American Journal of Emergency Medicine 37 (2019) 1907–1911

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Four-factor prothrombin complex concentrate for the reversal of factor Xa inhibitors for traumatic intracranial hemorrhage ☆

Daniel Dybdahl, PharmD [a,*], Grant Walliser, PharmD [a], M. Chance Spalding, DO, PhD [b], Michelle Pershing, PhD [c], Michelle Kincaid, MD [b]

[a] Department of Pharmacy, OhioHealth Grant Medical Center, 111 South Grant Avenue, Columbus, OH 43215, United States of America
[b] Department of Trauma, OhioHealth Grant Medical Center, 111 South Grant Avenue, Columbus, OH 43215, United States of America
[c] Department of Research, OhioHealth Research & Innovation Institute, 340 East Town Street, Suite 7-100, Columbus, OH 43215, United States of America

ARTICLE INFO

Article history:
Received 25 September 2018
Received in revised form 30 November 2018
Accepted 8 January 2019

Keywords:
Factor Xa inhibitor
Four-factor prothrombin complex concentrate
Intracranial hemorrhage
Trauma

ABSTRACT

Objective: The objective of this study was to determine the effectiveness and safety of four-factor prothrombin complex concentrate (4F-PCC) for the reversal of factor Xa inhibitors in patients with traumatic intracranial hemorrhage (ICH).
Methods: This was a retrospective cohort study of patients taking factor Xa inhibitors with traumatic ICH between March 1, 2015 and August 31, 2017 at two trauma centers. The primary outcome was in-hospital mortality in patients who received 4F-PCC (4F-PCC group) compared to those who did not (no reversal group). Secondary outcomes included functional recovery, hospital and intensive care unit (ICU) length of stay (LOS), and thromboembolic complications.
Results: There were 62 patients included in the study. Injury Severity Score (ISS) was significantly higher in the 4F-PCC group (17.6 vs. 12.1, p = 0.019). The 4F-PCC group had a significantly higher mortality (22.9% vs. 3.7%, p = 0.034) and longer ICU LOS (2.5 vs. 1.4 days, p = 0.0024). The no reversal group had a significantly higher incidence of ischemic stroke/transient ischemic attack (TIA) (0% vs. 14.8%, p = 0.019). After controlling for ISS, there was no significant difference in mortality (p = 0.20), ICU LOS (p = 0.64), or ischemic stroke/TIA (p = 0.94). There was no difference in hospital LOS, discharge disposition, final Activity Measure for Post Acute Care daily activity score, VTE, or MI.
Conclusion: Patients with a higher ISS received 4F-PCC preferentially, which led to an apparent mortality benefit the no reversal group. After adjusting for baseline differences between groups, there was no difference in mortality, functional recovery, hospital and ICU LOS, or thromboembolic complications.

1. Introduction

Oral anticoagulants are commonly used for the management of patients with atrial fibrillation, cardiac valve replacement, and venous thromboembolism (VTE). The primary complication associated with anticoagulants is bleeding. As a result of this potentially devastating adverse effect, reversal agents were developed. Idarucizumab is indicated for the reversal of the direct thrombin inhibitor dabigatran for emergent surgery and life-threatening or uncontrolled bleeding [1]. Warfarin can be reversed with vitamin K and four-factor prothrombin complex concentrate (4F-PCC) in the setting of acute major bleeding or an emergent surgery [2]. 4F-PCC replenishes the vitamin K-dependent proteins, factors II, VII, IX, X and proteins C and S.

Recently, the first reversal agent for the factor Xa inhibitors rivaroxaban and apixaban, andexanet alfa, was approved by the U.S. Food and Drug Administration (FDA) [3]. Prior to the approval of andexanet alfa, 4F-PCC has been used off-label for the reversal of factor Xa inhibitors in patients with life-threatening hemorrhage. 4F-PCC continues to be utilized for the reversal of factor Xa inhibitors due to the lack of product availability, high cost, and thromboembolic complications associated with andexanet alfa, in addition to guideline support for 4F-PCC [4,5].

The off-label use of 4F-PCC for the reversal of factor Xa inhibitors is based on animal and pharmacodynamics studies in healthy

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This work was presented as a poster at the ASHP Midyear Clinical Meeting on December 6, 2017 and as a brief lecture at the Great Lakes Pharmacy Resident Conference on April 26, 2018 and the OhioHealth Research Symposium on May 23, 2018.
* Corresponding author.
E-mail addresses: Daniel.Dybdahl@ohiohealth.com (D. Dybdahl), Grant.Walliser@ohiohealth.com (G. Walliser), Chance.Spalding@ohiohealth.com (M. Chance Spalding), Michelle.Pershing@ohiohealth.com (M. Pershing), Michelle.Kincaid@ohiohealth.com (M. Kincaid).

https://doi.org/10.1016/j.ajem.2019.01.008
0735-6757/

volunteers [6-14]. Additionally, three small retrospective studies assessed the outcomes associated with 4F-PCC for the reversal of direct oral anticoagulants (DOACs), which include factor Xa inhibitors and dabigatran [15-17]. Although the literature supporting the use of 4F-PCC for the reversal of factor Xa inhibitors is sparse, it is often utilized in the setting of severe intracranial hemorrhage (ICH) when the expected benefit of treatment outweighs the risk of thromboembolic events. The American College of Cardiology (ACC) recently published an expert consensus decision pathway on the management of bleeding in patients on oral anticoagulants. In patients taking a factor Xa inhibitor with a critical site or life threatening bleed, ACC recommends administering 4F-PCC 50 units/kg [5].

It is unknown if any study has specifically assessed the use of 4F-PCC for the reversal of factor Xa inhibitors in patients with traumatic ICH. Additionally, no study has compared safety and effectiveness outcomes in patients who did and did not receive 4F-PCC for the reversal of factor Xa inhibitors. The objective of this study was to evaluate the effectiveness and safety of 4F-PCC for the reversal of factor Xa inhibitors in patients with traumatic ICH. We hypothesized that 4F-PCC would improve clinical outcomes compared to no reversal.

2. Methods

2.1. Study design and population

This was a retrospective cohort study of patients who presented with traumatic ICH at two tertiary care teaching hospitals (with associated Level I and Level II Trauma Centers), between March 1, 2015 and August 31, 2017. This study was approved by the OhioHealth Institutional Review Board. Potential study subjects were identified via the institutional trauma database and the electronic medical record (EMR) by querying trauma patients with an ICH diagnosis and a factor Xa inhibitor (rivaroxaban, apixaban, or edoxaban) listed on the EMR as a medication prior to admission. Patients were included if the ICH was confirmed by head computed tomography (CT). ICH was defined as an epidural hematoma, a subdural hematoma, a subarachnoid hemorrhage, or an intracerebral hemorrhage.

Trauma surgeons and neurosurgeons utilized an institutional prescribing guideline to determine when to administer 4F-PCC for the reversal of factor Xa inhibitors in patients with a traumatic ICH based on international normalized ratio (INR). If the INR was at least 1.5, the guideline recommended administering 4F-PCC 50 units/kg, with a maximum dose of 5000 units. If the INR was 1.4 or less, the guideline did not recommend administering 4F-PCC. However, the prescribing guideline allowed providers to use their clinical judgement to administer 4F-PCC outside of the guideline recommendations.

2.2. Study protocol

Demographic and clinical variables were collected retrospectively by a single reviewer from the institutional trauma database via a SAS-based query or from the EMR via manual chart review using a standardized, electronic data collection tool. Data collected included demographics (age, gender, and actual body weight), medical history (prior to admission anticoagulant, indication for anticoagulation, prior to admission antiplatelet use, and history of VTE, stroke/transient ischemic attack [TIA], thrombophilia, and myocardial infarction [MI]), hospital information (date of admission, date of injury, mechanism of injury, site of injury, INR, initial Glasgow Coma Score [GCS], Injury Severity Score [ISS], admit location, hospital and intensive care unit [ICU] length of stay, neurosurgical interventions, disposition, and final Activity Measure for Post Acute Care [AM-PAC] daily activity score), anticoagulant reversal (4F-PCC administration and other reversal agent/blood product administration [e.g., activated charcoal, platelets, fresh frozen plasma, factor VIIa]), and thromboembolic events (VTE, stroke/TIA, and MI).

2.3. Outcomes

Patients were stratified into two groups for analysis: those who received 4F-PCC for factor Xa inhibitor reversal and those who did not receive 4F-PCC for factor Xa inhibitor reversal. The primary outcome was in-hospital mortality.

Secondary effectiveness outcomes included functional recovery, hospital length of stay, and ICU length of stay. Functional recovery was measured by assessing a patient's discharge disposition and AM-PAC daily activity score prior to discharge (Table 1). The AM-PAC daily activity score is a tool used by physical therapists and occupational therapists in the acute care setting to assess the extent of a patient's functional impairment and determine the appropriate discharge disposition [18].

Secondary safety outcomes included in-hospital VTE (defined as a diagnosis of deep venous thrombosis [DVT] or pulmonary embolism [PE]), stroke or TIA, and MI. Subgroups were defined a priori and subgroup analyses were performed to assess mortality based on age, gender, site of injury, antiplatelet use, and neurosurgical intervention.

2.4. Statistical analysis

Demographic and clinical characteristics were described using mean and standard deviation for continuous variables and frequencies and percentages for binary or categorical variables.

Means were compared between two independent groups using two-sample *t*-tests or nonparametric Wilcoxon tests. Analysis of covariance models were used to compare continuous outcomes between groups while controlling for ISS. Percentages were directly compared between two groups using chi-square tests. Logistic regression modeling was used to compare percentages while controlling for ISS. Differences were considered statistically significant for $p < 0.05$. Statistical analysis was conducted using SAS V7.13 (Cary, NC).

3. Results

3.1. Patient characteristics

Baseline characteristics of the 62 patients (4F-PCC: 35; no reversal: 27) included in the study are presented in Table 2. The majority of patients in the study were female (64.5%) with a mean age of 79.1 years, mean GCS of 13.6, and mean ISS of 15.2. Patients who received 4F-PCC had a significantly higher baseline ISS (4F-PCC: 17.6 ± 8.89; no reversal: 12.1 ± 6.4; $p = 0.019$). There were

Table 1
Activity Measure for Post Acute Care (AM-PAC) daily activity score [18].

How much help from another person does the patient currently need...	Total	A lot	A little	None
Putting on and taking off lower body clothing?	1	2	3	4
Bathing (including washing, rinsing, drying)?	1	2	3	4
Toileting (using toilet, bedpan or urinal)?	1	2	3	4
Putting on and taking off upper body clothing?	1	2	3	4
Taking care of personal grooming (such as brushing teeth)?	1	2	3	4
Eating meals?	1	2	3	4

Table 2
Baseline characteristics.

Baseline characteristics	4F-PCC (n = 35)	No reversal (n = 27)	p-Value
Age, mean (SD)	78.9 (8.86)	79.4 (11.52)	0.84
Female, n (%)	22 (62.9)	18 (66.7)	0.76
Initial GCS, mean (SD)	13.1 (3.83)	14.3 (1.59)	0.27
ISS, mean (SD)	17.6 (8.89)	12.1 (6.4)	0.019
Antiplatelet use, n (%)	18 (51.4)	9 (33.3)	0.15
Anticoagulant			0.80
Apixaban, n (%)	17 (48.6)	14 (51.9)	
Rivaroxaban, n (%)	18 (51.4)	13 (48.2)	
Anticoagulation indication			0.20
Atrial fibrillation, n (%)	30 (85.7)	18 (66.7)	
VTE, n (%)	4 (11.4)	7 (25.9)	
Atrial fibrillation and VTE, n (%)	1 (2.9)	2 (7.4)	
Site of injury			
Epidural hematoma, n (%)	1 (2.9)	3 (11.1)	0.19
Subdural hematoma, n (%)	26 (74.3)	15 (55.6)	0.12
Subarachnoid hemorrhage, n (%)	14 (40.0)	10 (37.0)	0.81
Intracerebral hemorrhage, n (%)	12 (34.3)	7 (25.9)	0.48
Multiple, n (%)	14 (40.0)	7 (25.9)	0.25
Mechanism of injury			0.49
Fall, n (%)	33 (94.3)	25 (92.6)	
MVC, n (%)	2 (5.7)	1 (3.7)	
Assault, n (%)	0 (0)	1 (3.7)	

4F-PCC: four-factor prothrombin complex concentrate; GCS: Glasgow Coma Score; ISS: Injury Severity Score; MVC: motor vehicle crash; SD: standard deviation; VTE: venous thromboembolism.

no other significant differences in baseline characteristics between patients that did and did not receive 4F-PCC for factor Xa inhibitor reversal.

3.2. Outcomes

The outcomes of the study are listed in Table 3. The 4F-PCC group had a significantly higher mortality rate than the no reversal group (4F-PCC: 22.9%; no reversal: 3.7%; p = 0.034). Prescribers adhered to the anticoagulation reversal guideline in 62.3% of patients included in the study. Among the guideline compliant patients (n = 38), the 4F-PCC group had a significantly higher mortality than the no reversal group (4F-PCC: 29%; no reversal: 5%; p = 0.038).

Subgroup analyses were conducted to explore whether the differences in mortality may be attributed to patient factors including age, gender, neurosurgical intervention, site of injury, or antiplatelet use. There was no significant difference in mortality between the 4F-PCC group and no reversal group by neurosurgical intervention, gender, antiplatelet use, or site of injury (Table 4). There was a significantly higher mortality in the 4F-PCC group among patients 65–79 years old (4F-PCC: 31%; no reversal: 0%; p = 0.036).

Discharge disposition was not significantly different between the two groups (p = 0.70) after excluding in-hospital deaths (Fig. 1). Among the patients with an AM-PAC daily activity score documented prior to hospital discharge (n = 36), there was no significant difference between the two groups (4F-PCC: 17.1 ± 3.27; no reversal: 16.2 ± 4.48; p = 0.46). The mean AM-PAC daily activity score correlated with a 50.11% and 53.32% functional impairment at hospital discharge in the 4F-PCC group and no reversal group, respectively (Fig. 2). The 4F-PCC group had a significantly longer ICU length of stay (2.5 days ± 3.19) than the no reversal group (1.4 days ± 3.77) (p = 0.0024). There was no difference in hospital length of stay between the two groups (4F-PCC: 6.4 days ± 5.58; no reversal: 5.2 days ± 5.61; p = 0.40).

The no reversal group had a significantly higher incidence of ischemic stroke or TIA than the 4F-PCC group (4F-PCC: 0%; no reversal: 14.8%; p = 0.019). There was no difference in the incidence of VTE (p = 0.38) or MI between the two groups. After controlling for ISS, there was no significant difference in mortality (p = 0.20), ICU length of stay (p = 0.64), or ischemic stroke or TIA (p = 0.94).

Table 3
Clinical outcomes for all patients.

Outcome	4F-PCC (n = 35)	No reversal (n = 27)	p-Value
Mortality, n (%)	8 (22.9)	1 (3.7)	0.034*
ICU length of stay (days), mean (SD)	2.5 (3.19)	1.4 (3.77)	0.0024†
Hospital length of stay (days), mean (SD)	6.4 (5.58)	5.2 (5.61)	0.40
Ischemic stroke/TIA, n (%)	0 (0)	4 (14.8)	0.019‡
VTE, n (%)	1 (2.9)	0 (0)	0.38
MI, n (%)	0 (0)	0 (0)	N/A

4F-PCC: four-factor prothrombin complex concentrate; ICU: intensive care unit; MI: myocardial infarction; SD: standard deviation; TIA: transient ischemic attack; VTE: venous thromboembolism.

* Difference was not statistically significant after controlling for ISS in a logistic regression model (p = 0.20).

† Difference was not statistically significant after controlling for ISS in an analysis of covariance model (p = 0.64).

‡ Difference was not statistically significant after controlling for ISS in a logistic regression model (p = 0.94).

Table 4
Comparing mortality by subgroup.

Subgroup	4F-PCC mortality	No reversal mortality	p-Value
Neurosurgical intervention			
Yes, n (%)	2 (40)	0 (0)	N/A
No, n (%)	6 (20)	1 (4)	0.06
Gender			
Male, n (%)	5 (38)	1 (11)	0.16
Female, n (%)	3 (14)	0 (0)	0.10
Antiplatelet use			
Yes, n (%)	6 (33)	1 (11)	0.21
No, n (%)	2 (12)	0 (0)	0.13
Age, years			
<65, n (%)	0 (0)	0 (0)	N/A
65–79, n (%)	4 (31)	0 (0)	0.036
≥80, n (%)	4 (21)	1 (8)	0.31
Site of injury			
Epidural hematoma[a], n (%)	0 (0)	0 (0)	N/A
Subdural hematoma[a], n (%)	7 (27)	1 (7)	0.11
Subarachnoid hemorrhage[a], n (%)	4 (29)	1 (10)	0.27
Intracerebral hemorrhage[a], n (%)	6 (50)	1 (14)	0.12
Multiple, n (%)	6 (43)	1 (14)	0.19

4F-PCC: four-factor prothrombin complex concentrate.

[a] Either with or without any other site.

4. Discussion

There are limited reversal agents available for factor Xa inhibitors, which poses a clinical challenge when treating patients that require emergent anticoagulant reversal. ACC published a consensus statement recommending 4F-PCC for patients with critical site or life-threatening bleed; however, the literature supporting the consensus is sparse and there are no published studies comparing outcomes between patients that receive 4F-PCC versus no reversal [5]. As such, the safety and effectiveness of 4F-PCC in patients with traumatic ICH is unknown. In this study, safety and effectiveness were compared between traumatic ICH patients that did and did

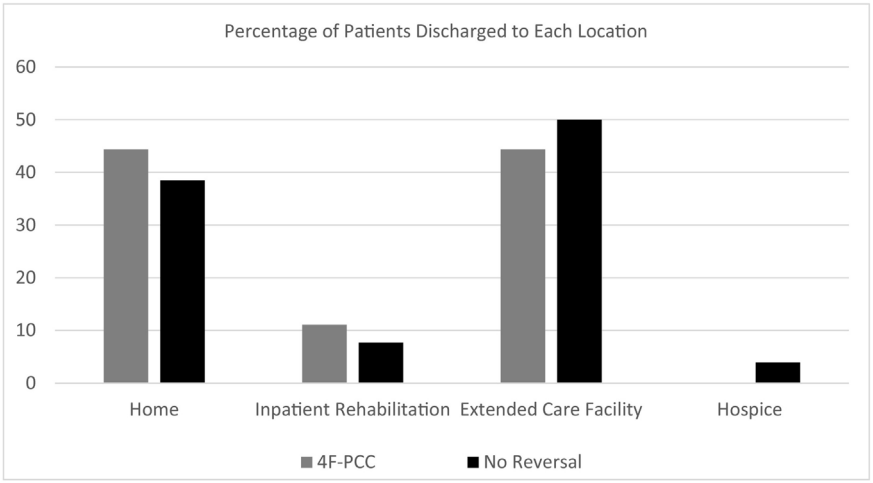

Fig. 1. Discharge disposition was not significantly different between the two groups (p = 0.70).

not receive 4F-PCC for the emergent reversal of factor Xa inhibitors.

Senger et al. performed a retrospective review of 17 patients with ICH on dabigatran or rivaroxaban who received 4F-PCC. Eight patients had a traumatic brain injury (TBI) and nine patients had a spontaneous ICH. Nine patients had a devastating outcome, including severe neurologic deficits, comatose status, or death [15]. Hedges et al. performed a relatively larger retrospective review of 193 patients who received either 4F-PCC or three-factor PCC for the reversal of rivaroxaban, dabigatran, apixaban, warfarin, or unknown anticoagulant. The majority of patients were taking warfarin prior to admission, while only 18 patients were taking a DOAC. The efficacy results were not specific for the type of anticoagulant, limiting the external validity of the study [16]. Finally, Grandhi et al. performed a retrospective, observational study of 18 patients who received 4F-PCC for the reversal of rivaroxaban or apixaban for ICH. Eight patients had a TBI and ten patients had a spontaneous ICH. One patient demonstrated hemorrhage progression on head CT, one patient had a VTE, six patients died in the hospital, and six patients had favorable outcomes at 90 days [17].

Recently, Engelbart et al. performed a case series of 42 patients assessing activated PCC (aPCC) for the reversal of DOAC-associated hemorrhage and prevention of hemorrhagic complications in patients requiring urgent procedures [19]. The ACC recommends aPCC as an alternative to 4F-PCC in patients taking a factor Xa inhibitor with a critical site or life threatening bleed [5]. The in-hospital mortality rate was 29% in all patients and 33% among patients with ICH. Thromboembolic complications occurred in 10% of patients [19].

The mortality rate in this study was 14.5% overall and 22.9% in the 4F-PCC group. This is consistent with previous studies that demonstrated mortality ranging from 17.6% to 33% in patients with ICH who received 4F-PCC for the reversal of DOACs [15,17]. Mortality was significantly higher in the 4F-PCC group compared to the no reversal group. This finding was contrary to our expectation that 4F-PCC would improve outcomes and is explained by the significant difference in ISS at baseline. After controlling for ISS, there

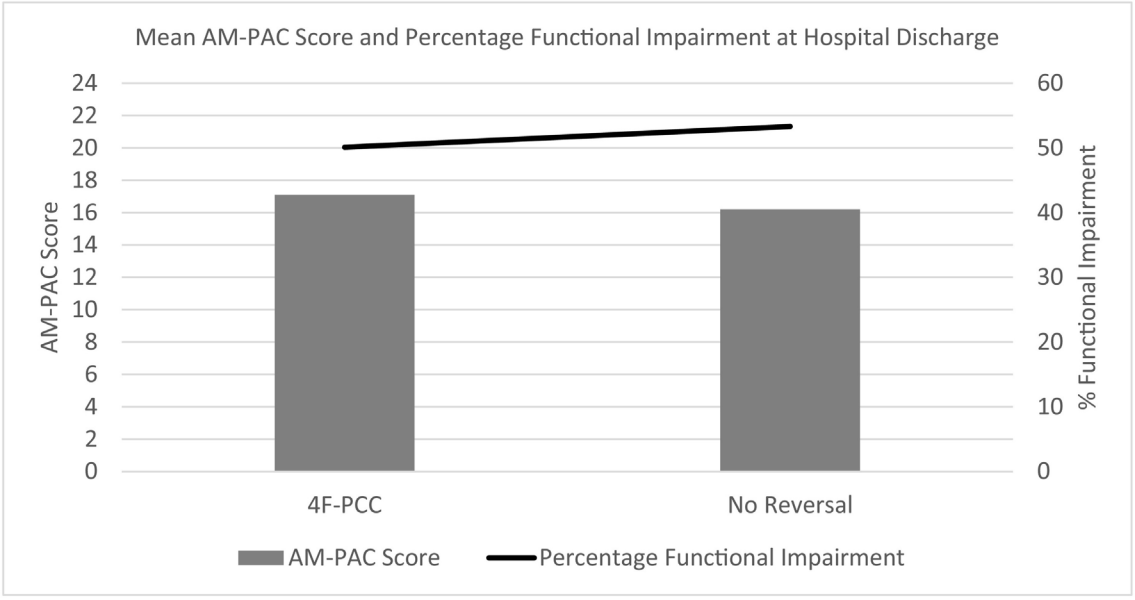

Fig. 2. Final AM-PAC daily activity score and corresponding percentage functional impairment among the 36 patients with a documented score was not significantly different between the groups (p = 0.46).

was no significant difference in mortality between the groups. The primary safety concern with the use of 4F-PCC is thrombosis. In this study, only one patient in the 4F-PCC group had a VTE and no patients in the 4F-PCC group had an ischemic stroke, TIA, or MI, demonstrating a low risk of thrombosis with 4F-PCC. It is possible that more thromboembolic events would have occurred in the 4F-PCC if the mortality rate were lower, as some of the patients died early in their hospital stay and did not have time to develop a thrombotic complication.

The anticoagulation reversal guideline utilized in this study was developed shortly after the approval of the factor Xa inhibitors. At that time, the factor Xa inhibitors were believed to have a more consistent effect on the INR. In reality, factor Xa inhibitors have demonstrated a variable impact on the INR, so the INR has been abandoned as a marker of anticoagulation in patients on factor Xa inhibitors. Since the completion of this study, the INR requirement has been removed from the anticoagulation reversal guideline for factor Xa inhibitors. While it is now recognized that the INR is not a reliable marker for factor Xa inhibitors, the anticoagulation reversal guideline created two cohorts. Prescribers followed the anticoagulation reversal guideline recommendations in 62.3% of patients. The remaining patients were treated according to the physician's clinical judgement. In an effort to remove the potential bias associated with the physician's judgement, we compared mortality between the two groups among the guideline compliant patients. Interestingly, the mortality remained significantly higher in the 4F-PCC group. This is likely a result of physicians ordering 4F-PCC for patients with more severe injuries as described previously.

Andexanet alfa was recently approved by the FDA for the reversal of rivaroxaban and apixaban in the setting of life-threatening or uncontrolled bleeding [3]. While this is the first FDA approved reversal agent for factor Xa inhibitors, 4F-PCC will likely continue to be used off-label for this indication. Given the recent approval of andexanet alfa, the product will not be immediately available to all hospitals. Pharmacy and Therapeutics committees will assess the cost effectiveness, efficacy, and safety of the agent prior to adding andexanet alfa to formulary. Furthermore, thrombotic events occurred in 18% of patients who received andexanet alfa, which could deter prescribers from routine use, especially given the low incidence of thrombosis associated with 4F-PCC in this study [4]. Additionally, guidelines continue to support the use of 4F-PCC for the reversal of factor Xa inhibitors [5]. This study provides effectiveness and safety data to compare 4F-PCC to andexanet alfa in the future.

There were several limitations to the study. First, this was a retrospective study. As a result, we were not able to control for all potential sources of bias. This was evidenced by the significantly higher ISS in the 4F-PCC group as it appears that physicians preferentially prescribed 4F-PCC to patients with more severe injuries. Second, although this was the largest study we identified, this study had a relatively small sample size. Power was not calculated, as the results of this study were intended to be hypothesis generating. Third, radiographic data was not reviewed to assess hemorrhage progression in this study. Lastly, the AM-PAC daily activity score was not documented on all patients. Additionally, it would have been ideal to compare change in AM-PAC daily activity score between the two groups, as it is likely that some patients had functional impairment at baseline. However, baseline AM-PAC daily activity score was not routinely documented.

5. Conclusion

In conclusion, the results of this study are hypothesis generating, but the clinical effectiveness of 4F-PCC remains unknown for factor Xa inhibitors. Prescribers tend to use 4F-PCC in patients on factor Xa inhibitors with higher ISS, which favors the no reversal group and limits the ability to detect a benefit in mortality and functional recovery. Finally, thromboembolic events are uncommon with 4F-PCC. This study sets the framework for a large multicenter, prospective, randomized controlled trial.

Conflict of interest

Michelle Kincaid, MD is a member of the Speakers Bureau for CSL Behring. All other authors have no relevant conflicts of interest to disclose.

References

[1] Praxbind® (idarucizumab) injection prescribing information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; October 2015.
[2] Kcentra® [prothrombin complex concentrate (human)] prescribing information. Kankakee, IL: CSL Behring; September 2014.
[3] ANDEXXA® [coagulation factor Xa (recombinant), inactivated-zhzo] prescribing information. South San Francisco, CA: Portola Pharmaceuticals; 2018.
[4] Connolly SJ, Milling TJ, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;375:1131–41.
[5] Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017;70(24):3042–67.
[6] Zhou W, Zorn M, Nawroth P, Bütehorn U, Perzborn E, Heitmeier S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with rivaroxaban. Stroke 2013;44:771–8.
[7] Perzborn E, Gruber A, Tinel H, Marzec UM, Buetehorn U, Buchmueller A, et al. Reversal of rivaroxaban anticoagulation by haemostatic agents in rats and primates. Thromb Haemost 2013;110:162–72.
[8] Herzog E, Kaspereit F, Krege W, Mueller-Cohrs J, Doerr B, Niebl P, et al. Correlation of coagulation markers and 4F-PCC-mediated reversal of rivaroxaban in a rabbit model of acute bleeding. Thromb Res 2015;135 (3):554–60.
[9] Herzog E, Kaspereit F, Krege W, Mueller-Cohrs J, Doerr B, Niebl P, et al. Four-factor prothrombin complex concentrate reverses apixaban-associated bleeding in a rabbit model of acute hemorrhage. J Thromb Haemost 2015;13 (12):2220–6.
[10] Herzog E, Kaspereit F, Krege W, Doerr B, Mueller-Cohrs Pragst I, et al. Effective reversal of edoxaban-associated bleeding with four-factor prothrombin complex concentrate in a rabbit model of acute hemorrhage. Anesthesiology 2015;122(2):387–98.
[11] Levi M, Moore KT, Castillejos CF, Kubitza D, Berkowitz SD, Goldhaber SZ, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. J Thromb Haemost 2014;12:1428–36.
[12] Perlstein I, Wang Z, Song Y, Wang J, Bedford B, Chang M, et al. Reversal of apixaban anticoagulation by 4-factor prothrombin complex concentrates in healthy subjects. Blood 2014;124(21):345.
[13] Kraft WK, Thomson L, Oppong Y, Bachman B, Chervoneva I, Nagalla S. 4-Factor prothrombin concentrate reverses apixaban inhibition of thrombin generation in healthy volunteers [abstract]. Clin Pharmacol Ther 2016;99(Supp1):S42.
[14] Zahir H, Brown KS, Vandell AG, Desai M, Maa JF, Dishy V, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. Circulation 2015;131(1):82–90.
[15] Senger S, Keiner D, Hendrix P, Oertel J. New target-specific oral anticoagulants and intracranial bleeding: management and outcome in a single-center case series. World Neurosurg 2016;88:132–9.
[16] Hedges A, Coons JC, Saul M, Smith RE. Clinical effectiveness and safety outcomes associated with prothrombin complex concentrates. J Thromb Thrombolysis 2015:1–5.
[17] Grandhi R, Newman WC, Zhang X, Harrison G, Moran C, Okonkwo DO, et al. Administration of 4-factor prothrombin complex concentrate as an antidote for intracranial bleeding in patients taking direct factor Xa inhibitors. World Neurosurg 2015;84(6):1956–61.
[18] Jette DU, Stilphen M, Ranganathan VK, Passek SD, Frost FS, Jette AM. Validity of the AM-PAC "6-clicks" inpatient daily activity and basic mobility short forms. Phys Ther 2014;94:379–91.
[19] Engelbart JM, Zepeski A, Galet C, Policeni B, Skeete DA, Faine BA. Safety and effectiveness of Factor Eight Inhibitor Bypassing Activity for direct oral anticoagulant-related hemorrhage reversal. Am J Emerg Med 2018. https://doi.org/10.1016/j.ajem.2018.05.023.