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Emergent reversal of oral factor Xa inhibitors with four-factor prothrombin complex concentrate

Louis Lipari [a], Sam Yang [b], Brian Milligan [c], Joseph Blunck [d,*]

[a] Department of Pharmacy, Research Medical Center, Kansas City, MO, USA
[b] Department of Anesthesiology, Saint Luke's Health System, Kansas City, MO, USA
[c] Department of Neurosurgery, University of Kansas Medical Center, Kansas City, KS, USA
[d] Department of Pharmacy, Saint Luke's Health System, Kansas City, MO, USA

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ABSTRACT

Background: Controversy exists regarding first-line use of the recently approved reversal agent andexanet alfa due to limitations of the ANEXXA-4 study, thrombotic risks, and high medication acquisition cost. The purpose of this study was to evaluate the safety and effectiveness of 4F-PCC for the reversal of emergent oral fXa inhibitor-related bleeding. Furthermore, we aimed to evaluate a subgroup using strict ANNEXA-4 patient selection criteria.

Methods: This was a retrospective study conducted utilizing chart review of adult patients that received 4F-PCC for oral fXa inhibitor-related bleeding. The primary endpoint was the rate of clinical success defined as achieving excellent or good hemostatic effectiveness following the administration of 4F-PCC. Secondary endpoints included in-hospital mortality and arterial/venous thromboembolism, and cost compared with andexanet alfa.

Results: A total of 119 patients were included, with 83 patients in the ANNEXA-4 criteria subgroup. Eighty-five of the 119 patients (71%) required reversal due to intracranial bleeding. Prior to reversal, 70 patients (59%) were taking apixaban and 49 patients (41%) were taking rivaroxaban. Clinical success was achieved in 106 of 119 patients (89%) and 74 of 83 patients (90%) in the strict criteria subgroup. Three of 119 patients (2.5%) had a thrombotic event during hospital stay and the overall mortality rate was 13%. The average cost increase of andexanet alfa compared to 4F-PCC would have been $29,500 per patient.

Conclusions: Administration of 4F-PCC for the reversal of oral fXa inhibitors was effective with relatively low thrombotic risk. Further direct prospective comparison of 4F-PCC to andexanet alfa is warranted.

1. Introduction

Oral factor Xa (fXa) inhibitors are anticoagulants with demonstrated utility in the treatment and prevention of thromboembolic disease including venous thromboembolism and reduction in the risk of stroke or systemic embolism in patients with nonvalvular atrial fibrillation [1,2]. FXa inhibitors prevent fibrin clot formation by binding to the active site of coagulation fXa leading to the inhibition of the coagulation cascade [3]. Conveniently, fXa inhibitors have consistent pharmacokinetic and pharmacodynamic properties that allow for a fixed dosing strategy without obligatory routine laboratory monitoring of anticoagulation effect. Commercially available oral fXa inhibitors in the United States include rivaroxaban, apixaban, edoxaban, and betrixaban.

The use of fXa inhibitors may increase a patient's risk for bleeding due to their inhibition of the coagulation cascade [3]. There may be a reduced risk of intracranial hemorrhage when compared to warfarin, a vitamin K antagonist [1,2]. To a greater extent than vitamin K antagonists, controversy exists regarding reversal strategies for oral fXa inhibitors [4]. Andexanet alfa, now labeled as inactivated coagulation fXa (recombinant) with trade name Andexxa®, was FDA approved in May of 2018 to reverse apixaban and rivaroxaban. The Phase 3b/4 trial evaluating the safety and efficacy of andexanet alfa, ANNEXA-4, was completed in February 2019 [5]. Ciraparantag is an investigational small molecule that binds and inactivates several anticoagulants and is currently undergoing clinical trials for reversal of bleeding associated with fXa Inhibitors [6].

4-factor prothrombin complex concentrate (4F-PCC), with trade name Kcentra®, was FDA approved in 2013 for the urgent reversal

Abbreviations: 4F-PCC, four-factor prothrombin complex concentrate; fXa, factor Xa; PCC, prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; ICH, intracranial hemorrhage; GCS, glasgow coma scale; GIB, gastrointestinal bleeding; ISTH, international society of thrombosis and hemostasis; Vd, volume of distribution.

* Corresponding author at: Saint Luke's Hospital, 4401 E Wornall Rd., Kansas City, MO 64111, USA.
E-mail addresses: louis.lipari@hcamidwest.com (L. Lipari), syang@saint-lukes.org (S. Yang), brianmilligan@alumni.stanford.edu (B. Milligan), jblunck@saint-lukes.org (J. Blunck).

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of oral vitamin-K antagonist associated coagulopathy. It contains the clotting factors II, VII, IX, and X, and antithrombotic proteins C and S [7]. Additionally, 4F-PCC is frequently used off-label to urgently reverse the anticoagulant effects of oral fXa inhibitors [8]. Although it is not FDA approved for this indication, limited evidence and current guidelines suggest prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (aPCC) are options for reversal of anticoagulation in the case of life-threatening bleeding in patients on fXa Inhibitors [9-29]. The recent approval of andexanet alfa, with its high acquisition cost and safety concerns, has added to the controversy regarding optimal oral fXa inhibitor reversal strategies. We aimed to perform a comprehensive evaluation of the effectiveness and safety of 4F-PCC for the management of emergent bleeding related to oral fXa inhibitors including a strict subgroup with inclusion/exclusion criteria similar to the ANEXXA-4 trial. This study will add to the body of literature surrounding this controversial topic and provide a cost analysis for health systems and formulary committees to consider.

2. Methods

2.1. Study design

This was a retrospective, observational study conducted at a multicenter health system in the United States. The health system consists of a flagship academic hospital, four community hospitals, and three critical access hospitals. The flagship hospital is a level 1 trauma center and comprehensive stroke center. Radiographic imaging, medication administration records, and laboratory data were collected from the electronic medical record. In-hospital mortality and thromboembolic events were assessed via patient chart review. Our oral Xa inhibitor reversal protocol is to treat patients with 4F-PCC (50 IU/kg, Kcentra®), with a maximum dose of 3500 IU (rounded to the nearest vial size).

Patients 18 years or older admitted between November 1, 2013 and January 31, 2019 with subacute/acute major bleeding associated with the administration of an oral fXa inhibitor were included. Patient selection for the overall cohort and ANNEXA-4 criteria subgroup are shown in Fig. 1. Patients were excluded if there was no obvious source of bleeding. ANNEXA-4 subgroup inclusion criteria were acute bleeding and completion of repeat imaging within 12 h of receiving 4F-PCC. Additional ANNEXA-4 exclusion criteria were invasive surgery within 12 h of receiving 4F-PCC or a thrombotic event in the previous 2 weeks. Intracranial hemorrhage (ICH) patients were also excluded from this subgroup for a Glasgow Coma Scale (GCS) score < 7, an estimated intracerebral hematoma volume > 60 ml as assessed by radiographic imaging [30], or expected mortality within 30 days. Expected 30-day mortality was assessed by an ICH score of 3 or higher, corresponding with an expected 30-day mortality of 72–100% [31]. Baseline patient characteristics are detailed in Table 1.

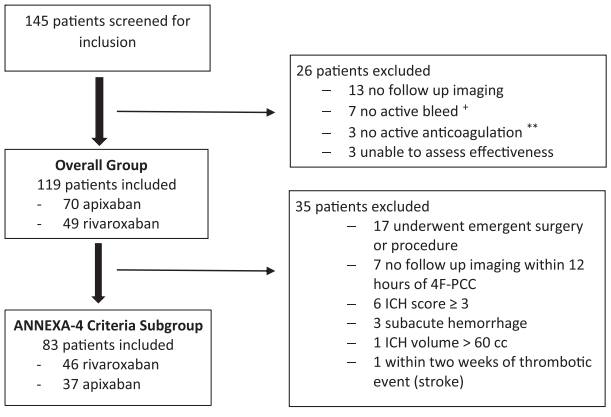

Fig. 1. Inclusion and exclusion flowchart. +Reversal given prior to procedures with no active bleeding. **Oral fXa inhibitor held >5 days prior to procedure/reversal.

2.2. Study outcomes

The primary endpoint was the rate of clinical success defined by achieving excellent or good hemostatic effectiveness following the administration of 4F-PCC. Hemostatic effectiveness definitions are described in Appendix A and mirror the definitions used in the ANNEXA-4 trial [5,32]. Secondary outcomes included in-hospital mortality, and the rate of arterial or venous thromboembolism during hospitalization. Cost analysis was performed for patients treated during 2018 ($n = 59$) for whom acquisition costs of both 4F-PCC and andexanet alfa were known. Total and average costs were calculated to compare actual 4F-PCC cost to the potential andexanet alfa cost had it been used according to the labeled dosing at the current $5500 per 200 mg vial acquisition cost [33]. For purposes of the cost analysis, patients were assigned to high dose andexanet alfa if the apixaban dose was greater than 5 mg or a rivaroxaban dose greater than 10 mg with last ingestion within previous 8 h of reversal or unknown. Chart review, radiographic interpretation, and endpoint assessment was conducted by unblinded study investigators.

Table 1
Baseline characteristics.

	Overall ($n = 119$)	ANNEXA-4 criteria sub group ($n = 83$)
Age, years, mean (SD)	77 (10)	78 (9.9)
Weight, kg, mean (SD)	85 (21)	82 (20)
Male n (%)	65 (55)	44 (53)
Creatinine clearance, n (%)		
>60 ml/min	62 (52)	40 (48)
30–60 mL/min	50 (42)	39 (47)
<30 mL/min	7 (5.9)	4 (4.8)
Factor Xa inhibitor, n (%)		
Apixaban	70 (59)	46 (55)
Rivaroxaban	49 (41)	37 (45)
Indication for anticoagulation, n (%)		
Atrial fibrillation	90 (76)	64 (77)
Venous thromboembolism	19 (16)	11 (13)
Multiple	5 (4.2)	5 (6.0)
Unknown/other	5 (4.2)	3 (3.6)
Type of bleed, n (%)		
Non-intracranial	34 (29)	19 (23)
Gastrointestinal	13 (11)	12 (14)
Prior to urgent surgery/procedure	12 (10)	–
Other life threatening	9 (7.5)	7 (8.4)
Intracranial	85 (71)	64 (77)
Intraparenchymal	38 (32)	27 (33)
Subdural	25 (21)	17 (21)
Subarachnoid	13 (11)	12 (16)
Intraventricular	2 (1.7)	2 (2.4)
Multiple intracranial	7 (5.9)	6 (7.2)
GCS score, median (IQR)	15 (13–15)	15 (14–15)
Mean (SD)*	13.5 (2.5)	14.2 (1.3)
Intraparenchymal volume, n (%)		
Hematoma volume ≤ 10 ml	19 (50)	17 (63)
Hematoma volume 11–30 ml	10 (26)	6 (22)
Hematoma volume 31–60 ml	7 (18)	4 (15)
Hematoma volume > 60 ml	2 (5.3)	-
Subdural thickness, n		
Maximal thickness ≤ 10 mm	13 (52)	10 (59)
Maximal thickness > 10 mm	12 (48)	7 (41)

SD Standard Deviation, GCS Glasgow Coma Scale, IQR interquartile range *mean reported in addition to median for ordinal data to show GCS score trend and mimic ANNEXA-4 reporting.

2.3. Statistical analysis

Data was evaluated using descriptive statistics. Results are reported as means (± standard deviation) or, in case of skewed distribution, as median and interquartile ranges as appropriate.

3. Results

A total of 145 patients were screened of which 119 were eligible for inclusion. Eighty-five of the 119 patients (71%) required reversal due to intracranial bleeding. Prior to reversal, 70 patients (59%) were taking apixaban and 49 patients (41%) were taking rivaroxaban. A successful hemostatic outcome was achieved in 106 of 119 patients (89%). (See Table 2) In the ANNEXA-4 criteria subgroup, 74 of 83 patients (90%) achieved a successful clinical outcome. The mortality rate prior to discharge was 13% overall and 9.6% in the ANNEXA-4 criteria subgroup, and 3 of the 119 patients (2.5%) experienced a thrombotic event prior to discharge. Three patients were excluded due to the inability to assess hemostatic effectiveness, including one with epistaxis where the bleeding cessation time was unclear and two with gastrointestinal bleeding (GIB) that transitioned to comfort care before follow up lab studies were drawn.

For patients treated in 2018 ($n = 59$), the total acquisition cost of 4F-PCC was $319,500 (Mean = $5400 ± $1300 per patient). (See Table 3) If andexanet alfa reversal were used in place of 4F-PCC during this timeframe, with our current acquisition cost of $27,500 for low-dose ($n = 38$) and $49,500 for high-dose ($n = 21$), the annual cost would have been $2,084,500. The potential average cost increase with andexanet alfa reversal was $29,500 ± $10,500 per patient.

4. Discussion

This study evaluated the clinical effectiveness, safety, and financial impact of using 4F-PCC for the reversal of oral fXa inhibitors. In an effort to compare our outcomes using 4F-PCC to previously published outcomes using andexanet alfa, we analyzed a subgroup created utilizing ANNEXA-4 inclusion and exclusion criteria.

The rate of successful clinical outcome of 89% in this study compares favorably to previously reported success rates with the use of 4F-PCC for this indication. A meta-analysis of 10 studies, including 340 total patients, reported successful hemostasis in 69% of patients from 2 studies using International Society of Thrombosis and Hemostasis (ISTH) criteria [34] and 77% of patients from 8 studies using non-ISTH criteria [29]. There was variability in PCC product and dosing in this meta-analysis with majority of patients receiving 4F-PCC doses of approximately 25 IU/kg [16,19,25]. Our results are similar to a recently published multicenter, retrospective observational cohort study evaluating PCC for oral fXa-related ICH demonstrated a 82% hemostatic efficacy rate utilizing an average dose of 40 units/kg [35]. The average 4F-PCC dose in our study was 41 ± 12 IU/kg. There may be a dose response with 4F-PCC for oral fXa inhibitor reversal as demonstrated in a human volunteer study where 37.5 and 50 IU/kg doses (but not 25 IU/Kg) reversed the depressed endogenous thrombin potential [36]. The Neurocritical Care Society and the Society of Critical Care Medicine and the American College of Surgeons recommend a 4F-PCC dose of 50 IU/kg for this indication [8,10]. Although our protocol is similar to guideline recommended dosing, it differs in regard to the maximum initial dose. Since clotting factors in 4F-PCC have a small volume of distribution (Vd = 0.045–0.114 L/Kg) [7], our protocol has a maximum initial dose of approximately 3500 IU with the intent to maximize cost-effectiveness and potentially improve safety.

The ANNEXA-4 trial evaluated the safety and efficacy of andexanet alfa for the reversal of anticoagulation with fXa inhibitors. The efficacy arm included 249 patients with an acute major bleed within 18 h after the administration of a fXa Inhibitor, of whom 204 (82%) achieved excellent or good hemostasis [5]. Using the equivalent hemostasis success definition, the rate of successful clinical outcome of 90% in our strict criteria subgroup is similar to the ANNEXA-4 trial.

In ANNEXA-4, 34 of 352 patients in the safety arm (10%) experienced a thrombotic event and 49 patients (14%) died within 30 days [5]. Three of 119 patients in our cohort (2.5%) developed a thromboembolism prior to discharge after receiving 4F-PCC. This study's lower thromboembolic rate may reflect the fact that thrombotic events and mortality could only be recorded until patient discharge. The thrombotic event rate of 2.5% in this study is similar to previously reported rates with the use of 4F-PCC to reverse oral fXa inhibitors. A meta-analysis of seven studies including 240 patients reported a thrombotic rate of 4% [29]. When combined with post meta-analysis studies, the mean thrombotic rate is 3.8% ($n = 999$ total) [26-29,35]. The phase IIIb clinical trial evaluating 4F-PCC for the reversal of vitamin K antagonists reported a "related" thrombotic rate of 3.9% (total thrombotic rate 7.8%) [32]. These event rates compare favorably to the 10% thrombotic event rate reported in the ANNEXA-4 trial [5].

Only 2 of the 59 patients in the 2018 cost analysis had documentation of last fXa inhibitor ingestion which likely led to increased assignment to the "high-dose" andexanet alfa group. A more conservative estimate might be to utilize the 16% rate of high-dose requirement in the ANNEXA-4 study, which would reduce our potential annual cost of andexanet alfa to $1,820,500. Using this methodology, the average cost of andexanet alfa would be $31,000 per patient compared to $5400 with 4F-PCC.

4F-PCC and andexanet alfa have not been compared in a head-to-head prospective study. However, a randomized, multicenter, open-label clinical trial comparing andexanet alfa to usual care in patients with an intracranial hemorrhage anticoagulated with a direct oral anticoagulant is under way (ClinicalTrials.gov number, NCT03661528).

This study is not without limitations. This study was conducted utilizing retrospective chart review, which inherently introduces a significant number of biases during study design and abstraction process, as well as limits the completeness and reliability of information collected from the patient chart. It is important to note that we are making indirect observations from two separate study results with no inferential statistical analysis for definitive comparison. Only two patients had documentation of last fXa inhibitor ingestion, and it is conceivable that a portion of the patients may not have been therapeutically anticoagulated. The retrospective design did not allow for measurement and exclusion of patients with low baseline anti-fXa activity which could contribute to the favorable success rate. However, anti-fXa reduction by andexanet alfa did not correlate with improved patient outcomes in ANNEXA-4 study [5]. Additionally, the high mean GCS score in this study was comparable to the ANNEXA-4 study patient population [5]. This may have contributed to the relatively low in-hospital

Table 2
Patient outcomes.

	Overall (n = 119)	Overall ANNEXA-4 criteria (n = 83)	ICH patients overall (n = 85)	ICH patients meeting ANNEXA-4 criteria (n = 64)
Effective hemostasis, n (%)	106 (89)	74 (90)	72 (85)	56 (88)
In-hospital mortality, n (%)	15 (13)	8 (10)	12 (14)	7 (11)
Thrombotic events, n (%)	3 (2.5)	2 (2.4)	2 (2.4)	0 (0)

ICH Intracranial Hemorrhage.

Table 3
Annual cost analysis for 2018.

High dose[a] Andexanet alfa cost potential (n = 21)	Low dose[b] Andexanet alfa cost potential (n = 38)	Total Andexanet alfa cost potential (n = 59)	4F-PCC acquisition cost[c]	Potential cost increase with Andexanet alfa vs 4F-PCC
$ 1,039,500	$ 1,045,000	$ 2,084,500	$ 319,500	$ 1,765,000

[a] Acquisition cost for high dose Andexanet alfa 800 mg IV load followed by 8 mg/min for 2 h is $49,500.
[b] Acquisition cost for low dose Andexanet alfa 400 mg IV load followed by 4 mg/min for 2 h is $27,500.
[c] Acquisition cost for 4F-PCC is $1.70 per IU; Mean dose per patient was 3192 ± 766 IU.

mortality rate in both trials. Lastly, our cost analysis was performed comparing incurred cost of 4F-PCC with the anticipated cost of treating those same patients with andexanet alfa.

5. Conclusion

Administration of 4F-PCC for the reversal of oral fXa inhibitors was effective with relatively low thrombotic risk. 4F-PCC appear to have similar clinical success rates when indirectly compared with andexanet alfa with reduced prothrombotic risk and cost. Randomized, prospective studies are warranted to further compare safety, efficacy and cost of 4F-PCC and andexanet alfa for this indication.

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Declaration of Competing Interest

All authors have declared they have no conflict of interest relevant to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2020.08.019.

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