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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Activated Prothrombin Complex Concentrate for Reversal of the Anticoagulant Effect of Apixaban and Rivaroxaban in Patients with Major Bleeding

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Abstract

Background The use of activated prothrombin complex concentrate (aPCC) to treat direct oral anticoagulant (DOAC)-associated bleeding is off-label and clinical experience is limited.

Objectives We aimed to assess the efficacy and safety of aPCC in reversing the anticoagulant effect of apixaban and rivaroxaban in patients presenting with major bleeding.

Methods A retrospective cohort study of adult non-randomized patients was conducted at a tertiary referral medical center in the United States (US) to investigate the use of aPCC for the reversal of the anticoagulant effect of apixaban and rivaroxaban in patients presenting with major bleeding. The primary outcome was achieving clinical hemostasis according to prespecified criteria. Safety outcomes included the occurrence of thrombotic events during hospitalization.

Results A total of 217 patients were included in the study. Intracranial hemorrhage (ICH) was the most common site of bleeding ($n = 100$, 46.1%), followed by gastrointestinal bleed ($n = 87$, 40.1%). Clinical hemostasis was achieved in 170 patients (78.3%), and the risk of not achieving hemostasis with ICH-related bleeding was significantly higher than that of non-ICH-related bleeding (2.5, 95% confidence interval [CI] 1.44–4.34; $p < 0.001$). Eight patients not achieving hemostasis died during hospitalization, all of whom were suffering from ICH, and mortality associated with non-ICH-related bleeding was significantly lower compared with ICH-related bleeding (0.91, 95% CI 0.86–0.97; $p < 0.001$). Thromboembolic events during hospitalization occurred in one patient (0.5%).

Conclusions The use of aPCC for the management of apixaban- or rivaroxaban-related major bleeding is effective in most cases and is associated with a low risk of thromboembolism.

Key Points

Activated prothrombin complex concentrates (aPCCs) can achieve hemostasis in the majority of patients with major bleeding who are taking rivaroxaban or apixaban.

Thrombotic events caused by aPCC during hospitalization in this setting are rare.

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1 Introduction

Anticoagulation therapy is necessary for the prevention and treatment of thromboembolic diseases. Direct oral anticoagulants (DOACs) have emerged as leading therapeutic alternatives to vitamin K antagonists (VKAs), especially for stroke prevention in patients with non-valvular atrial fibrillation (AF), as they provide healthcare providers and patients with more effective, safe, and convenient treatment options in thromboembolic settings [1, 2].

Bleeding is among the primary concerns related to oral anticoagulation. Oral anticoagulant-related bleeding can vary in severity, with the most severe, life-threatening bleeding necessitating prompt reversal of the pharmacotherapeutic agent. While andexanet alfa is a specific reversal agent/antidote for the DOACs apixaban and rivaroxaban, its high cost may limit its utilization. Non-specific prohemostatic agents such as prothrombin complex concentrates (PCCs; including 3- or 4-factor PCC and activated PCC [aPCC])

are frequently used for DOAC reversal. aPCC contains the clotting factors (II, IX, X, and VIIa [factor VII in the activated form]) purified from human plasma. FEIBA, the only aPCC available in the United States (US), is approved by the US FDA to control spontaneous bleeding episodes and to prevent bleeding with surgical interventions in hemophilia A and hemophilia B patients [3]. Andexanet alfa and PCCs have not been compared with each other directly in a randomized trial and there is insufficient evidence about risks and benefits to strongly favor one agent over the other. Furthermore, current guidelines recommend off-label use of PCC for DOAC reversal when specific agents are unavailable [4].

As no high-quality data exist to support the use of aPCC in DOAC-associated serious/life-threatening bleeding, and as descriptions of its utilization have been limited to case reports, small series, and preclinical research settings, this study was conducted to assess the efficacy and safety of aPCC in reversing the anticoagulant effect of apixaban and rivaroxaban in patients presenting with major, life-threatening bleeding.

2 Methods

This single-center, retrospective analysis evaluated patients from August 2019 through July 2022 at a tertiary care teaching center—Huntsville Hospital, Huntsville, AL, USA. Patients were included if they were at least 18 years of age, taking rivaroxaban or apixaban therapy prior to admission, and received FEIBA for the management of major bleeding. As per hospital protocol, FEIBA was administered intravenously at a dose of 25 units/kg, maximum of 2500 units, or 50 units/kg, maximum of 5000 units, for patients with intracranial hemorrhage (ICH), and 30 units/kg, maximum of 3000 units, for other life-threatening bleeding. The definition of major bleeding was according to the International Society of Thrombosis and Hemostasis (ISTH) definition for major bleeding in non-surgical patients: (1) fatal bleeding; (2) symptomatic bleeding in a critical area or organ; and (3) bleeding causing a fall in hemoglobin level ≥ 2 g/dL or leading to transfusion of two or more units of whole blood or red cells [5]. The efficacy of aPCC in achieving effective hemostasis was assessed according to ISTH Scientific and Standardization Subcommittee criteria [6]. We excluded patients who took their last dose of apixaban or rivaroxaban more than 24 h prior to admission, to ensure that the bleeding was related to the anticoagulants. In addition, patients who received aPCC for anticoagulation reversal prior to an emergency surgery or invasive procedure were excluded. The primary safety endpoint was the occurrence of arterial or venous thromboembolism after treatment with aPCC during hospitalization.

Data were collected from patients' electronic health records and included demographic information, physicians' orders and notes, laboratory values, and any other relevant details. Data were analyzed with descriptive statistics and frequency distributions. Statistical analyses were conducted with SPSS version 28.0.1.1 (14) [IBM Corporation, Armonk, NY, USA]. Nominal variables were evaluated using cross-tabulation and Pearson Chi-square, and continuous data were evaluated using the independent samples *t*-test. Correlation of quantitative variables with outcomes related to hemostasis and mortality were evaluated with logistic regression. Ethical approval for this study was obtained from Huntsville Hospital's Institutional Review Committee in July 2022.

3 Results

During the study period, 561 patients received FEIBA, of whom 217 met the inclusion criteria and were included in the study. Demographics of the study population are presented in Table 1.

The mean age of the study population was 76.2 years and 52.1% were males. The most common indication for anticoagulation use was AF ($n=173$, 79.7%) followed by deep venous thrombosis/pulmonary embolism (DVT/PE; $n=38$, 17.5%). The most common site of bleeding was intracranial hemorrhage (ICH; $n=100$, 46.1%), followed by gastrointestinal (GI) bleed ($n=87$, 40.1%) and visceral bleed ($n=15$, 6.9%).

After the administration of aPCC, clinical hemostasis was achieved in 170 patients (78.3%), while 47 patients (21.7%) did not achieve clinical hemostasis (Table 2). When analyzed according to the bleeding site, the hemostatic effectiveness of aPCC was assessed as effective in 68 of the 100 patients with ICH (68%), and 102 of the 117 patients with an extracranial bleeding location (87.2%). The risk of not achieving hemostasis for patients with ICH-related bleeding was significantly higher than that of non-ICH-related bleeding (2.5, 95% confidence interval [CI] 1.44–4.34; $p<0.001$). Eight patients not achieving hemostasis died during hospitalization, all of whom were suffering from ICH. Table 3 describes the characteristics of patients who did not achieve hemostasis and died during hospital stay. Furthermore, one patient with ICH achieved clinical hemostasis but died due to aspiration pneumonia complicated by septic shock. Mortality associated with non-ICH-related bleeding was significantly lower compared with ICH-related bleeding (0.91, 95% CI 0.86–0.97; $p<0.001$).

Thromboembolic events during hospitalization occurred in one patient (0.5%) who developed DVT on day 2 after receiving aPPC. This patient, who did not receive other

Table 1 Demographics of the study population ($N = 217$)

	Value
Characteristic	
Age, years	76.2 ± 11.8
Male sex	113 (52.1)
Weight, kg	84.8 (158–37)
Indication for anticoagulation	
AF	173 (79.7)
DVT/PE	38 (17.5)
Hip replacement	3 (1.4)
Other [CAD, HIT, restricted mobility]	3 (1.4)
DOAC used	
Apixaban	165 (76)
Rivaroxaban	52 (24)
Laboratory results at presentation	
INR	1.58 (0.9–13.6)
aPTT	34.53 (22.2–103)
Creatinine clearance, mL/min	46.1 (7.3–140.5)
Bleeding location	
ICH	100 (46.1)
GI	87 (40.1)
Visceral	15 (6.9)
Genitourinary	6 (2.8)
Musculoskeletal	5 (2.3)
Nose	2 (0.9)
Other [epidural, intraocular]	2 (0.9)
Length of hospital stay, days	8 (1–30)

Data are expressed as mean ± standard deviation, mean (range) or *n* (%)

AF atrial fibrillation, *aPTT* activated partial thromboplastin time, *CAD* coronary artery disease, *DOAC* direct oral anticoagulant, *DVT* deep venous thrombosis, *GI* gastrointestinal, *HIT* heparin-induced thrombocytopenia, *ICH* intracranial hemorrhage, *INR* international normalized ratio, *PE* pulmonary embolism

blood products, was a 67-year-old female patient who was receiving anticoagulation therapy for the treatment of DVT.

In addition to aPCC, patients received additional management to control bleeding: 80 patients received packed red blood cells, 12 patients received fresh frozen plasma, and 6 patients received platelet transfusion due to thrombocytopenia or concurrent antiplatelet therapy. Patients with GI bleeds also received proton pump inhibitors.

In total, 162 (74.6%) patients were receiving concomitant home medications that potentially interact with apixaban and rivaroxaban and can increase the risk of bleeding (Table 4). Antiplatelet therapy, including aspirin, clopidogrel, and ticagrelor, selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors (SSRIs/SNRIs), and diltiazem are the most commonly implicated medications.

4 Discussion

DOAC-associated bleeding is a concerning problem and there is considerable controversy surrounding available reversal strategies. The use of PCCs to treat DOAC-associated bleeding is off-label and most of the data come from 4-factor PCC and not aPCC. Data on patient outcomes are emerging from registries and other observational studies, as well as in case reports from clinical practice.

We report the results of one of the largest cohorts of patients to receive aPCC for the management of major bleeding related to apixaban or rivaroxaban. We found that 78.3% of patients achieved hemostasis after receiving aPCC. Among the small number of studies where aPCC was used for apixaban and rivaroxaban reversal, effective hemostasis ranged between 69 and 89% [7, 8]. This variability in achieving hemostatic efficacy among studies could be explained by the small sample size, trial design, and differences in implementation of criteria for effective

Table 2 Bleeding management outcome

Bleeding location	Clinical hemostasis		Clinical hemostasis by DOAC used	
	Yes	No	Apixaban (yes/no)	Rivaroxaban (yes/no)
ICH	68 (68)	32 (32)	55/22	13/10
GI	75 (86.2)	12 (13.8)	58/10	17/2
Visceral	12 (80)	3 (20)	10/2	2/1
Genitourinary	6 (100)	0 (0)	2/0	4/0
Musculoskeletal	5 (100)	0 (0)	3/0	2/0
Nose	2 (100)	0 (0)	1/0	1/0
Epidural	1 (100)	0 (0)	1/0	
Intraocular	1 (100)	0 (0)	1/0	
Total	170 (78.3)	47 (21.7)	131 (79.4)/34 (20.6)	39 (75)/13 (25)

Data are expressed as *n* (%) or *n*

DOAC direct oral anticoagulant, *GI* gastrointestinal, *ICH* intracranial hemorrhage

Table 3 Details of deaths during hospitalization

Patient	Age	Sex	DOAC used	Indication	CHA_2DS_2-VASc score	CrCl (mL/min)	Bleeding site	Use of antiplatelets	Day of death after aPCC
1	70	M	Rivaroxaban	AF	4	79	ICH	No	3
2	80	M	Apixaban	AF	5	27	ICH	Yes	7
3	83	F	Apixaban	AF	6	44	ICH	No	2
4	79	M	Rivaroxaban	AF	5	46	ICH	No	6
5	80	M	Apixaban	AF	4	57	ICH	Yes	6
6	43	M	Apixaban	PE	–	89	ICH	No	4
7	75	M	Apixaban	AF	5	25	ICH	No	5
8	62	M	Rivaroxaban	AF	2	94	ICH	Yes	5

AF atrial fibrillation, *aPCC* activated prothrombin complex concentrates, *CrCl* creatinine clearance, *DOAC* direct oral anticoagulant, *F* female, *ICH* intracranial hemorrhage, *M* male, *PE* pulmonary embolism

Table 4 Significant drug interactions with apixaban and rivaroxaban

Interacting drugs	*n*	Risk rating/severity
Aspirin	95	D (major)
SSRI/SNRI	63	C (moderate)
Diltiazem	30	C (moderate)
NSAID	18	D (major)
Clopidogrel	16	D (major)
Fish oil (omega-3 fatty acids)	10	C (moderate)
Dronedarone	6	D (major) with rivaroxaban C (moderate) with apixaban
Ticagrelor	1	D (major)
Fluconazole	1	C (moderate)

Risk rating D: Consider therapy modification

Risk rating C: Monitor therapy

NSAID nonsteroidal anti-inflammatory drug, *SNRI* serotonin and norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

hemostasis [9]. On the other hand, in studies involving 4-factor PCC, effective hemostasis ranged between 69 and 85% [10–14]. Furthermore, in the ANNEXA-4 trial, 82% of patients achieved excellent or good hemostatic efficacy 12 h after receiving andexanet alfa [15]. The hemostatic efficacy of 78.3% observed in this study compares well with the hemostatic efficacy observed in previous studies. Furthermore, this study adds some evidence that aPCCs could be an alternative to 4-factor PCC and andexanet alfa in the setting where urgent reversal of the anticoagulant effects of apixaban and rivaroxaban is needed.

In this study, 68% patients with ICH achieved clinical hemostasis, which is similar to the UPRATE study where 72% of their ICH subpopulation demonstrated effective hemostasis using 4-factor PCC [11]. On the other hand, 87% of patients with ICH who received aPCC achieved hemostasis when using different criteria for effective hemostasis, as reported by Castillo et al. [16].

In this study, patients with ICH-related bleeding had a higher risk of mortality and not achieving hemostasis as compared with those with non-ICH-related bleeding. While aPCCs may reverse the effects of apixaban and rivaroxaban, it cannot reverse the damage incurred by the bleeding, and ineffective clinical hemostasis may not necessarily reflect the lack of effect of the drug. ICH represents the severest form of stroke and is generally associated with poor outcomes and high in-hospital mortality rates approaching 50% [17].

PCCs contain high levels of coagulation factors and may have the potential to cause thrombosis at doses used to treat bleeding. In this study, thrombotic event rates were relatively low (1 in 217 patients [0.5%]), and in previous studies, the rate of thrombotic events in patients receiving aPCC for the reversal of the anticoagulant effect of apixaban and rivaroxaban ranged between 0 and 8.6% [7, 8, 16, 18]. This notable degree of thrombotic events variation among studies could be explained by the small study sample sizes. In addition, the risk of thrombosis may be increased based on the underlying condition for which anticoagulation was prescribed and/or the prothrombotic effects of some therapies.

Doses evaluated in this study have been previously reported [7]. Doses of 25–50 units/kg for ICH-related bleeding result in similar efficacy and safety outcomes when compared with 4-factor PCC and andexanet alfa [7, 8, 16, 18]. Doses of 30 units/kg for non-ICH-related bleeding continue to demonstrate adequate rates of hemostasis, resulting in hemostasis for 87.2% of patients evaluated in this study. No thrombotic complications were noted for any patient in this group. These findings help to support the potential efficacy,

Table 5 Cost-saving associated with the use of aPCC compared with andexanet alfa (ANDEXXA)

Regimen	Total cost per patient ($)
Low-dose ANDEXXA: 400 mg intravenous bolus, then 4 mg/min for 120 min = 880 mg ($12.19/mg)	10,722.80
High-dose ANDEXXA: 800 mg intravenous bolus, then 8 mg/min for 120 min = 1760 mg ($12.19/mg)	21,454.40
DOAC reversal, ICH FEIBA: 50 units/kg (5000 unit maximum dose) = 5000 units ($1.85/unit)	5550
DOAC reversal, ICH FEIBA: 50 units/kg (5000 unit maximum dose) = 5000 units ($1.85/unit)	9250

aPCC activated prothrombin complex concentrate, *DOAC* direct oral anticoagulant, *ICH* intracranial hemorrhage

safety, and pharmacoeconomic benefits related to this lower dosing strategy and need further evaluation to support this recommendation.

While current guidelines for oral factor Xa inhibitors reversal recommend aPCC use after PCC failure due to increased thrombotic complications [19], this study, as well as recent cases, show that aPCC can achieve adequate hemostasis with no increased risk of thrombotic events [20]. Furthermore, there is little or no high-quality evidence to estimate the risk of thrombosis associated with the use of different PCC products, and it is not possible to quantify the degree to which aPCC increases thrombosis risk compared with an unactivated PCC. A meta-analysis of the use of 4-factor PCC for the reversal of factor Xa inhibitors found a thromboembolism rate of 4% [21].

Three in four patients received home medications that interact with apixaban and rivaroxaban and could have contributed to their coagulopathies. Antiplatelets and nonsteroidal anti-inflammatory drugs (NSAIDs) have an interaction risk rating of D (consider therapy modification); interaction severity: major. In addition, diltiazem, SSRIs/SNRIs, and fish oil (omega-3 fatty acids) have an interaction risk rating of C (monitor therapy); interaction severity: moderate [22]. Healthcare professionals should consider the potential risks associated with concomitant use of other drugs that can interact with DOACs that may increase the risk of bleeding.

The use of aPCC for reversal of oral anticoagulation in severe bleeding may be associated with significant pharmacoeconomic benefit. Using dosing strategies from this study, we found significant cost savings of US dollars (US$) 200–US$3150 per dose for ICH-related bleeding and US$2560 per dose for non-ICH-related bleeding when compared with 4-factor PCC. This translates to total cost savings of US$20,000 for ICH-related bleeding and US$299,520 for non-ICH-related bleeding during the study period. When comparing costs with andexanet alfa, aPCC administration can lead to cost savings ranging from US$1472–US$15,904 per patient depending on the dose and bleeding location (Table 5).

This study is not without limitations. We conducted a single-center, retrospective chart review without a comparator group. In addition, the dose of aPCCs used at our hospital was based on data from limited studies and may not be the optimal dosing regimen. While acknowledging these limitations, this study contributes new and important information involving the use of aPCCs for the reversal of the effects of apixaban and rivaroxaban.

5 Conclusion

This study suggests that aPCC is effective in achieving clinical hemostasis in patients presenting with major bleeding while taking apixaban or rivaroxaban, and patients presenting with ICH have a higher risk of mortality and not achieving hemostasis. In addition, the use of aPCC is associated with a relatively low in-hospital thrombotic event rate and could have significant financial advantages. Hospitals with limited resources may consider aPCC instead of andexanet alfa or 4-factor PCC given the observed clinical outcomes supporting its use.

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Declarations

Conflict of interest Marwan Sheikh-Taha, Holly L. Clark, and R. Monroe Crawley declare they have no conflicts of interest.

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Ethical approval Ethical approval for this study was obtained from Huntsville Hospital's Institutional Review Committee.

Consent to participate Not applicable.

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Code availability Not applicable.

Author contributions Conception, design of the work, data collection, interpretation of data, drafting the work, and substantively revising it: MST. Statistical analysis, interpretation of data, drafting the work, and revising it: RMC and HLC.

Data availability Data will be made available on reasonable request

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