Evaluation of 4-Factor Prothrombin Complex Concentrate (4F-PCC) for the reversal of bleeding associated with direct oral anticoagulant therapy

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Background

- Direct oral anticoagulant (DOAC) therapy does not utilize any specific testing to routinely monitor or determine the degree of anticoagulation
- Patients who experience bleeding on DOAC therapy must be evaluated to assess time of last dose, severity, location, and the presence of active bleeding
- 4F-PCC is a human product indicated only for the reversal of coagulation factor deficiency that is associated with Vitamin K antagonist therapy
- Literature currently supports the administration of 4F-PCC for use in patients who require reversal for life-threatening hemorrhage associated with non-vitamin K antagonist anticoagulation – an off-label use
- Patients who require reversal of bleeding while on DOAC therapy are treated with 4F-PCC at this community medical center
- With the recent development of andexanet alfa (Coagulation Factor Xa), the clinical necessity of a specific reversal agent is unclear.

Objectives

- Assess the impact of 4F-PCC on patient mortality
- Standardize the treatment and reversal of bleeding associated with DOAC therapy

Methodology

- Retrospective chart review in which medical records of all patients who received a dose of 4F-PCC between September 1, 2017 and August 31, 2019 were assessed for eligibility
- Data was collected for all patients age >18 years who received a dose of 4F-PCC
- Patients were divided into the following sub categories: Apixaban, Rivaroxaban, and Other DOACs
- Patient specific data collected at baseline included:
  - Demographic information (age, gender, weight)
  - Past medical history
  - Renal and hepatic function
  - Specific DOAC taken by the patient
  - Indication for anticoagulation
  - Dose of DOAC
  - Time of last DOAC dose
  - Hemoglobin and platelet levels
- Imaging and mortality data were also recorded. This information was assessed from the electronic health records.
- Medication administration records were used to determine the number of 4F-PCC doses charted, the number of units given to respective patients, and the administration of any adjunctive therapies
- Documentation in charts was used to determine if patients experienced a terminal bleed

Results

Figure 1: Outpatient anticoagulation

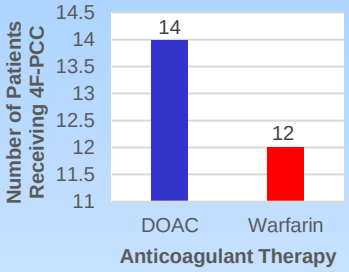

Table 2: 4F-PCC Dosing

Dose of 4F-PCC	Total (n=14)	Apixaban (n=8)	Rivaroxaban (n=6)
25 units/kg	2	1	1
26-49 units/kg	2	0	2
50 units/kg	10	7	3
> 50 units/kg	0	0	0

Table 1: Baseline Characteristics

Patient Characteristics	Total (n=14)	Apixaban (n=8)	Rivaroxaban (n=6)	Other DOAC (n=0)
Age – mean (y)	76.50	79.25	72.83	0 (0)
Male Gender, n (%)	8 (57.14)	4 (50)	4 (66.66)	0 (0)
Indication for DOAC, n (%)				
Atrial fibrillation	11 (78.57)	7 (87.50)	4 (66.66)	0 (0)
History of DVT*/PE*	2 (14.29)	1 (12.50)	1 (16.66)	0 (0)
Other	1 (7.14)	0 (0)	1 (16.66)	0 (0)
Hemoglobin, average		11.9	11.1	
Length of Stay in days – mean	6.5	7	5.83	0
Discharge Disposition, n (%)				
Died	5 (35.71)	4 (50)	1 (16.66)	0 (0)
Home	1 (7.14)	0 (0)	1 (16.66)	0 (0)
Home with Hospice	3 (21.43)	2 (25)	1 (16.66)	0 (0)
Rehabilitation facility	4 (28.57)	1 (12.50)	3 (50)	0 (0)
Transfer	1 (7.14)	1 (12.50)	0 (0)	0 (0)
DOAC continued at discharge, n (%)				
No	7 (50)	3 (37.50)	4 (66.66)	0 (0)
Yes	2 (14.29)	1 (12.50)	1 (16.66)	0 (0)
N/A (Death)	5 (35.71)	4 (50)	1 (16.66)	0 (0)

*DVT=Deep vein thrombosis; PE=Pulmonary embolism

Results (Cont.)

Table 3: Bleeding Characteristics

Bleeding Characteristics	Total (n=14)	Apixaban (n=8)	Rivaroxaban (n=6)
Indication for 4F-PCC, n(%)			
Intracranial	9 (64.29)	6 (75)	3 (37.50)
Gastrointestinal	1 (7.14)	0 (0)	1 (16.66)
Other	3 (21.43)	2 (25)	1 (16.66)
No bleeding	1 (7.14)	0 (0)	1 (16.66)
Received fresh frozen plasma (FFP), n (%)	4 (28.57)	2 (25)	2 (33.33)
Received packed red blood cells (pRBC), n (%)	2 (14.29)	2 (25)	0 (0)
Received phytonadione, n (%)	4 (28.57)	3 (37.50)	1 (16.66)
Received platelets, n (%)	4 (28.57)	2 (25)	2 (33.33)
Received tranexamic acid, n (%)	3 (21.43)	3 (37.50)	0 (0)

Discussion

- Five of fourteen patients included in this study died during the recorded admission, with an average age of 78 amongst these individuals. Based on cause of death reported, three out of these five deaths are attributable to the bleeding episode.
- Consistent with other studies, patients in this evaluation received adjunctive therapies such as FFP, pRBC, platelets, phytonadione, and tranexamic acid. Both phytonadione and tranexamic acid are generally not recommended for use in Factor Xa reversal. Overall the impact of adjunctive therapies cannot be determined.
- There was no evidence of thromboembolic events occurring within 14 days of 4F-PCC administration. Regardless of dose administered, patients do not appear to be at increased risk of complications due to 4F-PCC administration.
- Limitations include the retrospective, single-center, cohort study design. Reliability of data was limited to the accuracy of nursing and physician documentation.

Conclusion

- 4F-PCC, when dosed appropriately at 50 mg/kg, does not appear to present a notable safety risk when used in Factor Xa reversal.
- Patients who received suboptimal doses of 4F-PCC were found to have order comments suggesting a max and target dose based on INR. Further evaluation of these order parameters at this community hospital could potentially improve patient outcomes following 4F-PCC administration.
- It would be beneficial to make further comparisons to 4F-PCC use in patients on warfarin during this time period.

Disclosures

All authors have nothing to disclose.

References available upon request.