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A Retrospective Review of Four-Factor Prothrombin Complex Concentrate for Factor Xa Inhibitor-Related Bleedings

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Abstract

Background: The use of factor Xa inhibitors has grown in popularity; however, the risk of major bleeding events requires for the appropriate reversal agent. The recent approved agent for factor Xa inhibitor reversal, andexanet alfa, has limited clinical efficacy and safety data, and it can be a financial burden on healthcare systems due to its high cost. Four-factor prothrombin complex concentrate (4F-PCC) has been utilized off label in patients with factor Xa inhibitor-related bleedings. **Objective:** The aim of this study was to assess the safety and efficacy of 4F-PCC in managing factor Xa inhibitor-related bleedings. **Methods:** This is an observational, retrospective review of 4F-PCC usage in treating factor Xa inhibitor-related bleeds from May 2014 to December 2018 at a single health system. Efficacy was evaluated using the assessment criteria described by Sarode et al. Secondary outcomes analyzed included thromboembolic events, length of stay, mortality, and discharge disposition. **Results:** Fifty-nine patient charts were reviewed, and 48 patients were included in the study analysis. The administration of 4F-PCC achieved effective hemostasis in 33 patients (68%), and effective hemostasis was achieved in 12 patients (86%) who had intracranial hemorrhage and did not receive any surgical intervention. Thromboembolic events occurred in 4 patients within 30 days from 4F-PCC use. A majority of patients (85.4%) were discharged from the hospital to home or long-term care; 7 patients (14.6%) expired in the hospital. **Conclusion:** Efficacy was achieved in over half of the patient population in this cohort who received 4F-PCC for factor Xa inhibitor-related bleeding events.

Keywords

factor xa inhibitors, andexanet alfa, 4F-PCC

Introduction

The use of factor Xa (fXa) inhibitors in patients with atrial fibrillation and venous thromboembolism has grown in popularity due to rapid onset of therapeutic anticoagulation, lack of routine monitoring, and ease of administration route. With the increasing use of agents such as apixaban and rivaroxaban also comes the risk of major bleeding events, calling for appropriate reversal of such agents. The newest reversal agent, andexanet alfa or AA, is the first to receive Food and Drug Administration (FDA) approval for the reversal of rivaroxaban and apixaban. It is a recombinant modified human fXa decoy that binds to and sequesters fXa inhibitors and able to bind to and inhibit tissue factor pathway inhibitor. The sequestration of the fXa inhibitors allows for restoration of thrombin generation and clot formation.[1] Prior to AA, 4-factor prothrombin complex concentrate (4F-PCC) were recommended for fXa inhibitors-associated life threatening bleeds in multiple guidelines. For instance the Neurocritical Care Society and Society of Critical Care Medicine suggests to use 50 units/kg of 4F-PCC or activated PCC if intracranial hemorrhage (ICH) occurred in patients taking fXa inhibitors.[2,3] 4F-PCC contains factors II, VII, IX, X, protein C and S and is indicated for the urgent reversal of vitamin K antagonist. Despite of the current approval for 4F-PCC use, it has been utilized off label to neutralize the anticoagulation effect of fXa inhibitors.[4] Several studies have revealed 65 – 93% hemostatic efficacy in varying dosing schemes of 4F-PCC in managing fXa inhibitors-related bleeds.[5-11]

The efficacy and safety data of andexanet alfa in clinical practice are insufficient, and the available trials comparing AA versus 4F-PCC in patients with an apixaban- or rivaroxaban-related bleeds show mixed results. In a retrospective review

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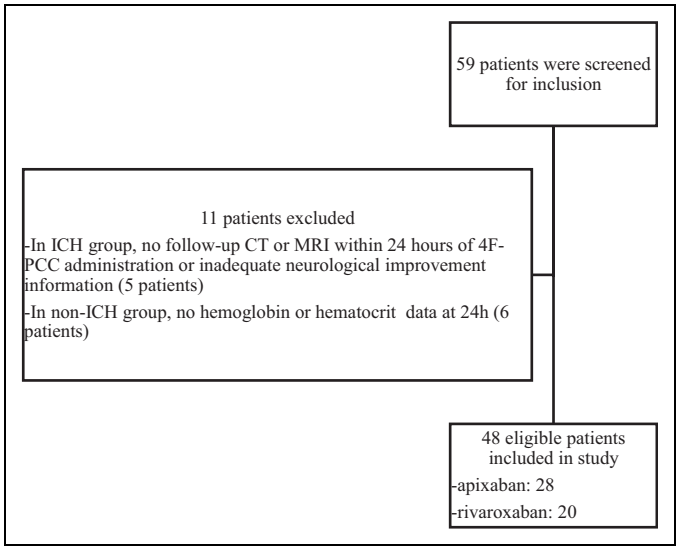

Figure 1. Patient selection. ICH: intracranial hemorrhage, CT: computed tomography, MRI: magnetic resonance imaging Non-ICH includes gastrointestinal bleeding, chest wall hematoma, vaginal bleeding, rectal sheath hematoma, epidural hematoma, or other reversal necessary for urgent surgery.

comparing AA versus 4F-PCC in adult patients with fXa-related ICH, Barra and colleagues reports 88.9% of good or excellent hemostatis in AA group versus 60% of that in 4F-PCC.[12] However, in another similar retrospective cohort comparing AA versus 4F-PCC in ICH, Ammar and colleagues found no difference in neuroimaging stability, functional outcome and thrombotic events in 2 groups.[13] Given the current gap in the literature, this study was aimed to evaluate hemostatic efficacy and safety of 4F-PCC in patients who presented with apixaban- or rivaroxaban-related bleedings at our facility.

Methods

Study Design

This observational study was completed retrospectively at a single health system. This health system features a level I trauma and level I stroke center at its flagship location. Patients received 4F-PCC in the emergency department, intensive care units, and operating rooms. All laboratory data, radiographic imaging, or medication records were abstracted from Cerner Electronic Medical Record (EMR) or MedHost EDIS EMR.

Patients

All adult patients who received 4F-PCC for the reversal of apixaban or rivaroxaban from May 2014 to December 2018 were screened. Patients received 4F-PCC either for the treatment of an acute life-threatening bleed or required anticoagulant reversal prior to an emergent surgery. Fifty-nine patients were screened, and 48 patients were included in the study results (Figure 1). Patients were excluded due to a lack of follow-up computerized tomography (CT) or magnetic resonance imaging (MRI) within 24 hours of receiving 4F-PCC or inadequate neurological improvement information within the ICH group, and no hemoglobin and hematocrit data at 24 hours in the non-ICH group.

Outcomes

The primary purpose of this study was to determine the hemostatic efficacy achieved following the administration of 4F-PCC. The effectiveness of hemostasis was categorized based on the criteria set forth by Sarode et al[14] (Table 1). Safety outcomes included the incidence of a thromboembolic event within 30 days of 4F-PCC administration and all-cause mortality rate within 30 days of 4F-PCC. Other secondary outcomes included length of hospitalization, level of care required following discharge, resumption of anticoagulation therapy post-hospitalization, and the time required to prepare and administer 4F-PCC following order placement.

Treatment

Patients received 4F-PCC based on the anticoagulation dosing protocol (Figure 2) in place at the time of administration. Majority of patients received a dose of 50 units/kg with a maximum dose of 5000 units.

Statistical Analysis

Descriptive statistics were employed to describe the data collected. Normally distributed data was reported in mean values, and non-normally distributed data was reported with median values.

Results

Fifty-nine patients were screened, and 48 were determined eligible for final analysis. The median age of patients was 74 and 58.3% were male. Treatment with 4F-PCC was initiated to manage bleedings from apixaban (58.3%) and rivaroxaban (41.7%). The fXa inhibitors were prescribed primarily for atrial fibrillation (75%). The mean dose of 4F-PCC administered was 4136 units or 48.5 units/kg. Twenty patients (41.7%) received 4F-PCC for ICH, 13 patients (27%) received 4F-PCC for gastrointestinal bleeding, and 15 patients (31.3%) received 4F-PCC for other bleeding events (Table 2). The median order-to-needle time was 36 minutes. In addition to 4F-PCC, 25 patients (52.1%) were given blood products, with 3 patients (6.3%) receiving FFP. No patients in our study required a second dose of 4F-PCC (Table 3).

Based on modified Sarode et al[14] criteria, 33 patients (68%) achieved good hemostasis. Of the patients with ICH, 14 patients (70%) achieved good hemostasis, and 12 of them did not receive any surgical intervention. Of the 28 patients who received 4F-PCC for non-ICH indications, 19 patients (68%) achieved good hemostasis (Table 4).

Thromboembolic events occurred in 4 patients within 30 days of 4F-PCC treatment, including pulmonary embolism,

Table 1. Effectiveness Assessment Guide, Modified From Sarode et al.[14]

Rating	Visible bleeding	Non-visible bleeding
Good	Cessation of bleeding ≤1 h after the end of infusion and no additional coagulation intervention required	– Musculoskeletal bleeding : pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 h after the end of infusion; and the condition has not deteriorated during and after 24h – ICH: ≤20% increase in hematoma volume compared with baseline on repeat CT scan performed and/or any neurological improvement noted over the following 12 h or-if the patient was progressively deteriorating until the treatment with FEIBA-even a stabilization of the condition – Non-visible bleeding that is not described above (e.g. GI bleeding): ≤10% decrease in both Hb/Hct at 24 h compared with baseline
Moderate	Cessation of bleeding >1 and ≤4 h after the end of infusion and no additional coagulation intervention required	– Musculoskeletal bleeding : pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 h and ≤4 h after the end of infusion; and the condition has not deteriorated during and after 24h – ICH: >20%, but ≤35 % increase in hematoma volume compared with baseline on repeat CT scan performed and/or minimal deterioration of neurological condition. – Non-visible bleeding that is not described above : >10% to ≤20% decrease in both Hb/Hct at 24 h compared with baseline
Poor/None	Cessation of bleeding >4h after the end of the infusion, and/or additional coagulation intervention required (plasma, whole blood or coagulation factors)	– Musculoskeletal bleeding: no improvement by 4 h after the end of infusion and/or the condition has deteriorated during the 24-h period – ICH: >35% increase in hematoma volume compared with baseline on repeat CT scan performed at the 24h time point and/or clear deterioration of the condition or death. – Non-visible bleeding that not listed above: >20% decrease in both Hb/Hct at 24 h compared with baseline

Abbreviations: CT, computed tomography; GI, gastrointestinal; ICH, intracranial hemorrhage.

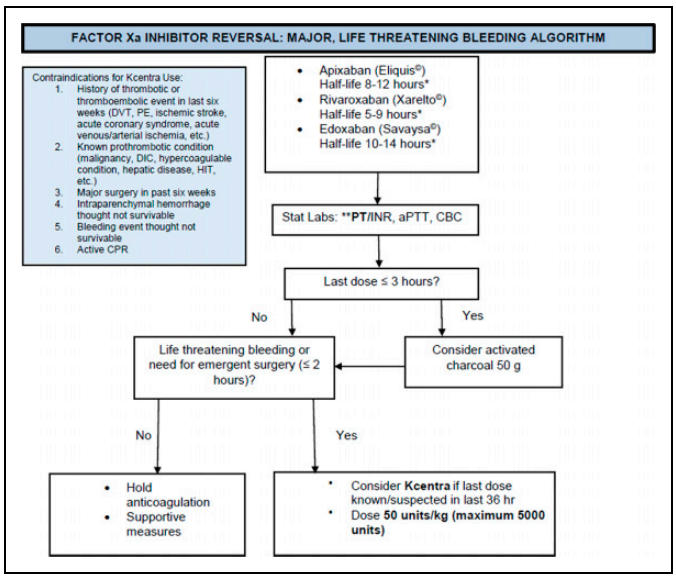

Figure 2. Fxa inhibitor reversal algorithm.

superficial thrombus in right upper extremity, ischemic stroke, and midbrain infarct (Table 5 and 6). The median length of hospital stay was 5 days. Upon discharge, most patients either returned to home (54.7%) or were discharged to a skilled nursing facility, rehabilitation hospital, or a specialty hospital (31.3%). Anticoagulation was resumed following 4F-PCC administration in 28 patients (58.3%). In total, 7 patients (15.9%) expired in the hospital within 30 days of receiving 4F-PCC (Table 5).

Discussion

Prior to 2018, the reversal agent for fXa inhibitors was not available, and PCC has been utilized off-label in reversing fXa inhibitors. Several studies have demonstrated good hemostatic efficacy and safety outcomes of PCC in treating apixaban- and rivaroxaban-associated major bleedings.[5-11]

This analysis is a retrospective review conducted at a single health system. Fifty-nine charts were reviewed, and 48 were included in the efficacy and safety analysis. The study shows effective hemostasis occurred in 33 patients or 68% of the patient population according to Sarode et al modified criteria.[14] Previous studies by Majeed et al and Schulman et al in which PCC was also used for major bleeding in patients on fXa inhibitors, demonstrated similar efficacy results of 73% and 69%, respectively.[5,6] In addition, more recent retrospective analyses

Table 2. Patient Characteristics.

Variables	n = 48
Age, years, median	74
Weight, kg, median	87.7
Male, n (%)	28 (58.3)
Creatinine clearance, n (%)	
<30 mL/min	7 (14.6)
30-60 mL/min	17 (35.4)
>60 mL/min	24 (50)
Hemoglobin prior to 4F-PCC, median	11.7
non-ICH group,median	10.1
Hemoglobin post 4F-PCC, median	10.5
non-ICH group, median	10.3
Indication for anticoagulation, n (%)	
Atrial fibrillation	36 (75)
DVT/PE/CVA/Portal Vein Thrombosis	12 (25)
DOAC, n (%)	
Apixaban	28 (58.3)
Rivaroxaban	20 (41.7)
Type of bleed, n (%)	
ICH[†]	20 (41.7)
GI bleed	13 (27.1)
Other[‡]	15 (31.3)
Intervention or surgery to stop bleeding, n (%)*	
Yes	8 (16.7)
No	40 (83.3)

Abbreviations: 4F-PCC, 4 factor-prothrombin complex concentrate; DVT, deep vein thrombosis; PE, pulmonary embolism; CVA, cerebrovascular accident; DOAC, direct oral anticoagulants; GI bleeding, gastrointestinal bleeding; ICH, intracranial hemorrhage
[†]Subdural hematoma, subarachnoid hemorrhage, intracerebral hemorrhage, cerebellar hemorrhage, parenchymal hemorrhage, brain hemorrhage, or intracranial hemorrhage
[‡]Chest wall hematoma, vaginal bleeding, rectal sheath hematoma, epidural hematoma, or other reversal necessary for urgent surgery
*Craniectomy and evacuation of hemorrhage, craniotomy, evacuation of hematoma, argon plasma coagulation of arteriovenous malformations in stomach, embolization of ruptured mesenteric aneurysm, or other interventional radiology attempt to repair GI bleed

Table 3. 4F-PCC and Blood Products.

Agents	**Result**
Dose of 4F-PCC, units, mean	4136.33
Dose of 4F-PCC, n (%)	
25 units/kg dosing	2 (4.2)
Actual Dose, mean, units/kg	23.6
50 units/kg dosing	46 (95.8)
Actual Dose, mean, units/kg	48.5
Repeat Dose of 4F-PCC, n (%)	0 (0)
4F-PCC order-to-needle time, minutes, median (n = 46)	36
Blood Products, n (%)	
Blood Product Given	25 (52.1)
FFP Given	3 (6.3)

Abbreviations: 4F-PCC, 4 factor prothrombin complex concentrate; FFP, fresh frozen plasma

Table 4. Hemostatic Efficacy Results**.

Category	Hemostatic Efficacy, n (%)	Hemostatic Inefficacy, n (%)	Total patient, n
All patients (ICH + non-ICH)	33 (68)	15 (32)	48
ICH	14 (70)	6 (30)	20
• ICH with intervention	• 2 (14)	• 3 (50)	5
• ICH without intervention	• 12 (86)	• 3 (50)	15
Non ICH	19 (68)	9 (32)	28

**Modified Sarode et al effective assessment guide was used[14]; Hemostatic inefficacy, moderate or poor/none rating

Table 5. Patient Outcomes.

Outcomes	**n (%)**
Thromboembolic event within 30 days from 4F-PCC use	
Yes[#]	4 (8.3)
No	39 (81.3)
Inadequate information	5 (10.4)
Length of Hospital Stay, day, median	5
Mortality at 30 days, n (%) (n = 44)	7 (15.9)
Discharge Destination, n (%)	
Home without HHC or hospice	18 (38)
Home with HHC or hospice	8 (16.7)
SNF/Rehab/Specialty Hospital	15 (31.3)
Deceased in Hospital	7 (14.6)
Anticoagulation restarted post hospitalization, n (%)	
Yes	28 (58.3)
No	20 (41.2)

Abbreviations: HHC, home health care; SNF, skilled nursing facility
[#] Pulmonary embolism, superficial thrombus in right upper extremity, ischemic stroke, midbrain infarct

Table 6. Patient Information for Thromboembolic Events.

Patient	AC	Bleeding Site	Thromboembolic event	AC Restart Day post 4F-PCC
Patient 1	apixaban	rectal sheath hematoma	midbrain infarct	day 10
Patient 2	rivaroxaban	epidural hematoma	superficial thrombus in RUE	day 14
Patient 3	apixaban	GI bleed	acute ischemic stroke	never restarted
Patient 4	rivaroxaban	subdural hemorrhage	acute pulmonary emboli	day 24

Abbreviations: AC, anticoagulation, RUE, right upper extremity, GI, gastrointestinal

by Smith et al and Sheik-Taha concluded 80.6% and 72.4% of their patients achieved hemostatic efficacy (Table 7). The dose of 4F-PCC used in Smith et al and Sheik-Taha is similar to the dose in our study, 50 units/kg with the maximum dose of 5000 units.[9,10] Our analysis also assessed the hemostatic efficacy in intracranial and non-intracranial subgroups. Twenty

Table 7. Efficacy and Safety Comparison Among PCC Studies on Management of fXa Inhibitor-Related Bleeds.

Study reference/ Outcomes	Majeed et al[5] (n = 84)	Schulman et al[6] (n = 66)	Sheikh-Taha[9] (n = 29)	ANNEXA-4 [15,16] (Efficacy n = 254; Safety n = 352)	Smith et al[10] (n = 31)	This study (n = 48)
Efficacy assessment using Sarode et al.[14] for ICH						
Excellent or good, n (%)	Not done	25 (76)	Not done	204 (81.9)	25 (80.6)	33 (68)
Effectiveness assessment using ISTH[17] criteria for ICH						
Effective	43 (73)	25 (69)	21 (72.4)	Not done	Not done	Not done
Safety assessment within 30 days of PCC administration						
Mortality	27 (32)	9 (13.9)	6 (20.7)	49 (13.9)	5 (16.1)	7 (15)
Thromboembolic events	3 (3.6)	5 (7.6)	1 (3.4)	34 (9.7)	0	4 (8.3)

Abbreviations: ICH, intracranial hemorrhage; PCC, prothrombin complex concentrate; ISTH, International Society on Thrombosis and Hemostasis

patients suffered an intracranial bleed, and hemostasis was achieved in 12 patients (86%) who did not receive any surgical intervention (Table 4).

Following treatment with 4F-PCC, 4 patients in this study had developed thromboembolic events within 30 days. Unfortunately, anticoagulation was not restarted in patient 3 who developed acute ischemic stroke while it was restarted in the others within 30 days of 4F-PCC administration (Table 6). The thromboembolic rate is under 10%, which is resembling the rate in most studies listed in Table 6. Seven patients expired within 30 days of 4F-PCC administration; 4 of them suffered ICH bleed.

In 2018, andexanet alfa was approved by the FDA for the reversal of the anticoagulation effects of rivaroxaban and apixaban in instances of life-threatening or uncontrolled bleeding. Currently, there are 3 finalized and published trials utilizing andexanet alfa in humans for anticoagulation reversal. The results of the ANNEXA-4 study confirm the efficacy and safety results of the ANNEXA-R/A studies for reversal of anticoagulation laboratory values in healthy volunteers receiving andexanet alfa.[15,16] In the ANNEXA-4 study, 81.9% of patients had excellent or good hemostasis in the efficacy population, and 80% of ICH patients achieved excellent or good efficacy. Investigators in ANNEXA-4 detected 10% thromboembolic events and 14% of patients expired within 30 days of the treatment. Being the only approved reversal agent, andexanet alfa has been mentioned in several guidelines for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding.[18-20] Although ANNEXA-4 showed a reduction in anti-Xa activity and good hemostatic efficacy, there was no significant relationship between them. In addition, due to the paucity of clinical experience and high cost, it is not widely used in clinical practice yet. Data from future prospective and randomized studies are warranted.[21-24]

In comparison to our analysis, ANNEXA-4 shows a higher percentage of excellent or good efficacy. However, ANNEXA-4 was conducted at multi-centers in North America and Europe with a larger sample size, and the inclusion and exclusion criteria are different.

Limitations

This study has several limitations. It is a small sample size, retrospective analysis at a single health system without a comparator group, which can affect the external validity of the study. Secondly, we were not able to follow patients after hospital discharge, which can explain the low rate of thromboembolic events and mortality rate. Since this is a chart review study, human errors are inevitable. Furthermore, we did not have the ability to measure anti-factor Xa to accurately measure the coagulation status prior to 4F-PCC administration. On the other hand, this study shows similar efficacy and safety results of 4F-PCC (Table 7) in managing fXa inhibitor-related bleeds with the utilization of Sarode et. al. assessment tool.

Conclusions

This analysis demonstrates 4F-PCC can be effective in managing apixaban- or rivaroxaban-related bleedings with a small rate of thromboembolic events. Efficacy was achieved in over half of the patient population in this cohort who received 4F-PCC for factor Xa inhibitor-related bleeding events. However, this is a small retrospective cohort and more studies are warranted to prove the efficacy and safety of 4F-PCC.

Declaration of Conflicting Interests

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