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CE - LETTER TO THE EDITOR

Non-activated prothrombin complex concentrates for major bleeding in patients on apixaban and rivaroxaban

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Dear Sir,

In a previous study published in the Journal, we reported the efficacy and safety of 4-factor prothrombin complex concentrate (4F-PCC) in achieving clinical hemostasis in 29 patients receiving the direct oral anticoagulants (DOACs) apixaban or rivaroxaban presenting with major bleeding necessitating the use of a reversal agent [1]. We hereby report the results of 12 additional patients who received the same hemostatic agent for the same indication from July 1, 2018 to June 30, 2019.

The 12 studied patients' mean ± SD age was 78.8 ± 14.5 years and seven (58.3%) of them were females. The most common indication for apixaban and rivaroxaban use was atrial fibrillation (AF) ($n = 9$, 75%), followed by deep venous thrombosis (DVT)/pulmonary embolism (PE) ($n = 2$, 16.7%), and peripheral arterial disease ($n = 1$, 8.3%). The most common site of bleeding was intracerebral hemorrhage (ICH) ($n = 10$, 83.3%) followed by gastrointestinal (GI) bleed ($n = 1$, 8.3%) and musculoskeletal bleed ($n = 1$, 8.3%). All patients received the last DOAC dose on the same day of hospital admission and had normal platelet counts and liver enzyme levels.

Patients received a single time dose the 4F-PCC Kcentra at a dose of 50 units/kg intravenously based on actual body weight (maximum of 5000 units). Clinical hemostasis, assessed according to International Society of Thrombosis and Hemostasis (ISTH) Scientific and Standardization Subcommittee criteria, was achieved in eight (66.7%) patients. Patients who did not achieve clinical hemostasis (4, 33.3%) suffered from ICH and three of them died during hospitalization except one who was discharged with neurologic deterioration. Table 1 describes bleeding management outcomes. In addition to the 4F-PCC, three patients received packed red blood cells and one patient with GI bleed received a proton pump inhibitor to control bleeding.

In our study, the achievement of clinical hemostasis, 66.7%, was comparable to 65% as reported by Schulman et al. [2], 69.1% as reported by Majeed et al. [3], and 72.4% as reported in our previous study [1]. On the other hand, hemostasis was achieved in 80.6% of patients as reported by Smith et al. [4]. Four patients (33.3%) failed to achieve hemostasis and all of them suffered from ICH (three died during hospitalization and one suffered from neurologic deterioration upon hospital discharge).

One patient (8.3%), a 78-year-old male suffering from ICH developed right leg DVT on day 8 after receiving 4F-PCC. He was on apixaban 5 mg twice daily for DVT/PE treatment. The occurrence of thromboembolism in our study is comparable to other studies, where between 2.1 and 8% of the patients had a thromboembolic event [1–5]. This patient carried a high risk of developing a thrombotic event due to his previous history of DVT/PE. Given the underlying prothrombotic conditions, necessitating the DOAC use and the fact that 4F-PCC contains high levels of coagulation factors, it is expected for patients receiving 4F-PCC to have high thrombotic risk. Clinicians should be highly vigilant of these complications.

In conclusion, the efficacy and safety outcomes of the current study were very similar to our previously reported one. Both studies add to the limited data available, suggesting that 4F-PCC can be effective in achieving clinical hemostasis in patients on apixaban or rivaroxaban who develop major bleeding, necessitating the administration of a reversal agent. In addition, several current clinical practice guidelines suggest that the administration of PCC should be considered in these patients.

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Table 1 Bleeding management outcome

Bleeding location	Clinical hemostasis		Clinical hemostasis by DOAC used			
	Yes *n* (%)	No *n* (%)	Apixaban		Rivaroxaban	
			Yes (*n*)	No (*n*)	Yes (*n*)	No (*n*)
ICH	6 (60)	4 (40)	2	3	4	1
GI	1 (100)	0 (0)	1	0		
Musculoskeletal	1 (100)	0 (0)			1	0
Total	8 (66.7)	4 (33.3)	3	3	5	1

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

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest related to the publication of this manuscript.

Statements of human and animal rights This article does not contain any studies with human participants or animals performed by any of the author.

Informed consent For this retrospective review, formal consent is not required.

References

1. Sheikh-Taha M (2019) Treatment of apixaban-and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate. Intern Emerg Med 14(2):265–269
2. Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L, Carrier M, Crowther MA, Ghosh I, Lazo-Langner A, Zondag M (2018) Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. Thromb Haemost 118(05):842–851
3. Majeed A, Ågren A, Holmström M, Bruzelius M, Chaireti R, Odeberg J, Hempel EL, Magnusson M, Frisk T, Schulman S (2017) Management of rivaroxaban-or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood 130(15):1706–1712
4. Smith MN, Deloney L, Carter C, Weant KA, Eriksson EA (2019) Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. J Thromb Thrombolysis 2:1–6
5. Tao J, Bukanova EN, Akhtar S (2018) Safety of 4-factor prothrombin complex concentrate (4F-PCC) for emergent reversal of factor Xa inhibitors. J Intensive Care 6(1):34