



Efficacy and Safety of Three-Factor Prothrombin Complex Concentrates for the Management of Oral Direct Factor Xa Inhibitor-Associated Major Bleeding

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Background

Andexanet alfa is the standard of care for reversing oral direct Factor Xa inhibitors. However, it is not available in certain countries. In such cases, three-factor prothrombin complex concentrate (3F-PCC) may serve as an alternative, although evidence supporting its use remains limited.

Aims

This study aimed to assess the efficacy and safety of 3F-PCC for the management of major bleeding associated with oral direct Factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), focusing on hemostatic efficacy, 45-day all-cause mortality, and thromboembolic events.

Methods

We conducted a retrospective, descriptive study at a single tertiary center. Consecutive patients who received 3F-PCC for the reversal of Factor Xa inhibitor-associated major bleeding between 2018 and 2022 were enrolled. The primary outcome was hemostatic efficacy, assessed using an effectiveness assessment guide modified from Sarode et al.¹ Secondary outcomes included the incidence of thromboembolic events and 45-day all-cause mortality. Patient characteristics and outcomes were reported as mean ($\pm$ SD), median ($\pm$ IQR), or number (percentage).

Result

Forty-seven patients met the inclusion criteria, with a median age of 79 years (IQR: 70–87). Thirty patients (63.83%) were male. The median length of hospital stay was 6 days (IQR: 3–12). The proportions of patients with excellent, good, and poor/none hemostatic effectiveness were 48.94%, 38.30%, and 12.77%, respectively. The rates of excellent or good efficacy for each bleeding site were as follows: 82.6% for gastrointestinal bleeding, 93% for intracranial bleeding, and 83.3% for intramuscular bleeding. Twenty-eight patients (59.57%) received red blood cell transfusions. Thromboembolic events occurred in 8.51% of patients within 45 days, and the 45-day all-cause mortality rate was 24.53%.

Baseline Characteristics of the Study Population

Characteristics	Rivaroxaban (n=15)	Apixaban (n=19)	Edoxaban (n=13)	All (n=47)
Age—year (IQR)	82 (73–87)	77 (72–87)	77 (66–84)	79 (70–87)
Male sex—no. (%)	12 (80.00)	11 (57.89)	7 (53.85)	30 (63.83)
Body weight—kg	69.00 $\pm$ 15.21	59.58 $\pm$ 13.91	67.15 $\pm$ 12.03	64.68 $\pm$ 14.23
Body mass index—kg/m ²	25.02 $\pm$ 4.80	22.99 $\pm$ 4.23	25.40 $\pm$ 3.63	24.31 $\pm$ 4.32
Creatinine clearance—no. (%)				
>90	1 (6.67)	2(10.53)	1 (7.69)	4 (8.51)
60-89	5 (33.33)	3 (15.79)	6 (46.15)	14 (29.79)
45-59	4 (26.67)	3 (15.79)	1 (7.69)	8(17.01)
30-44	4 (26.67)	3 (15.79)	3 (23.08)	10 (21.28)
15-29	0 (0.00)	4 (21.05)	2 (15.38)	6 (12.77)
<15	1 (6.67)	0 (0.00)	0 (0.00)	1 (2.13)
Hemodialysis	0 (0.00)	4 (21.05)	0 (0.00)	4 (8.51)
Indication for anticoagulant—no. (%)				
Atrial fibrillation	13 (86.67)	16 (84.21)	12 (92.31)	41 (87.23)
Venous thromboembolism	1 (6.67)	3 (15.79)	1 (7.69)	5 (10.64)
Other	1 (6.67)	0 (0.00)	0 (0.00)	1 (2.13)
Medical history—no. (%)				
Myocardial infarction	3 (20.00)	9 (47.37)	4 (30.77)	16 (34.04)
Stroke	3 (20.00)	10 (52.63)	3 (23.08)	16 (34.04)
Deep-vein thrombosis	1 (6.67)	3 (15.79)	0 (0.00)	4 (8.51)
Pulmonary embolism	0 (0.00)	2 (10.53)	2 (15.38)	4 (8.51)
Atrial fibrillation	14 (93.33)	16 (84.21)	11 (84.62)	41 (87.23)
Heart failure	4 (26.67)	6 (31.58)	3 (23.08)	13 (27.66)
Diabetes mellitus	5 (33.33)	6 (31.58)	4 (30.77)	15 (31.91)
CHA ₂ DS ₂ -VASc score (IQR)	4 (4-5)	6 (4-7)	4 (3-6)	4 (3-6)
Time from presentation until PCC—hour (IQR)	9 (5-34)	15 (8-48)	23 (10-34)	15 (8-34)
Time from the last dose—hour (IQR)	11 (9-19)	20 (14-25)	15 (14-28)	17 (11-25)

The symbol "±" which is used to indicate the standard deviation (SD).
The total of the percentages may not add up to 100 due to rounding.

Conclusion

For major bleeding associated with Factor Xa inhibitors, 3F-PCC demonstrated high rates of excellent or good hemostatic efficacy. Therefore, it may be a beneficial alternative where andexanet alfa is unavailable, although the risks of thromboembolism remain uncertain. Clinicians should carefully weigh the benefits and risks to ensure an acceptable rate of thrombotic events when treating individual patients.

Keywords: Direct oral anticoagulants, Factor Xa inhibitors, major bleeding, 3-factor prothrombin complex concentrate, hemostatic efficacy