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Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate

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Abstract
There is limited clinical experience with the use of coagulation concentrates to reverse the effect of direct oral anticoagulants. We assess the achievement of effective clinical hemostasis with the use of 4-factor prothrombin complex concentrate (PCC) in patients on apixaban or rivaroxaban presenting with major bleeding. A retrospective chart review was conducted at a tertiary referral medical center in the USA. We assess the achievement of clinical hemostasis using 4-factor PCC in patients on chronic apixaban or rivaroxaban therapy presenting with major bleeding. Clinical hemostasis was assessed by the International Society of Thrombosis and Hemostasis Scientific and Standardization Subcommittee criteria. A total of 29 patients are included in the study. The most common site of bleeding was intracranial hemorrhage (ICH) (72.4%), followed by gastrointestinal bleed (13.8%). Clinical hemostasis was achieved in 21 (72.4%) patients. Patients who did not achieve clinical hemostasis (27.6%) suffered from ICH, and all of them died during hospitalization except for two patients who were discharged with neurologic deterioration. One patient developed multiple brain infarctions after receiving 4-factor PCC. Sixteen patients (55.2%) were receiving concomitant medications that interact with apixaban and rivaroxaban and increase the risk of bleeding. Four-factor PCC appears to be effective in achieving clinical hemostasis in patients on apixaban or rivaroxaban presenting with major bleeding. It may be an alternative to patients who need anticoagulation reversal if the specific antidote, andexanet alfa, is not available.

Keywords Apixaban · Rivaroxaban · DOACs · Prothrombin complex concentrate · Major bleeding

Introduction

Apixaban and rivaroxaban are direct oral anticoagulants (DOACs) that inhibit factor Xa. They are used to prevent stroke in patients with atrial fibrillation (AF), and to treat and prevent deep venous thrombosis (DVT) and pulmonary embolism (PE). Clinical trials have shown that when compared to vitamin K antagonists, DOACs are at least as effective in venous thromboembolism recurrence prevention, stroke prevention in AF, or thromboprophylaxis after knee and hip surgery with a lower risk of intracranial bleeding [1, 2]. Because of ease of prescribing and lack of monitoring, DOACs account for most new anticoagulant prescriptions [3]. As with other antithrombotic therapies, DOACs have a low, but significant risk for bleeding complications.

Calibrated anti-Xa activity assays can be used to assess coagulation activity of apixaban and rivaroxaban. However, very few clinicians have access to these tests in a timely fashion. On the other hand, routine coagulation testing cannot reveal the anticoagulation status of patients receiving the drugs. While prolonged coagulation times can help in determining residual anticoagulant effect, normal coagulation testing cannot eliminate the possibility of clinically important concentrations of the drugs [4, 5].

Andexanet alfa is a specific antidote that has been recently approved for the reversal of activated factor Xa inhibitors, but it is not in widespread clinical use due to lack of clinical experience, limited availability due to limited manufacturing capacity, and very high cost.

The article is part of the Topical Collection on Direct Oral Anticoagulants (DOACs).

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Prothrombin complex concentrates (PCCs) are concentrates of coagulation factors derived from pooled human plasma. Four-factor PCCs contain coagulation factors II, VII, IX, and X in inactive forms. The use of PCCs to treat factor Xa inhibitor-associated major bleeding is off-label, and the evidence to support their use in this setting is scanty and limited to observational studies, studies in healthy volunteers, and animal models. The aim of our study is to assess the achievement of effective clinical hemostasis using 4-factor PCC in patients on chronic apixaban or rivaroxaban therapy presenting with major bleeding.

Methods

A retrospective chart review was conducted in a tertiary care teaching center, Huntsville Hospital, Alabama, USA, from June 1, 2016 to June 30, 2018. Patients presenting with major bleeding while receiving apixaban or rivaroxaban, and who received the 4-factor PCC available in the United States, Kcentra (CSL Behring, King of Prussia, PA), are included in the study. Major bleeding was defined according to International Society of Thrombosis and Hemostasis (ISTH) definition for major bleeding in nonsurgical patients [6]. The efficacy of 4-factor PCC in achieving effective hemostasis was assessed according to ISTH Scientific and Standardization Subcommittee criteria [7]. We excluded patients who needed reversal of anticoagulation for an emergency surgery or procedure (a surgery or procedure that should be performed without delay otherwise there is a risk of permanent disability or death).

Data were collected from the medical records of patients, including demographic information, physicians' orders and notes, laboratory values, and any other relevant details. Thromboembolic complications included myocardial infarction, stroke, transient ischemic attack, DVT, and PE. Estimation of creatinine clearance (CrCl) was calculated using the Cockroft–Gault formula. Patients were followed until discharge or death. Ethical approval for this study was obtained from Huntsville Hospital's Institutional Review Committee. Data were analyzed with descriptive statistics and frequency distributions.

Results

A total of 29 patients met the inclusion criteria, and were included in the study. Their mean ± SD age was 73.8 ± 12.0 years (76% were older adults), and 16 (55.2%) of them were females. The most common indication for DOAC use was AF ($n = 23$, 79.3%), followed by DVT/PE ($n = 5$, 17.2%). The most common site of bleeding was intracerebral hemorrhage (ICH) ($n = 21$, 72.4%), followed by gastrointestinal (GI) bleed ($n = 4$, 13.8%). The mean ± S.D. creatinine clearance (CrCl) at admission was 48.6 ± 21.5 ml/min. Table 1 describes patient demographic and clinical characteristics. The mean activated partial thromboplastin time (aPTT) and international normalized ratio (INR) before treatment with 4-factor PCC was 36.1 (range 27–63.4) and 1.5 (range 1–2.9), respectively. Baseline aPTT and INR were elevated in 20.7% and 37.9% of patients, respectively. All patients received the last DOAC dose on the same day of

Table 1 Patient characteristics

	n	%
Age (years)		
Mean ± SD	73.8 ± 12.0	
Sex		
Male	13	44.8
Female	16	55.2
Indication for DOAC		
AF	23	79.3
DVT/PE	5	17.2
Hip replacement	1	3.4
DOAC used		
Apixaban	13	44.8
Rivaroxaban	16	55.2
Bleeding site		
ICH	21	72.4
GI	4	13.8
Nose	2	6.9
Genitourinary	1	3.4
Musculoskeletal	1	3.4
Baseline coagulation tests [Mean (range)]		
INR (all patients)	1.5 (1.0–2.9)	
aPTT (all patients)	36.1 (27–63.4)	
INR (apixaban patients)	1.4 (1–2.4)	
aPTT (apixaban patients)	35.7 (26.3–62.8)	
INR (rivaroxaban patients)	1.7 (1.1–2.9)	
aPTT (rivaroxaban patients)	37.4 (26.7–63.4)	
Length of hospital stay (days)		
Mean (range)	5.9 (2–15)	
Number of comorbidities	5.2	
Mean ± SD	1.4	
Concomitant drugs used		
Mean ± SD	9.2 ± 4.0	
CrCl (ml/min)		
> 60	7	24.1
30–59	15	51.7
< 30	7	24.1
Mean ± SD	48.6 ± 21.5	

AF atrial fibrillation, *DVT* deep venous thrombosis, *PE* pulmonary embolism, *ICH* intracerebral hemorrhage, *GI* gastrointestinal, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *CrCl* creatinine clearance

Table 2 Bleeding management outcome

Bleeding location	Clinical hemostasis		Clinical hemostasis by DOAC used			
			Apixaban		Rivaroxaban	
	Yes *n* (%)	No *n* (%)	Yes *n*	No *n*	Yes *n*	No *n*
ICH	13 (61.1)	8 (38.9)	5	6	8	2
GI	4 (100)	0 (0)	2	0	2	0
Nose	2 (100)	0 (0)			2	0
Genitourinary	1 (100)	0 (0)			1	0
Musculoskeletal	1 (100)	0 (0)			1	0
Total	21 (72.4)	8 (27.6)	7	6	14	2

ICH intracerebral hemorrhage, *GI* gastrointestinal

Table 3 Details of deaths during hospitalization

Patient	Age	Sex	DOAC used, daily dose	Indication for DOAC	CrCl (ml/min)	Bleeding site	Other agents given	Reason behind death	Day of death after PCC
1	83	M	Apixaban, 5 mg×2	AF	43	ICH		ICH/brain infarction	6
2	72	F	Apixaban, 5 mg×2	AF	51	ICH		ICH	14
3	91	F	Apixaban, 2. 5 mg×2	AF	23	ICH		ICH	5
4	76	F	Apixaban, 2. 5 mg×2	AF	48	ICH		ICH	4
5	64	F	Rivaroxaban, 15 mg×1	AF	25	ICH, traumatic		ICH	2
6	79	M	Rivaroxaban, 20 mg×1	AF	59	ICH, traumatic	FFP	ICH	2

CrCl creatinine clearance, *AF* atrial fibrillation, *ICH* intracerebral hemorrhage, *FFP* fresh frozen plasma

hospital admission, except for one patient who presented with severe epistaxis where the last dose was received 2 days prior to admission. All patients had normal platelet counts and liver enzyme levels.

Patients received a single time dose the 4-factor PCC Kcentra at a dose of 50 units/kg intravenously based on actual body weight (maximum of 5000 units). Clinical hemostasis was achieved in 21 (72.4%) patients. Patients who did not achieve clinical hemostasis (8, 27.6%) suffered from ICH, and all of them died during hospitalization except for two patients who were discharged with neurologic deterioration. Table 2 describes bleeding management outcomes and Table 3 describes the characteristics of patients who died during hospital stay.

An 83-year-old male suffering from ICH developed multiple brain infarctions, as confirmed by CT scan, after receiving 4-factor PCC and died 5 days after hospitalization. He was on apixaban 5 mg twice daily for AF and had a CrCl of 43 ml/min.

Other than 4-factor PCC, patients received additional management to control bleeding; six patients received packed red blood cells (pRBCs), one patient received fresh frozen plasma (FFP) before PCC administration, and two patients who were on the anti-platelet clopidogrel received platelet transfusions. In addition, patients with GI bleeds received proton pump inhibitors.

Table 4 Significant drug interactions with apixaban and rivaroxaban

Interacting drugs	*n*	Risk rating	Severity
Aspirin	7	D*	major
SSRI	6	C**	moderate
NSAIDs	5	D*	major
Prasugrel	1	D*	major
Clopidogrel	2	D*	major
Omega 3	1	C**	moderate

Two patients were on dual antiplatelet therapy

SSRI selective serotonin reuptake inhibitors, *NSAIDs* non-steroidal anti-inflammatory drugs

*Consider therapy modification

**Monitor therapy

Sixteen patients (55.2%) were receiving concomitant medications that interact with apixaban and rivaroxaban that can increase the risk of bleeding. Anti-platelets, non-steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs) were the most commonly implicated medications. Table 4 describes the

significant drug interactions with apixaban and rivaroxaban among participants.

Discussion

PCCs have been used to reverse the effect of DOACs even though their efficacy has not been firmly established in prospective randomized clinical trials. We assessed the achievement of hemostasis using 4-factor PCC in patients receiving apixaban or rivaroxaban who developed major bleeding.

In our study, 4-factor PCC achieved hemostasis in 72.4% of patients suffering from major bleeding, which is comparable to 69.1% as reported in a cohort study by Majeed et al. [8] that assesses the use of 4-factor PCCs in patients with apixaban- or rivaroxaban-associated major bleeding. Similarly, in the ANNEXA-4 study andexanet alfa achieves effective hemostasis in 79% of the patients [9]. One patient (3.4%) had a thromboembolic event in our study, which is also comparable to 2.4% as reported by Majeed et al., but lower than 18% in the ANNEXA-4 study [8, 9]. However, while in both studies patients were followed for up to 30 days after treatment, we could not follow patients after hospital discharge.

Eight patients (27.6%) failed to achieve hemostasis, and all of them suffered from ICH (six died during hospitalization and two suffered from neurologic deterioration upon hospital discharge). Mortality and morbidity after ICH remain high [10, 11]. Patient prognosis depends upon several factors, including the location of hemorrhage, size of hematoma, patient age, and comorbidities [12–14]. Four-factor PCC may reverse the effect of apixaban and rivaroxaban, but cannot reverse the damage due to bleeding. Therefore, the ineffective hemostatic outcome may not necessarily reflect the lack of effect of the agent.

In our study, nine patients received other supportive hemostatic measures, in addition to 4-factor PCC. Six patients received pRBCs due to low hemoglobin, one patient received FFP, but did not achieve hemostasis that necessitated adding 4-factor PCC, and two patients received platelets transfusions to reverse the effect of the antiplatelet clopidogrel.

Baseline aPTT and INR were elevated only in 20.7% and 37.9% of patients, respectively, supporting the reality that routine coagulation testing cannot reveal the anticoagulation status of patients on DOACs, and normal levels do not eliminate the possibility of clinically important concentrations of the drugs. Anti-Xa assays were not ordered in our study.

More than half of the patients received home medications which interact with apixaban and rivaroxaban that could have contributed to their coagulopathies and severe bleeding. Eight were on antiplatelet agents (aspirin, clopidogrel, and prasugrel), and five were on NSAIDs (interaction risk rating D (*consider therapy modification*); interaction severity: major). Furthermore, six were on SSRIs, agents with antiplatelet properties, and one was on omega 3 fatty acid supplement that can enhance the anticoagulant effect of dabigatran (interaction risk rating C (*monitor therapy*); interaction severity: moderate) [15]. Prescribers should consider the potential risks associated with concomitant use of other drugs that can interact with apixaban and rivaroxaban.

Our study has several limitations. This study was retrospective, with drawbacks entailed by such a design. In addition, we excluded patients who received PCC for emergency surgery or procedure, and we were not able to follow patients after hospital discharge. Our study included a small number of patients, and most of them suffered from ICH. Furthermore, the coagulation parameters assessed in the study were INR, and aPTT, and they are not as accurate as measuring an anti-factor Xa. The dose of 4-factor PCC used in our study is based on data from limited studies, may not be the optimal dosing regimen, and we did not have a control group in the study. Furthermore, thromboembolic complications were recorded by reviewing the medical records. On the other hand, we adopted the ISTH standardized definitions for effective hemostasis as they are considered uniform and practical definitions.

Conclusion

The use of 4-factor PCC appears to be effective in achieving clinical hemostasis in patients on apixaban or rivaroxaban with major bleeding. In view of the quite wide availability, the agent may be an alternative to patients with major bleeding if andexanet alfa is not available.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights We obtained ethical approval from hospital's Institutional Review Committee.

Informed consent This is a retrospective study. Informed consent is not needed/possible.

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