (Minutes:Seconds) [95% CI]	43:00 [32:48, 53:12]	28:58 [25:01, 35:54]	0.015*
Neurosurgical Intervention, *n* (%)			
Patients Received Surgery	6 (31.6%)	5 (18.5%)	0.502

±95% confidence intervals (95% CI). *p values ≤0.05 were considered significant.

The temporal administration of 4F-PCC demonstrated significant differences between the groups. In comparison of the initial pharmacy order to administration time, there was an approximate 15-minute decrease in time for the fixed-dose strategy (P = 0.015). Furthermore, timing from basal INR to administration revealed a mean 103-minute reduction with the fixed dose treatment group (P = 0.047).

Patient outcomes

In addition, **Table 4** indicates that despite differences in the dosing noted above, the outcomes for hospital length of stay (LOS) (P = 0.441), ICU LOS (P = 0.169), and mortality (P = 0.641) were not significantly different between the groups.

Moreover, post-4F-PCC treatment, neither group showed significant differences in either deep venous thrombosis (DVT) or ischemic stroke (P = 1.000). In both patient groups, no other classic thrombotic events were observed such as myocardial infarction or pulmonary embolism (PE). However, three patients within their respective treatments received inferior vena cava filters due to their past medical histories: a female with a history of DVT and PE (weight-based dose); a male with bilateral lower extremity DVT (fixed-dose); and a male with a history of PE (fixed-dose).

Table 4. Patient outcomes

	Weight Based (*n* = 19)	Fixed Dose (*n* = 27)	*p* Value
Outcomes			
Hospital Length of Stay, Mean days [95% CI]	7.8 [3.1, 12.5]	5.8 [3.5, 8.1]	0.441
Intensive Care Unit Length of Stay, Mean days [95% CI]	3.1 [1.3, 4.9]	1.8 [1.3, 2.4]	0.169
Mortality, *n* (%)	7 (36.8%)	7 (25.9%)	0.641
Cost per Patient, Mean US Dollars [95% CI]	4090.59 [3388.6, 4792.6]	2629.68 [2454.5, 2804.9]	<0.001*
Select Adverse Events Post Four-factor prothrombin complex, *n* (%)			1.000
Deep Vein Thrombosis	0 (0.0%)	1 (3.7%)	
Ischemic Stroke	1 (5.3%)	0 (0.0%)	

±95% confidence intervals (95% CI). *p values ≤0.05 were considered significant.

Discussion

This retrospective study of 46 patients in a Level 2. Trauma center in the northwestern United States found that a fixed-dose strategy reduced time to 4F-PCC administration for warfarin reversal in ICH as compared to a weight-based dose strategy. Because baseline characteristics were statistically equivalent, and INR reversal success and total INR change were comparable, the fixed dose strategy improved the process and management of warfarin-related ICH.

The primary objective of the current study was to examine the introduction of a fixed-dose strategy of 4F-PCC for treatment of ICH in patients on warfarin, focusing on reversal efficacy and temporal improvements in administration. Previous studies have suggested that the time difference from baseline INR to factor product administration for weight-based dosing is a potential opportunity for process improvement in management of these anticoagulated patients [14]. A multicenter retrospective pragmatic registry study indicated that with weight-based dosing, the mean time from basal INR to 4F-PCC administration was 2.4 hours [14], which is directly in line with the time frame in this study of 2 hours and 26 minutes. The time to reversal is key when treating anticoagulated patients due to temporal ICH hematoma expansion [10, 11], and here we show implementation of a fixed-dose strategy reduced the basal INR to administration time to 43 minutes.

The current anticoagulation rapid reversal pathway at this facility includes a dose of 1500 U of 4F-PCC for intracranial hemorrhage. The efficacy of this dose has been supported by previous retrospective studies [16, 21, 22]. More recently, the 2020 American College of Cardiology expert consensus decision pathway provides a fixed dose option for reversal of warfarin-based bleeding, and their recommendation for ICH is also 1500 U [23]. This dosing is substantially higher than initial fixed-dose studies which evaluated a dose of 1000 U but required an additional dose in up to 32% of patients [15]. This rate contrasts with the current study which demonstrates 11% of patients requiring an additional dose. However, it should also be noted Abdoellakhan *et al*. (2017) concluded the 1000 U fixed dose used was too low and further determined their median fixed dose as 13 U/kg [15], far lower than the mean 19.2 U/kg in the fixed dose group observed in the current study (**Table 3**).

Additionally, the rate reversal success in reducing patient INRs (≤1.5) is a concern when comparing the fixed-dose strategy to the weight-based dosage. Three previous studies utilizing a 1500 U fixed dose on patient groups with mixed indications of reversal, i.e., ICH, gastrointestinal bleed, and emergent surgery, found similar results for successful INR reduction (≤1.5) in approximately 70% of patients [16, 21, 22]. However, the current study directly compares weight and fixed dosing 4F-PCC strategies and only focuses upon ICH patients, and we demonstrate comparable INR reduction success >84% for both (P = 1.000) treatment strategies, with only one patient from each group having an adverse event (a DVT in the fixed dose or ischemic stroke in the weight-based group).

Despite implementing a strategy of 1500 U per patient with a possible additional dose, overall administration with a fixed-dose strategy substantially reduced both units per patient and

dose per kg compared to weight-based dosing. This resulted in a mean cost saving of $1461 per patient, based on contract pricing (as emergent cases, these patients are not charged directly).

The distance from a trauma center and time to treatment are well documented sources of disparity in rural care. The hospital service area for this associated study spans a total of 127,801 square miles, which is larger than the state of New Mexico. Fifteen percent of patients in this study travelled a mean of 157.9 miles to the hospital for definitive care. Previous studies have demonstrated that states with poor trauma center access and increased time to treatment have a relatively higher burden of mortality [24]. Thus, the importance of expedited time to 4F-PCC administration is further magnified in this type of care environment. While there was no difference in mortality between fixed and weight-based dosing in the current study, future investigation may expose critical differences in those patients transferred long distances to definitive care.

The current study does have limitations. This was a non-randomized, retrospective, observational, single-center study which may be subject to selection and/or surveillance bias. As a retrospective analysis, the project could be subject to some intrinsic limitations including the potential for missed enrollment due to possible errors in documentation and varying adherence to the institutional practice recommendations which could have resulted in selection bias.

Conclusions

A fixed-dosed strategy reduced the time to administration of 4F-PCC for warfarin reversal in ICH as compared to a weight-based strategy, with equal reversal success. There was no increase in comparable length of stay, mortality, or need for additional 4F-PCC dosing. Further, fixed dosing decreased the overall dose requirement leading to significant facility per patient cost savings. Future studies should include a prospective evaluation of outcomes between these two respective group dosing strategies.

Disclosure of conflict of interest

None.

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