



Full Length Article

Effect of low and moderate dose FEIBA to reverse major bleeding in patients on direct oral anticoagulants

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ABSTRACT

Objective: Management of acute, major or life threatening bleeding in the presence of direct acting oral anticoagulants (DOAC) is unclear. In the absence of a specific antidote, or in situations where there is a need for adjunctive therapy, the ideal prothrombin complex concentrate and dose is unclear. The goal of our study was to evaluate the outcomes of our reduced dosing strategy with FEIBA in patients experiencing a DOAC-related bleeding event.

Design: Retrospective analysis of patients treated with FEIBA for a DOAC-related bleeding event.

Setting: Academic medical center

Patients: Consecutive patients between May 2011 and April 2017 receiving FEIBA for a DOAC-related bleed

Interventions: None

Measurements & main results: Of the 64 patients included in this analysis, 38 patients received low dose FEIBA (mean 10.0 ± 3.6 units/kg) and 26 received moderate dose (mean 24.3 ± 2.1 units/kg) FEIBA; an additional dose was requested in 6 patients. Six dabigatran patients received idarucizumab. 30 day event rates included 5 thromboembolic events (8%) and 9 (14%) patients expired. Follow-up CT-imaging for ICH, endoscopy/colonoscopy, or interventional radiology exams did not reveal any clinically concerning active bleeding or hematoma expansion except in 2 ICH patients with slight expansion between imaging sessions.

Conclusions: Low (< 20 units/kg) to moderate (20–30 units/kg) doses of FEIBA, with the option for a repeat dose, may be an effective management strategy for obtaining hemostasis in DOAC-related major bleeding events.

1. Introduction

Over the past few years, several new direct acting oral anticoagulants (DOAC) have recently been introduced as alternatives to vitamin K antagonists. A key advantage with the DOACs in clinical trials was a lower incidence of hemorrhagic bleeding [1]. Use of DOACs in high bleeding risk populations, occurrence of traumatic events, and potential for excessive serum concentrations in populations commonly excluded in clinical trials may lead to increased bleeding events. Besides holding the anticoagulant, use of idarucizumab or hemodialysis to specially remove dabigatran effects, means to reverse anticoagulants' effects and manage bleeding remains unclear [2]. Emergent hemostasis using concentrated clotting factors including prothrombin complex concentrates (PCC) or activated prothrombin complex concentrates (aPCC) have been explored in-vitro/ex-vivo in non-bleeding patients and case reports/small series with bleeding risk patients [2]. A recent

published review of the literature noted that most experiences were either in animals, laboratory analysis in-vitro or ex-vivo and involved healthy volunteers where the aPCC dose ranged from 25 to 160 units/kg [3]. Use of PCC or aPCC in acute bleeding is mostly confined to case reports or small case series. Two recent assessments from Sweden and separately Canada exploring the use of 1500 to 4200 units of a non-activated 4 factor PCC suggested this approach may be effective in management of bleeding patients with low risk of thrombosis receiving apixaban or rivaroxaban [4,5].

Recently, idarucizumab became available for reversing the pharmacological effects of dabigatran, with an onset to hemostasis within several hours observed in non-central nervous system bleeding [6]. A separate agent for reversal of anti-Xa activity inhibitors, andexanet alfa, was recently approved though not readily available for reversal of apixaban and rivaroxaban [7,8]. Both agents appear to have a rapid onset of activity to neutralize the respective circulating DOACs, but

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have shown a delay in observed hemostasis [6,9]. Because of the delay in hemostasis, FEIBA may be advantageous as a primary or adjunctive hemostatic agent in DOAC related major or life threatening bleeds.

Since we reported the first case of successfully managing a life threatening cardiac bleed on dabigatran where rapid, marked slowing of bleeding after the first 8 units/kg of the aPCC FEIBA administered, with physician discretion for additional doses based on the urgency and bleeding location, we have utilized a low-dose strategy with the option for repeat doses [10]. Moderate initial doses (MD) of 25–30 units/kg or high dose 50 units/kg aPCC could be requested in intracranial hemorrhage (ICH) or eminent life threatening massive bleeds. Based on successful early experiences, the hospital's pharmacy and therapeutics committee determined that FEIBA would be the primary reversal approach for DOAC related bleeding events and potentially, adjunctive therapy to a readily available antidote. Our overall experience with the off label use of FEIBA to reverse the effects of patients prescribed a DOAC is described. The goal of our analysis was to evaluate the outcomes of our dosing approach in patients prescribed a DOAC and experiencing a bleeding event.

2. Patients/methods

This is a single center, retrospective analysis conducted between May 2011 and April 2017 at a large, tertiary academic medical center of all consecutive DOAC patients who received FEIBA to treat a bleeding event or mitigate potential bleeding during a high-risk procedure. Treatments including idarucizumab for dabigatran related bleeding events began in late 2015 after addition to the health system formulary and market availability. All patients receiving FEIBA were identified by an independent search of all orders for its use in the electronic medical record. Patients were excluded if they were not receiving a DOAC, had any form of hemophilia, were pregnant, a prisoner, or < 18 years of age. This was an unfunded, IRB approved analysis conducted at the University of California - Davis. Patient baseline demographics and laboratory information collected and analyzed included hemoglobin and hematocrit 12- and 24-hour post FEIBA dose, FEIBA dose administered, DOAC used along with dosing and indication, DOAC serum levels if available, number of packed red blood cells and frozen plasma units administered between 6 h before and 1 h after FEIBA administration and 1 h to 24 h post FEIBA dose, documented post FEIBA administration bleeding, any new thrombotic events at 30 days, survival to discharge, and 30-day mortality.

Serum concentrations for dabigatran were determined using an ecarin clotting assay method and anti-Xa activity assay calibrated separately to rivaroxaban or apixaban [11,12]. Patients on dabigatran with lower emergent bleeding concerns managed with idarucizumab alone were excluded. Potential bias is that FEIBA is the only agent for DOAC reversal used per institution policy, the authors were directly involved in management and final dosing was at the discretion of the treating physician. Analysis was based on available data and results identified the number available in each assessment.

Data was analyzed using Microsoft Excel (Microsoft Office Professional Plus 2010, Version: 14.0.7190.5000).

3. Results

64 patients received 66 separate admission and treatment courses: apixaban ($n = 20$), dabigatran ($n = 16$) and rivaroxaban ($n = 28$). 38 patients received LD (< 20 units/kg) FEIBA (mean 10.0 ± 3.6 units/kg) while 26 patients a MD (mean 24.3 ± 2.1 units/kg) (Table 1).

Of the 6 patients to receive a second dose (Table 2), 2 with an ICH received a total FEIBA dose of 50 units/kg. Six patients with bleeding on dabigatran received Idarucizumab (added to formulary shortly after FDA approval) and FEIBA as it was observed that severe bleeding did not sufficiently slow enough to meet clinical goals.

Descriptions of the ICH occurrences are described in Table 1.

Table 1
Demographics.

Factor	Total (N = 64)	Low dose (n = 38)	Moderate dose (n = 26)
Age (years) ^a	74 ± 14 (24–96)	73 ± 15 (24–95)	75 ± 13 (37–96)
Wt (kg) ^a	87 ± 24 (52–177)	88 ± 27 (52–177)	84 ± 18 (54–121)
Dabigatran (n)	16	12	4
Apixaban (n)	20	14	6
Rivaroxaban (n)	28	12	16
Indication (n)			
AF	51	29	22
VTE	11	8	3
PAD	1		1
CVA	1	1	
Bleeding location (n) ^c			
ICH	28 (29)	12 (13)	16
Non-ICH	36 (37)	26 (27)	10
GI	15 (16)	12 (13)	3
Cardiovascular	4	1	3
Lung	5	4	1
Other	12	9	3
Dose (Units) ^a	1332 ± 840 (250–3159)	902 ± 542 (250–1964)	2008 ± 951 (1524–3159)
Dose (Units/kg) ^a	15.4 ± 7.6 (4.5–50)	10.0 ± 3.6 (4.5–19)	24.3 ± 2.1 (20.6–50)
Time (minutes) from order to administration ^b	72.2 ± 41.8 (5–189)	75.2 ± 44.4 (5–189)	66.3 ± 37.9 (13–186)

Note: 64 patients with 2 patients being readmitted for total 66 courses.

Wt – weight; n – number; AF – atrial fibrillation; VTE – venous thromboembolism; PAD – peripheral arterial disease; CVA – cerebrovascular accident; ICH – intracranial hemorrhage; GI – gastrointestinal; kg – kilograms; SD = standard deviation.

^a Mean ± SD (Range).

^b On call to operating room excluded.

^c Patients could have more than one bleeding location.

Overall, 9 patients expired prior to the 30 day maximum follow-up period where information was available. Five thromboembolic events (TE) occurred (Tables 3 and 4).

Follow-up post FEIBA CT exams for ICH, and endoscopy/colonoscopy or interventional radiology exams for GI bleeding did not reveal any clinically concerning active bleeding or notable hematoma expansion with the potential exception of 2 ICH patients who subsequently expired (Table 4). Serum DOAC levels were measured in 49 of the 66 courses with mean values suggesting presence of therapeutic anticoagulation (Table 5). The level was 40 ng/ml or higher in 37 patients.

4. Discussion

The ideal approach to managing bleeding in the presence of a DOAC and role of PCC's remains unclear. Early investigations using in-vitro or ex-vivo analysis explored the effect of activated recombinant factor VII (rFVIIa), non-activated PCC and aPCC (FEIBA) on thrombin generation potential. Overall, these experiences with variability between methods and doses yielded mixed and inconsistent results [13–16]. In general, these assessments were not as encouraging for rFVIIa or non-activated PCC, and some limited suggestion favoring aPCC [15–17]. As noted in our 2013 case report, we observed through the cardiac window marked slowing of the bleed within minutes of the first 8 units/kg having been administered, suggesting that low doses of FEIBA than previously explored may be potentially effective in major bleeding [10]. A subsequent dose was given later that evening; however, excess edema from the massive transfusions was most likely the source of the symptoms instead of re-bleeding. Additional experiences with FEIBA demonstrated a rapid achievement of management goals using initial low

Table 2
Description of repeat dosing.

FEIBA dose	Comment
10 units/kg for 2 doses 2–4 h apart 13.6 and 6.7 units/kg – 26 h apart	See Table 4. Hgb dropped from 16 to 8 mg/dL with a dabigatran level of 2260 ng/ml. Case previously reported. (24) See Table 4. PCA infarct left occipital lobe with rivaroxaban level of 357 ng/ml and administered PCC3 (Proflinone 3500 units) prior to transfer to our facility.
8.9 units/kg for 2 doses – 1.5 h apart	AF on rivaroxaban. Admitted for GI bleed, Hgb of 6.1 with massive transfusion protocol. Patient became hypotensive, pulseless and CPR began, and level of 94 ng/ml. EGD next day showed no bleeding.
25 units/kg for 2 doses 11 h apart – on call OR	AF on rivaroxaban. Admitted for SDH and ICH with rivaroxaban level < 40 ng/ml. Repeat CT of the head showed possible slight worsening of IPH, bilateral SDH and SAH - repeat FEIBA dose given.
8 and 7 units/kg – 7 days apart	DVT on rivaroxaban. Needed to place external ventricular drain for VP shut malfunction. Rivaroxaban level was 56 ng/ml. Second dose given during surgery to replace a new drain.
23.6 units/kg for 2 doses 5 h apart	AF on rivaroxaban admitted for SDH. FEIBA initially given with an additional dose for prior to going to the OR.

kg – kilograms; hr- hours; dL – deciliter; Hgb – hemoglobin; GI – gastrointestinal; PCC3–3 factor prothrombin complex concentrate; SDH – subdural hematoma ICH – intracerebral hemorrhage; IPH – intraparenchymal hemorrhage; CPR- cardiopulmonary resuscitation CT- computed tomography SAH- subarachnoid hemorrhage FEIBA- Factor Eight Inhibitor Bypassing Activity; ng – nano grams; ml – milliliters; OR-operating room; PCA- posterior cerebral artery DVT- deep venous thrombosis EGD- esophagogastroduodenoscopy.

Table 3
Observed hemoglobin and transfusions prior to and after administrations of FEIBA, mortality and VTE events.

Outcome	All		Low dose (n = 39)		Moderate dose (n = 25)	
	N	Mean ± SD (range)	N	Mean ± SD (range)	N	Mean ± SD (range)
Hgb observed						
Hgb pre	68	10.8 ± 3.3 (4.5–18)	43	10.0 ± 3.3 (4.5–15.1)	25	12.1 ± 4.2 (6.3–18)
Hgb 12 post	32	10.7 ± 4.5 (6.9–16.8)	13	10.1 ± 4.4 (6.9–15.5)	19	11.6 ± 5.8 (8–16.8)
Hgb 12–24 h	46	10.0 ± 5.3 (6.5–15.6)	32	10.2 ± 5.0 (6.5–15.2)	14	11.2 ± 5.9 (7.7–15.6)
Transfused (n)						
PRBC pre	25	3.2 ± 3.0 (0–14)	18	2.9 ± 2.1 (0–8)	7	4.0 ± 4.7 (1–14)
PRBC post	16	1.4 ± 1.6 (0–6)	14	1.7 ± 1.8 (0–6)	2	0.4 ± 0.8 (0–2)
FFP pre	12	2.8 ± 3.8 (0–14)	8	2.5 ± 2.9 (0–9)	4	3.6 ± 5.9 (0–14)
FFP post	10	0.9 ± 1.1 (0–4)	8	1.2 ± 1.2 (0–4)	2	0.4 ± 0.5 (0–1)
Death (n)	9	(Dabigatran 25%) (Apixaban/Rivaroxaban 10%)	3	–	6	–
VTE (n)	5	(Dabigatran 12%) (Apixaban/Rivaroxaban 6%)	3	–	2	–

Pre = 6 h prior to and 1 h post FEIBA admin time; Post = 1 h to 24 h post FEIBA.

doses (LD) of around 8–12 units/kg, with the option to repeat. [18] This included prevention of bleeding during procedures such as dialysis catheter placement, intrapleural tap, and intracardiac tap to drain blood from isolated sites with the dose of FEIBA administered just prior to the procedure. [19] As experiences progressed, our practice evolved into starting at lower doses with the ability to give more if necessary.

Our analysis is a real world experience in patients requiring emergent reversal of their anticoagulation. 30-day cut off dates were chosen to be consistent with the timing for events reported in the RE-VERSal Effects of idarucizumab on Active Dabigatran (RE-VERSE AD) and Andexanet Alfa, a novel Antidote for the Anticoagulation Effects of FXA inhibitors (ANNEXA-4) trials exploring antidotes to the DOACs [6,9]. Many of our patients had exsanguinating bleeding events and might have expired within hours if hemostasis was not achieved. This may be one difference when comparing our observations and other case series and reports to randomized, controlled trials. Of the 9 patients that expired, 5 would most likely not have been enrolled in with the RE-VERSE AD or ANNEXA-4 trials (Table 4).

As this was a retrospective analysis, we could not assess directly the cessation of bleeding beyond noting the need for additional doses, which only occurred in 6 courses, 4 of which were in the LD group with a total dose 20 units/kg or less. In the MD group, 2 patients experiencing a severe ICH received a total dose of 50 units/kg (Table 2). Transfusions required after administration of the FEIBA, and stabilization of hemoglobin (Hgb) values are reported in Table 3. In cases we could assess, subjectively, non-CNS bleeding appeared to cease fairly rapidly within the hour after administration, consistent with our initial observations previously reported [10]. In 14 of the 16 patients with gastrointestinal bleeding events, follow up endoscopy or colonoscopy typically done by the next day did not reveal any active bleeding. Using

the ANNEXA-4 definition of ‘hemostatic efficacy’ [9], 92% of our Factor Xa inhibitor-related GI bleeds achieved a rate of excellent ($n = 14$) or good ($n = 1$) hemostasis. The percentage increases to 94% if we include patients receiving dabigatran.

In the RE-VERSE AD trial involving idarucizumab, it was observed that bleeding ceased at a mean 2.5 h after drug administration [6]. For gastrointestinal bleeding and other bleeding not associated with an intracranial hemorrhage, this was prolonged to 3.5 to 4.5 h [20,21]. In the ANNEXA-4 trial, 37 of the 47 patients in the efficacy population (confirmed drug present) were noted to have excellent to good hemostasis within 12 h [9]. Unlike the process for randomized clinical trials, the time from the initial order to administration of FEIBA was slightly over 1 h (Table 1). No delays occurred for contacting an investigator, assessment, consent and randomization. Our assessment included patients with emergent bleeding events that may not have been enrolled in the clinical trials. In the ANNEXA-4 trial, the mean time from presentation to the ED to drug administration was 4.8 ± 1.9 h [6,9]. For the experiences with PCC reported by Majeed et al. and Schulman et al., time from estimated bleeding time to PCC administration was 6 h (2–10h) and 8.6 h (4.8–18.1 h), respectively. Many of our patients had emergent issues including receiving cardiopulmonary resuscitation, massive transfusion, or emergent surgical procedures upon admission to the hospital and potentially would not have been alive or stable enough to be included in the clinical trials with the exception of the Majeed analysis criteria [3].

Of the 64 patients, 9 (14%) expired (Tables 3 and 4) within 30 days. Of these, 6 most likely were too critical to be included in the ANNEXA-4 trial, which was more restrictive than the RE-VERSE AD trial [6,9,22]. Our 25% 30-day mortality in those receiving dabigatran (2 of the 6 whom received idarucizumab) was a higher than the 13.5% in bleeding

Table 4
Description of 30 day thromboembolism and mortality observations post FEIBA administration.

Thromboembolism	Bleed	30 Day mortality	Description
Acute superficial VTE right upper arm and left cephalic vein	No	No	AF on dabigatran fell and found down with C3-C6 fracture – Level was 235 ng/ml and 8 h of hemodialysis was initiated prior to subsequent C3–6 laminoplasty surgery on day of admission. VTE occurred 6 days postFEIBA 6.3 units/kg.
Upper extremity VTE	No	No	Chronic DVT and PE on rivaroxaban with recent ventriculoatrial shunt requiring declogging. Anticoagulation held and PICC associated upper extremity VTE noted 17 days after FEIBA 19 units/kg.
Possible septic PE	No	No	Readmitted for recurrent GI bleed after restarting apixaban (level 92 ng/ml) and Hgb drop to 4.5 g/dL. Potential septic PE and possible thromboembolic on CT of the chest 8 days after FEIBA 5.6 units/kg.
Extensive bilateral pulmonary emboli	No	Yes	AF on dabigatran with right frontal tumor. Subacute right frontal infarction with a small focal parenchymal hemorrhage after a fall. PE observed 7 days post FEIBA 23.3 units/kg. Ultrasound for DVT was negative. Prognosis poor and patient expired 10 days later with sepsis.
PCA infarct L occipital lobe	Yes	Yes	AF on rivaroxaban after a fall with bilateral SDH and midline shift. Prior to transfer, PCC3 (Profilnine 3500 units) was given. The rivaroxaban level was 357 ng/ml 2 h prior to right frontal craniotomy for SDH evacuation, and 12–14 h post FEIBA 13.6 units/kg. A repeat dose of 6.9 units/kg was given 26 h after the initial dose due to interval re-accumulation of right holo-hemispheric SDH without significant midline shift (and rivaroxaban level of 44 ng/ml). CT on admit showed severe chronic microvascular disease. Patient expired 2 days later of severe pneumonia and sepsis.
Expired prior to discharge No	Perforated Stomach	Yes	Cerebrovascular accident on apixaban. Found down at skilled nursing facility in cardiac arrest 1 h prior to admission and admitted under CPR. Apixaban level was 125 ng/ml and given FEIBA 6.1 units/kg in operating room for necrotic stomach from PEG tube perforation. Pt expired that evening from septic shock with pH of 7 and continued bleeding despite FEIBA.
No	Toxic Megacolon and Surgery	Yes	AF with a dabigatran level over 1170 ng/ml who required abdominal surgery with poor prognosis. 5 g Idarucizumab post-surgery to drop level by approximately 1000 ng/ml. FEIBA 21 units/kg given in operating room, but expired post-surgery. Case previously reported [28].
Yes ^a	Bleeding from multiple sites	Yes	AF on dabigatran. Hgb dropped from 16 to 8 mg/dL. INR over 13 and dabigatran level of 2260 ng/ml. Idarucizumab 5 g given, but level still high at 1440 ng/ml and bleeding noted at intravenous access sites. FEIBA 10 units/kg given and hemodialysis initiated. Additional FEIBA 10 units/kg and a second 5 g dose of idarucizumab were given. Patient expired from multiple issues. Case previously reported [28].
Yes ^a	SAH	Yes	AF on dabigatran. 5 g of Idarucizumab 2.5 g × 2 doses at outside hospital prior to transfer for progressing SAH. FEIBA 17.2 units/kg given and repeat CT showed no change. Patient expired 2 days later with sustained ICP elevations and continued clinical deterioration with fixed and dilated pupils.
No	Emergent Vascular Surgery	Yes	AF on rivaroxaban. Found to have a pulseless blue foot with arterial embolism in iliac artery requiring emergent surgery. FEIBA 25 units/kg pre-operative 14 h after the last rivaroxaban dose. Patient decompensated in operative room.
Yes ^a	Bilateral SDH/SAH	Yes	AF on rivaroxaban. Patient with history of ASD and closure. Complained of 4 days of headaches and subsequently transferred with SAH/SDH and cerebellar ischemic stroke. FEIBA 13.7 units/kg given with bilateral lower extremity ultrasound 13 days later negative for VTE. MRI showed new T2 flare and central pontine myelinolysis versus ischemia. Expired 23 days later after failure to recover and thus placed on comfort care.
No	SDH/IPH	Yes	AF on rivaroxaban. Post fall and transfer from an outside hospital with repeat CT on admission 5 h later showed worsening large SDH and IPH with subfalcine and uncal-herniation. FEIBA 30.5 units/kg given. Pupils were fixed and dilated and support withdrawn as injury was determined to be non-survivable.

AF – atrial fibrillation; C – cervical; VTE – venous thromboembolism; FEIBA- Factor Eight Inhibitor Bypassing Activity; kg – kilograms; ng – nano grams; ml – milliliters; DVT- deep venous thrombosis; PE – pulmonary embolism; PICC – peripherally inserted central catheter; Hgb – hemoglobin; CT- computed tomography; MRSA – methicillin resistant staph aureus; SDH - subdural hematoma; PCC3–3 factor prothrombin complex concentrate; PEG – percutaneous endoscopic gastrostomy; SAH- subarachnoid hemorrhage; ICP – intracranial pressures; ASD – atrial septal defect; MRI – magnetic resonance imaging; T – thoracic; IPH – intraparenchymal hemorrhage; ^a – pre-existing ischemia.

Table 5
Serum concentration values per patient near the time of FEIBA administration.

Dosing group	Time (min)	Dabigatran (ng/ml)		Apixaban (ng/ml)		Rivaroxaban (ng/ml)	
		N	Mean ± SD (Range)	N	Mean ± SD (Range)	N	Mean ± SD (Range)
All	17	13	374 ± 522 (14–1440)	12	94 ± 69 (5–193)	24	127 ± 103 (4–357)
Low dose	–71*	10	376 ± 544 (14–1440)	10	108 ± 68 (5–193)	13	171 ± 92 (44–357)
Moderate dose	198	3	369 ± 547 (45–1000)	2	26 ± 14 (16–36)	11	75 ± 93 (4–283)
Value below 40 ng/ml	–	4	–	4	–	4	–

Time = Average time in minutes between FEIBA administration [point of reference] and DOAC level. *Reflects a negative time value as it was prior to the FEIBA. Ng – nanograms; ml – milliliters; FEIBA – Factor Eight Inhibitor Bypassing Activity.

patients from the RE-VERSE AD trial [6]. For those receiving apixaban or rivaroxaban ($n = 48$ for 50 courses), our 10% 30-day mortality was lower than the 15% in ANNEXA-4 trial “safety population”, 14% reported by Schulman et al., and the 32% reported by Majeed et al (mortality primarily patients with ICH) [4–6,9]. We observed an 8% (LD = 3, MD = 2) new thromboembolism rate at 30 days in the overall 66 courses. Of these events, 6% were receiving either apixaban ($n = 1$) or rivaroxaban ($n = 2$) in 50 courses, while 12% received dabigatran ($n = 2$) of 16 courses (Tables 3 and 4). This rate of 6% was lower than the 18% rate observed in the ANNEXA-4 trial safety population, similar to the 8% reported by Schulman and 6% by Majeed. In the dabigatran subgroup, the 12% thromboembolism rate was higher than the 4.8% observed in the RE-VERSE AD trial bleeding group [4–6,9]. This difference between these event rates might be owed to the small denominator ($n = 16$) in our subgroup. Of note, the two TE events occurred in patients prior to idarucizumab market availability. In a retrospective assessment of 56 patients with life-threatening major hemorrhage and oral anti-factor Xa agents, a 30-day thromboembolic event rate of 11% and mortality rate of 21% was observed, noting that this population had a higher proportion of patients with GI bleeding, and lower rate of ICH compared to our population [23]. Overall, this suggests that from a safety perspective, our management strategy did not appear to create additional risks. Given the diverse nature of our population and notable additional co-morbid conditions, it is difficult to determine if the TE rate is influenced by our usage of a lower dosing alone.

Early experience in patients with notable major gastrointestinal bleeding who received the low dose FEIBA with rapid cessation of bleeding and absence of bleeding noted on subsequent colonoscopy supported the continued use of the LD titration strategy. For patients with CNS bleeding, it was unclear what the dosing approach should be, but in general the moderate dose was used due to the potential consequences of continued bleeding and inability to reassess until repeat head CT was done. However, at physician discretion, 12 of 28 patients with CNS bleeding received the lower dosing approach. As with the recent analysis in the RE-VERSE AD trial, CNS bleeding related outcomes can be difficult to describe due to limitations on the ability to reassess bleeding [6].

Relative to CNS bleeding events, we are currently undertaking a separate in depth assessment of this population. In the 29 patients with some sort of CNS bleeding event, repeat CT suggested no or very minimal mass effect in 26 patients. A repeat CT was not done on 2 patients - one with an ICH and multiple pelvic fractures with extravasation discharged 19 days later, and a second with a SDH and IPH placed on comfort care 3 h after the FEIBA. Additional mass effect was potentially present in 1 patient with a CT done shortly after FEIBA administration. Overall, our observations suggested that doses lower than the 50 units/kg recommended by the neurocritical society may need further comparative assessments in CNS bleeding events [24]. Of note is that it was difficult to know if any continued bleeding seen on the repeat CT occurred prior to the administration of the FEIBA, or if the process irrespective of any reversal therapy would have already run its course.

Some evidence with warfarin-related CNS bleeds suggests that improved outcomes occur if the intervention is within 4 to 5 h and INR values below 1.4 to 1.5 are achieved [25,26]. Despite some delay in the initial CT and FEIBA administration, we did not observe in most cases any expanded mass effects. This may question any overall benefits observed in processing patients in randomized clinical trials or intervention delays after a relatively short time period.

Serum concentrations were available in 49 of the 66 courses, for which mean values suggested adequate anticoagulation, noting however that 12 patients most likely had minimal DOAC effects present (Table 5). Timing of the DOAC level after the most recent dose was difficult to determine. Repeat courses were requested in 6 patients as noted above, for which 2 had a level below 40 ng/ml. The patients who

received the LD strategy tended to have levels drawn around 1 h prior to the FEIBA dose compared to several hours after the high dose was given. This in part might explain why the low dose cohort had higher levels on average than the moderate dose cohort.

One additional concern with direct antidotes is the potential for only partial reversal in the setting of extremely high DOAC concentrations [27]. One previously reported patient, had an initial dabigatran level over 2000 ng/ml and was still therapeutic despite 2 courses of 5 g Idarucizumab [28]. In the RE-VERSE AD bleeding subgroup, there were 18 administrations of concentrated clotting factors of which 5 were aPCC [20]. Patients receiving andexanet alpha in the ANNEXA-4 trial and concentrated clotting factors prior to, or within 12 h, of the andexanet alpha infusion were excluded from analysis [9]. This still brings into question the roles of antidotes that have no additional hemostatic effects, use of concentrated clotting factors or both. Another question to resolve regards the dose of concentrated clotting factors necessary to manage emergent major bleeding with or without administration of an antidote, and the overall cost related to the management strategy. Additionally, the current limitations of market available andexanet alpha despite recent FDA approval makes FEIBA an attractive option. Given the average wholesale price for FEIBA is approximately \$1.65/Unit, a low (10 units/kg) to median (25 units/kg) dose course in a 70 kg patient would be \$1155 and \$2887 respectively, which could be financially attractive [29].

4.1. Limitations

Limitations include that this was a single center, non-randomized retrospective analysis with no comparator in patients who received a specific agent. Only a low and moderate FEIBA dosing cohort was evaluated, limiting any comparison to higher doses that have been explored. Follow-up for some patients may have been only days after FEIBA administration as they either expired from their critical condition or transfer out to another health care facility if not directly discharged. Full medication histories for concurrent antiplatelet agents was difficult to accurately determine, and objective assessment for timing of post FEIBA administration hemostasis onset.

5. Conclusions

The ideal approach to managing bleeding events on DOAC's remains unclear. We report the use of two different dosing strategies using the aPCC FEIBA for reversing DOAC anticoagulation effects. Low dose FEIBA with an option to repeat, and moderate dose FEIBA, depending on the urgency of the situation, may be an effective management strategy with a positive net clinical benefit for major DOAC bleeding events. 25 units/kg FEIBA or lower may be a potential strategy for ICH or massive life threatening bleeding events. These strategies appear to be safe and have the potential to expedite hemostasis in critical bleeding settings. The role of reversal including the dose of a concentrated clotting factor in the setting of ICH remains unclear, but there may be an option to consider doses lower than 50 units/kg. More data and experiences however, are needed to determine the best approach to emergently manage major life threatening acute bleeding events with DOAC therapy.

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Robert C Gosselin.

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