Evaluating Protocol Adherence During Anti-Inhibitor Coagulant Complex Administration for Reversal of Xa Inhibitors for Life-Threatening Bleeding

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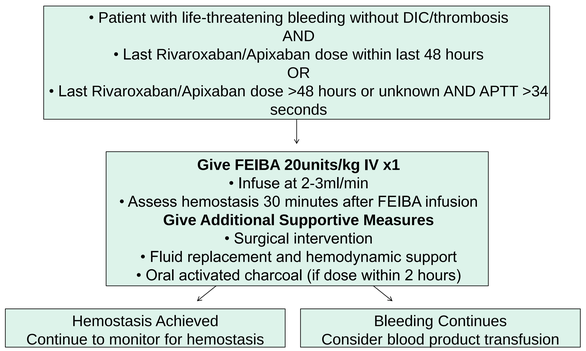
Introduction

Anti-inhibitor coagulant complex (FEIBA®) contains the coagulation factors II, VIIa, IX, and X. FEIBA® is FDA approved for controlling bleeding in patients with hemophilia. Rivaroxaban, apixaban, and edoxaban are Factor Xa (Fxa) inhibitors with no currently FDA approved reversal agent. Evidence from ex vivo studies by Marlu et al[1] and Levi et al[2] demonstrated that FEIBA® may work to reverse the anticoagulant effect induced by these agents, but these studies only utilized blood samples drawn from healthy volunteers exposed to rivaroxaban. FEIBA® also has been shown to improve coagulation assays, although this has not been proven in large, randomized controlled trials in patients with life-threatening bleeding. How FEIBA's effect on coagulation assays correlates to clinically significant reversal is unknown at this time as no randomized, controlled trials with FEIBA® in patients with life-threatening bleeding have been conducted. The purpose of our study is to examine the FEIBA® administration protocol at Allegheny General Hospital. Our protocol utilizes a 20units/kg dosing strategy adapted from the original Marlu study[1], with the dose of FEIBA® given rounded to the nearest vial size. Our institution's protocol for FEIBA administration for life-threatening bleeding in patients taking FXa inhibitors is as follows:



Methods

- This is a single-center retrospective cohort study in patients with life-threatening bleeding as a result of an event that occurred while the patient was taking an oral anticoagulant such as apixaban, rivaroxaban, edoxaban, or dabigatran
- Study period is from November 1, 2012 to August 31, 2015, at Allegheny General Hospital
- Institutional Review Board approved
- Medication administration was evaluated using the Sunrise Clinical Manager system and outcomes were evaluated by reviewing Sunrise Clinical Manager and the medical chart
- Patients were included if they were ≥ 18 years of age and received FEIBA for reversal of an oral FXa inhibitor or dabigatran

Objectives

Primary Endpoint

- Adherence to AGH protocol for FEIBA administration
  - Non-adherent: Patient received FEIBA and had one or more of the following:
    - Patient did not have physician documentation a life-threatening bleed
    - Patient was not taking an oral FXa inhibitor
    - Patient did not have the last dose of the FXa inhibitor within 48 hours or time is unknown and the aPTT was < 34 seconds
  - Adherent: Patient received FEIBA per the AGH protocol and met all applicable criteria for adherence

Secondary Endpoints (all patients on FXa inhibitor included regardless of adherence to protocol)

- Safety of FEIBA administration for reversal of FXa inhibitors
- Endpoints: Incidence of thromboembolic event within 7 days of FEIBA administration or hospital discharge
- Clinical parameter of FEIBA administration to reverse the anticoagulant effect of FXa inhibitors
  - Endpoints: Yes or No to the following:
    - Patient received additional blood products within 6-48 hours of FEIBA administration, including: FFP, PRBCs, cryoprecipitate, platelets, and/or vitamin K
    - Patient went to the operating room within 48 hours of administration due to continued bleeding
    - Patient had worsening of Glasgow Coma Score (GCS) after FEIBA administration at 24 or 48 hours
    - Patient experienced a decrease in hemoglobin of > 3mg/dL within 48 hours of FEIBA administration
- Median change from baseline in INR, PT, and aPTT after FEIBA administration (on coagulation assays drawn within 8 hours of administration)
- In-hospital mortality
- Effect of clinical pharmacy specialist involvement on adherence to FEIBA protocol

Preliminary Results

Table 1: Baseline Characteristics

	Total (n = 42)	Adherent (n = 20)	Non-adherent (n = 22)
Age (years), median (range)	77 (37 to 92)	78 (55 to 88)	73 (37 to 92)
Male sex, n (%)	23 (55)	11 (55)	12 (55)
Weight (kg), median (range)	81.2 (40.3 to 142.8)	77.6 (49.6 to 107)	80 (40.3 to 142.8)
Anticoagulant, n (%)			
Rivaroxaban	30 (71)	14 (70)	16 (84)
Apixaban	9 (21)	6 (30)	3 (16)
Dabigatran	3 (7)	0 (0)	3 (14)
Indication for anticoagulant, n (%)			
Atrial fibrillation/ Atrial flutter	34 (81)	16 (80)	15 (79)
DVT/PE	6 (14)	3 (15)	3 (16)
Other	2 (5)	1 (5)	1 (5)
Median FEIBA dose, units (Range)	1561 (906 to 2718)	1509 (906 to 2120)	1577 (978 to 2718)
Median FEIBA dose, units/kg (Range)	20 (10.3 to 34.7)	20 (10.3 to 34.7)	20 (14.5 to 24.3)

Table 2: Primary Endpoint – Non-adherence to Protocol

Total non-adherent to protocol, n (%)	22 (52)
Not on FXa inhibitor, n (%)	4 (10)
Not a life-threatening bleed, n (%)	6 (14)
Last dose > 48 hrs or unknown and aPTT < 34 seconds, n (%)	14 (33)

Table 3: Secondary Endpoints

	Adherent (n = 20)	Non-adherent (n = 19)
Incidence of thromboembolic events, n (%)	1* (5)	0 (0)
In-hospital mortality, n (%)	4 (20)	3 (16)
Cases where clinical specialist was involved, n (%)	10 (50)	5 (26)

*One patient on apixaban for atrial fibrillation was diagnosed with a CVA 5 days after receiving FEIBA for a subdural hematoma.

Table 4: Secondary Endpoints (continued)

	Adherent (n = 20)	Non-adherent (n = 19)
Post-FEIBA® additional products, n (%)	5 (25)	4 (21)
FFP	2 (10)	1 (5)
PRBCs	3 (15)	2 (11)
Cryoprecepitate	1 (5)	0 (0)
Platelets	2 (10)	0 (0)
Vitamin K	4 (20)	2 (11)
OR due to continued bleeding, n (%)	2 (10)	0 (0)
Median GCS score		
Pre-FEIBA	15	14
At 24 hrs	14	14
At 48 hrs	15	14
Post-FEIBA® hemoglobin drop of > 3mg/dL, n (%)	0 (0)	2 (11)
Median change in INR	-0.5 (-2.4 to 0)	-0.1 (-1.9 to +0.5)
Median change in PT (seconds)	-4.9 (-18 to 1)	-0.7 (-13.7 to +4.5)
Median change in aPTT (seconds)	-3.5 (-8 to -1)	+2.0 (-22 to +10)

Discussion and Conclusion

- Non-adherence to our FEIBA protocol was most often due to unknown timing of the last dose of the FXa inhibitor or aPTT <34 seconds
- There was a higher percentage of clinical pharmacy specialist involvement in protocol adherent patients (50% vs. 36%)
- Our protocol dose of 20 units/kg appears to be safe given only one thromboembolic event occurred within 7 days of FEIBA administration in one adherent patient
- FEIBA® appeared to have the most impact on coagulation parameters in protocol adherent patients
- Based on clinical parameters of hemoglobin, GCS score, surgical procedures performed, and the use of additional products, FEIBA® appears to have prevented further bleeding in our small sample of patients
- Limitations of our study include difficulty determining the time of the last dose of FXa inhibitor, which may have overestimated the number of non-adherent patients, and relying on retrospective documentation of outcomes

Disclosures

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Alicia Sacco: Nothing to disclose
Sarah Young: Nothing to disclose

References

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3. FEIBA® [package insert]. Westlake Village, CA: Baxter Healthcare Co; 2011.