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ORIGINAL WORK

Andexanet Alfa Versus 4-Factor Prothrombin Complex Concentrate for Reversal of Factor Xa Inhibitors in Intracranial Hemorrhage

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Abstract

Background/Objective: There are limited data on the risks and benefits of using andexanet alfa (AA) in comparison with four-factor prothrombin complex concentrate (4F-PCC) to reverse factor Xa inhibitors (FXi) associated intracranial hemorrhage (ICH). We sought to describe our experience with AA or 4F-PCC in patients with oral FXi-related traumatic and spontaneous ICH.

Methods: We conducted a retrospective review of consecutive adult patients with FXi-related ICH who received AA or 4F-PCC. FXi-related ICH cases included traumatic and spontaneous intracranial hemorrhages. Our primary analysis evaluated ICH stability on head computed tomography scan (CT), defined as a similar amount of blood from the initial scan at the onset of ICH to subsequent scans, at 6-h and 24-h post-administration of AA or 4F-PCC. For the subset of spontaneous intraparenchymal hemorrhages, volume was measured at 6-h and 24-h post-reversal. In secondary analyses, we evaluated good functional outcome at discharge, defined as a Modified Rankin Score of less than 3, and the incidence of thrombotic events after AA or 4F-PCC adminstration, during hospitalization.

Results: A total of 44 patients (16 traumatic and 28 spontaneous ICH) with median age of 79 years [72–86], 36% females, with a FXi-related ICH, were included in this study. The majority of spontaneous ICHs were intraparenchymal 19 (68%). Twenty-eight patients (64%) received AA and 16 patients (36%) received 4F-PCC. There was no difference between AA and 4F-PCC in terms of CT stability at 6 h (21 [78%] vs 10 [71%], $p=0.71$) and 24 h (15 [88%] vs 6 [60%], $p=0.15$). In a subgroup of patients with spontaneous intraparenchymal hemorrhage, there was no difference in the degree of achieved hemostasis based on hematoma volume between AA and 4F-PCC at 6 h (9.3 mL [6.9–26.4] vs 10 mL [9.4–22.1], adjusted $p=0.997$) and 24-h (9.2 mL [6.1–18.8] vs 9.9 [9.4–21.1], adjusted $p=1$). The number of patients with good outcome based on mRS on discharge were 10 (36%) and 6 (38%) in the AA and 4F-PCC groups, respectively (adjusted $p=0.81$). The incidence of thromboembolic events was similar in the AA and 4F-PCC groups (2 [7%] vs 0, $p=0.53$).

Conclusion: In this limited sample of patients, we found no difference in neuroimaging stability, functional outcome and thrombotic events when comparing AA and 4F-PCC in patients with FXi-related ICH. Since our analysis is likely underpowered, a multi-center collaborative network devoted to this question is warranted.

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Introduction

Andexanet alfa (AA) is the first and currently, the only FDA-approved selective reversal agent for the treatment of life-threatening bleeding associated with oral factor Xa inhibitors (FXi) [1]. Despite the approval of AA, current guidelines provide little guidance on the preference of either AA or alternative therapies such as four-factor prothrombin complex concentrate (4F-PCC) as the reversal agent for oral FXi [2, 3]. A recently published American College of Cardiology expert consensus statement for the management of bleeding in patients on oral anticoagulants states that it is reasonable to use AA over 4F-PCC for reversal of oral FXi (moderate recommendation with moderate quality of level of evidence-based on nonrandomized studies) [4]. Evidence leading to AA's approval as a reversal agent included a phase II trial of healthy older volunteers [5] and a landmark open-labeled trial (ANNEXA-4) of patients presented with major acute bleeding and received apixaban, rivaroxaban, edoxaban or enoxaparin [6]. Connolly et al. reported a 92% reduction in the median anti-FXa activity for both apixaban and rivaroxaban, with 82% of the patients achieving excellent or good hemostasis 12 h post-AA infusion [6]. The largest and most comprehensive trial to date assessing the safety and efficacy of 4F-PCC for oral FXi-related intracranial hemorrhage (ICH) reported a high rate of excellent or good hemostasis in 354 patients out of 422 patients (81.8%; 95% confidence interval 77.9–85.2) at 24 h and a low rate of thrombosis (3.8%) in the retrospective multi-center non-comparative analyses [7].

With the lack of prospective comparative studies between AA and available reversal agents such as 4F-PCC in patients with FXi-related ICH, there is currently no evidence that AA is superior to other therapies used for rivaroxaban or apixaban reversal. For oral FXi-related ICH reversal, institutions therefore, use a pragmatic approach based on drug availability and local clinical preferences to make formulary decisions in terms of using AA versus other similar therapies such as 4F-PCC [8]. Given the absence of comparative evidence for AA to 4F-PCC, we aimed to describe our experience with AA and 4F-PCC to reverse intraparenchymal (IPH), subarachnoid, subdural ICH and other intracranial bleeds in the setting of treatment with apixaban or rivaroxaban.

Methods

Study Design and Participants

We conducted a retrospective, single-center study that included a consecutive series of adult patients admitted to Yale New Haven Health System from July 2018 to April 2019, presenting with a life-threatening traumatic or spontaneous intraparenchymal, subarachnoid, subdural hemorrhages and other intracranial bleeds in the setting of FXi (apixaban or rivaroxaban) therapy. Patients were treated with either at least one dose of AA or 4F-PCC within the health system. AA was dosed according to the product labeling for life-threatening bleeding associated with factor Xa inhibitors and 4F-PCC dosed with 25 units/kg up to 2,500 units per dose. We excluded patients that received both AA and 4F-PCC during the same hospitalization. Our study was approved by the Yale New Haven Hospital Institutional Review Board and was exempted for minimal risk status.

Exposure and Outcomes of Interest

Our exposure of interest was the use of AA or 4F-PCC as oral FXi reversal therapy. Our primary outcome was a stable head computed tomography (CT) scan at 6 and 24 h post-administration of AA or 4F-PCC, defined as for IPH as no significant increase in volume (less than 6 mL or 33% of baseline volume) [9, 10], and adjudicated by an experienced provider for all other bleeds. Secondary outcomes included good functional outcome at discharge, defined as a Modified Rankin Score (mRS) of 0–3, in-hospital thrombotic events after reversal therapy, short-term mortality (in-hospital mortality or discharge to hospice), length of stay (hospital and ICU) and disposition on discharge.

Variable Definitions and Neuroimaging

Data extracted from the electronic medical records included patients' demographics, clinical, imaging and laboratory information. Each brain imaging study was independently reviewed by three experienced providers blinded to the treatments and outcome and rated for stability based on the brain imaging obtained at 6 and 24 h. Stability was defined as a similar amount of blood from one scan to the next. For intraparenchymal hemorrhages, the volume of the hematoma was calculated using the ABC/2 volume estimation method [11]. In IPH, a similar amount of blood was defined as a volume growth of less than 6 mL or 33% from baseline CT and adjudicated by the three experienced independent providers. Thrombotic events were identified via chart review and

included upper and lower extremity deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, myocardial infarction (MI), catheter-associated thrombosis and any other thromboses documented between reversal agent administration and hospital discharge. For all documented thromboembolic events, supportive evidence from relevant imaging and laboratory studies were required.

Statistical Analyses

Continuous variables are presented as median (interquartile range [IQR]) and categorical variables as count (percentage [%]). Differences in continuous variables among the groups were tested using Mann–Whitney U test and differences in categorical variables using chi-square or Fisher's exact test, as appropriate. For selected outcomes (CT scan stability, functional outcome and mortality), logistic regression was used to adjust for age and sex. A subgroup analysis was performed in patients with IPH, adjusting additionally by baseline IPH volume. All analyses were performed using R version 3.6 software (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value of 0.05 or less was considered statistically significant.

Results

Baseline Demographics

A total of 44 patients, AA ($n=28$ [64%]) and 4F-PCC ($n=16$ [36%], presenting with an ICH in the setting of recent administration of oral FXi therapy were included in the study. Of the included ICH cases, 16 (36%) were traumatic and 28 (64%) were spontaneous hemorrhages. Most spontaneous ICHs were intraparenchymal ($n=19$, 68%) and most traumatic ICHs were multicompartmental ($n=12$, 75%). Both treatment groups had similar characteristics at baseline (Table 1). Most study participants were male (AA, 17 [61%] and 4F-PCC, 11 [69%], $p=0.84$) with similar median age (AA, 78 years [70–87] and 4F-PCC, 80 years [74–84], $p=0.88$) and Glasgow Comma Scale on admission (AA, 14 [11–15] and 4F-PCC, 14 [7–15], $p=0.65$). There was no difference in the indication for anticoagulation therapy between groups, with the majority of patients receiving oral FXi for the indication of atrial fibrillation (AA vs 4F-PCC, 21 [75%] vs 13 [81%], $p=1.00$) followed by venous thromboembolism (AA vs 4F-PCC, 6 [21%] vs 3 [19%], $p=1.00$). There was no difference between groups with regard to type of bleed, majority of patients had spontaneous IPH (AA vs 4F-PCC, 13 [46%] vs 6 [38%], p = 0.20) followed by traumatic multicompartmental bleed (AA vs 4F-PCC, 7 [25%] vs 5 [31%], $p=0.20$). More patients in the AA group (11 [39%]) received concomitant antiplatelet therapy at baseline compared to 4F-PCC (1 [6%]), $p=0.03$. For patients with IPH, there was no significant difference in hematoma volume at baseline between groups (AA vs 4F-PCC, 8.5 mL [5.8–23] vs 11 mL [8.3–46.6], $p=0.22$). Further information regarding treatment characteristics is included in Supplemental Appendix Table 1.

Hemostatic Efficacy and Safety Outcomes

We found no significant differences when evaluating our primary and secondary outcomes (Table 2). When considering all hemorrhages, there was no significant difference in the proportion of patients with stable neuroimaging assessment between AA and 4F-PCC at 6 h (21 [78%] vs 10 [71%], $p=0.71$) and 24 h (15 [88%] vs 6 [60%], $p=0.15$, respectively). These results remained non-significant after adjusting for age and sex ($p=0.62$). In the subgroup of patients with spontaneous IPH, there was no significant difference in the proportion of patients with stable neuroimaging assessment between AA and 4F-PCC at 6 h (13 [87%] vs 4 [100%], $p=1$) and 24 h (7 [87%] vs 4 [100%], $p=1$, respectively). Additionally, there was no difference in the degree of achieved hemostasis based on hematoma volume between AA and 4F-PCC at 6 h (9.3 mL [6.9–26.4] vs 10 mL [9.4–22.2], adjusted $p=0.997$) and 24 h (9.2 mL [6.1–18.8] vs 9.9 [9.4–21.1], adjusted $p=1$). The number of patients with good outcome upon discharge in the AA and 4F-PCC groups was 10 (36%) and 6 (38%), respectively ($p=0.81$). The incidence of thrombotic events was similar in the AA and 4F-PCC groups (2 [7%] vs. 0), $p=0.53$.

Discussion

In this single-center, observational study, AA and 4F-PCC for reversal of oral FXi in patients with ICH were evaluated. We included both spontaneous and traumatic intraparenchymal, subarachnoid and subdural hemorrhages. We evaluated the stability of the intracranial bleed in subsequent head CTs, the functional outcome of these patients upon discharge from the hospital and the incidence of thrombotic events during the corresponding admission. We did not find any significant differences between the AA and 4F-PCC groups in the stability of their intracranial bleed in subsequent imaging, mRS scores at hospital discharge and the incidence of thrombotic events.

Oral FXis have been associated with major and fatal bleeding events, including ICH. In randomized controlled trials, both rivaroxaban and apixaban have been associated with ICH at rates that range from 0.1 to 4% [12–15]. For patients at imminent risk of death from bleeding associated with oral FXi anticoagulation, expert opinion recommends using either 4F-PCC or AA to

Table 1 Baseline characteristics of all included patients

	Andexanet alfa N = 28	4F-PCC N = 16	*p*
Age (years)	78 [70–87]	80 [74–84]	0.88
Gender, female	11 (39)	5 (31)	0.84
Race			
African American	2 (7)	1 (6)	0.84
White or Caucasian	24 (86)	13 (81)	
Patient refused/unknown	2 (7)	2 (13)	
BMI (kg/m^2)	28 [22–44]	28 [26–33]	0.94
Baseline SrCr (mg/dL)	1.1 [0.8–1.3]	0.91 [0.6–1.1]	0.17
GCS on admission	14 [11–15]	14 [7–15]	0.65
Past medical history			
Atrial fibrillation	20 (71)	10 (62)	0.74
Myocardial infarction	8 (29)	1 (6)	0.12
Stroke	8 (29)	1 (6)	0.12
Deep venous thrombosis	4 (14)	2 (12)	1.00
Pulmonary embolism	5 (18)	2 (12)	1.00
Heart failure	7 (25)	2 (12)	0.45
Diabetes mellitus	9 (32)	2 (12)	0.28
Coronary artery disease	5 (18)	1 (6)	0.40
Concomitant medication			
Aspirin	11 (39)	1 (6)	0.03
Clopidogrel	2 (7)	0 (0)	0.53
Anticoagulation indication			
Atrial fibrillation/flutter	21 (75)	13 (81)	1.00
Deep venous thrombosis	6 (21)	3 (19)	
Other	1 (4)	0 (0)	
Apixaban	19 (68)	12 (75)	0.74
5 mg twice daily	14	11	0.36
2.5 mg twice daily	5	1	
Rivaroxaban	9 (32)	4 (25)	0.74
20 mg daily	4	4	0.30
15 mg daily	4	0	
Dose unknown	1	0	
Hemorrhage type			
Spontaneous ICH	20 (71)	8 (50)	0.20
IPH with or without IVH	13 (46)	6 (38)	
IVH without IPH	2 (7)	0	
SAH	2 (7)	0	
Hemorrhagic conversion of ischemic stroke	1 (3.6)	1 (6)	
SDH	1 (3.6)	0	
Hemorrhagic tumor	1 (3.6)	1 (6)	
Traumatic ICH	8 (29)	8 (50)	
Multicompartmental hemorrhage	7 (25)	5 (31)	
SDH	0	3 (19)	
Contusions	1 (4)	0	
IPH Hematoma volume (mL)			
Hematoma volume baseline	8.5 [5.8–23]	11 [8.3–46.6]	0.22

Nominal data presented as *n* (%) and continuous data as median [IQR]

BMI body mass index, *GCS* Glasgow coma scale, *IPH* intraparenchymal hemorrhage, *IVH* intraventricular hemorrhage, *SAH* subarachnoid hemorrhage, *SDH* subdural hematoma, *SrCr* serum creatinine

Table 2 Outcomes for all patients included

	Andexanet alfa N = 28	4F-PCC N = 16	*p*	*P* adjusted
CT scan stability				
All included patients				
Stable CT scan at 6 h[a]	21 (78)	10 (71)	0.71	0.62
Stable CT scan at 24 h[b]	15 (88)	6 (60)	0.15	0.10
Spontaneous IPH only				
Stable CT scan at 6 h[c]	13 (87)	4 (100)	1.00	0.91
Stable CT scan at 24 h[d]	7 (87)	4 (100)	1.00	0.74
Spontaneous IPH Hematoma volume (mL)				
Hematoma volume at 6 h post-reversal[c]	9.3 [6.9–26.4]	10 [9.4–22.1]	0.67	0.997
Hematoma volume at 24 h post-reversal[d]	9.2 [6.1–18.8]	9.9 [9.4–21.1]	0.57	1
Unstable CT scan at 24 h[b]				
Non-traumatic ICH				
IVH without IPH	1	0	1	
Traumatic ICH				
SDH	0	1	0.242	
Multicompartment bleed	1	3		
Good outcome (mRS < = 3) on discharge	10 (36)	6 (38)	1	0.81
Mortality				
Death/hospice on discharge	11 (39)	6 (38)	1	0.86
Length of stay				
Hospital LOS	7 [4–15]	6 [2–11]	0.20	
ICU LOS	2 [1–4]	4 [1–8]	0.38	
VTE events				
Deep venous thrombosis on discharge	2 (7)	0 (0)	0.53	
Disposition				
ARF	5 (18)	1 (6)	0.71	
Dead/hospice	11 (39)	6 (38)		
Home	6 (21)	4 (25)		
SNF	6 (21)	5 (31)		

Nominal data presented as *n* (%) and continuous data as median [IQR]

ARF acute rehab facility, *CT* computed tomography *ICU* intensive care unit, *IPH* intraparenchymal hemorrhage, *LOS* length of stay, *mRS* Modified Rankin Score, *SNF* skilled nurse facility, *VTE* venous thromboembolic

[a] Evaluable CT scans AA = 27, 4F-PCC = 14

[b] Evaluable CT scans AA = 17, 4F-PCC = 10

[c] Evaluable CT scans AA = 15, 4F-PCC = 4

[d] Evaluable CT scans AA = 8, 4F-PCC = 4

reverse the anticoagulation effect [3, 16]. Unfortunately, the field lacks evidence from observational or experimental studies to select the best reversal approach to pursue in this challenging clinical scenarios. In this study, we found no difference in hemostasis, defined as a stable amount of blood in subsequent head CTs, when comparing AA and 4F-PCC at both 6 and 24 h post-reversal. In line with these neuroimaging results, both groups had a similar distribution of functional outcomes upon discharge, as evaluated by the mRS. These findings are consistent with the results of prior studies that separately evaluated these two reversal strategies, finding 82% adequate hemostasis achieved in AA studies [5] and 75 to 82% adequate hemostasis when using 4F-PCC [7, 17]. Similarly, in an observational, retrospective assessment of efficacy, safety and cost of 4FPCC in patients with oral FXi-related bleeding, Smith and colleagues reported an effective hemostasis rate (80.6%) in recipients of 4F-PCC and no thrombotic events [18]. A recent single-center retrospective case series of 29 IPH patients by Barra and colleagues reported a higher good or excellent hemostatic effectiveness at around 24 h in AA group (88.9%) compared to the 4FPCC group (60%) [19]. However, patients in the 4FPCC group had a lower Glasgow Coma

Scale (GCS) on admission compared to the AA group (10 [6–13] vs 15 [14–15]) [19]. In our included patients with similar GCS scores on admission, we report similar hemostasis effectiveness between AA (87%) and 4FPCC (100%) in our spontaneous IPH patients at 24 h.

Beyond the hemostatic efficacy of AA and 4F-PCC in the setting of an ICH, the incidence of adverse events constitutes another important factor to consider when making clinical decisions about their use. Among all possible adverse effects, the occurrence of thrombotic events is especially important given the inherent procoagulant effect of these interventions. From this perspective, two patients in the AA group (7%) and none in the 4F-PCC group sustained in-hospital thrombotic events. A recently published study comparing the incidence of thrombotic events from multiple studies reported a higher calculated 30-day cumulative incidence of thrombotic events in AA (10%) in comparison with 4F-PCC (6%) [20]. However, this study was not focused on the reversal of FXi in the specific setting of ICH.

When comparing the results of our single-center observational study to previously reported studies, it is important to take into consideration the variability in treatment patterns, the mechanism of intracranial hemorrhages and baseline severity of illness, including baseline GCS and hematoma volume of IPH. In our study, more patients in the AA group (39%) received concomitant antiplatelet therapy at baseline compared to 4F-PCC (6%). While the risk of ICH in the setting of antiplatelet monotherapy is uncertain, concomitant antiplatelet and anticoagulant therapy may certainly confound the reversal effects noted. The most important limitation of our study is its limited sample size. It is possible that some of our findings represent false-negative results triggered by a limited statistical power to detect underlying differences between the two evaluated groups. Of note, the point estimates for the proportions of patients with stable CT scans at 24 h were different in AA and 4F-PCC groups (88% vs. 60%, respectively), although this difference did not reach statistical significance ($p = 0.15$). This 28% difference in CT stability should be assessed further by follow-up studies evaluating larger numbers of ICH patients. However, multi-institutional (and perhaps international) collaborations will be needed to achieve these larger sample sizes, as the occurrence of oral FXi-related ICH is a relatively rare event.

Conclusion

We found no significant difference in the degree of achieved hemostasis based on CT stability, functional outcomes at discharge and thrombotic events during admission when comparing AA and 4F-PCC for the reversal of oral FXi in the setting of ICH. Large observational and randomized studies comparing the efficacy and safety of AA and 4F-PCC in patients with acute intracranial hemorrhage are needed.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-020-01161-5) contains supplementary material, which is available to authorized users.

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None.

Author contributions
AAA, MAA, KAO, GJF conceived the study design and methodology. All authors had input on study design and execution. AAA, MAA, KAO, SCB, FK, AAE contributed to data collection. SCB, FK, AAE reviewed radiographic images. JNA performed data analysis. AAA, MAA, KAO, JNA, GJF contributed to preparing the manuscript. All authors critically revised the manuscript and approved the manuscript in its final form.

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Conflict of interest
The authors declare that they have no conflict of interest.

Ethical Approval/Informed Consent
All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Yale New Haven Hospital Institutional Review Board and was exempted for minimal risk status.

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