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NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Impact of Factor Xa Inhibitor Reversal with Prothrombin Complex Concentrate in Patients with Traumatic Brain Injuries

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Abstract

Background: Anticoagulant use prior to trauma has been associated with increased incidence of traumatic brain injury (TBI), intracranial hemorrhage (ICH) progression, and mortality. Prothrombin complex concentrates (PCCs) are commonly used as off-label treatments for factor Xa inhibitor-associated life-threatening hemorrhage. At this time, there is no consensus regarding appropriate indication, target dose, or outcomes of PCC administration in patients presenting with traumatic ICH. This study seeks to evaluate the impact of reversal with PCC on hemorrhage progression and outcomes in patients with TBI on preinjury factor Xa inhibitors.

Methods: This single-center retrospective cohort study included patients ≥ 18 years presenting with an acute TBI of any severity on apixaban or rivaroxaban from September 1, 2016, to September 1, 2019. Patients were grouped on the basis of receipt of PCCs for reversal (i.e., reversal or no reversal). Exclusion criteria included spontaneous ICH or known coagulopathy. Propensity score matching was conducted with the following variables: age, Abbreviated Injury Scale (head) score, and Charlson Comorbidity Index score. The primary outcome was hemorrhage stability within 48 h. Secondary outcomes included degree of hemorrhage progression, in-hospital mortality, discharge disposition, and incidence of thromboembolic events.

Results: Of the 115 patients meeting inclusion criteria, 84 were included in the propensity score matched data set. Baseline characteristics, comorbidities, and TBI severity were similar. The majority of patients in the reversal group (35 [83.3%]) and the no reversal (NR) group (40 [95.2%]) experienced a mild TBI (admission Glasgow Coma Scale score of 14 to 15). In the reversal group, patients received 34.3 units/kg activated PCC, 30.5 units/kg four-factor PCC, or 54.9 units/kg four-factor PCC and activated PCC on average. There was no difference observed in the incidence of hemorrhage progression (10.8% NR vs. 15.0% reversal; $p = 0.739$) or in median change in ICH volume (0 mL NR vs. 1 mL reversal; $p = 0.2199$) between groups. Additionally, reversal did not affect in-hospital mortality (3 [7.1%] NR vs. 4 [9.5%] reversal; $p > 0.999$). One patient in the reversal group developed a deep vein thrombosis (DVT) during the hospitalization; however, this did not result in a statistically significant difference in the occurrence of DVT ($p > 0.999$).

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Conclusions: This study demonstrated that PCC used for the treatment of factor Xa inhibitor-associated ICH related to mild TBI did not significantly impact the incidence or degree of hemorrhage progression, and PCC treatment did not result in increased thromboembolic events.

Keywords: Prothrombin complex concentrate, Factor Xa inhibitor, Traumatic brain injury, Trauma

Introduction

Unintentional falls, particularly in the elderly, are a leading cause of traumatic brain injury (TBI)-related hospitalizations and mortality in the United States [1]. Anticoagulant use prior to injury has been associated with an increased incidence of TBI, intracranial hemorrhage (ICH) progression, and mortality [2]. In addition, as compared with patients who are not receiving anticoagulant therapy, patients who receive anticoagulants prior to a TBI are more likely to have poor functional outcomes at discharge and are less likely to be discharged home [2].

Because of their reliable efficacy, minimal monitoring, and improved safety profile, factor Xa inhibitors have become preferred agents for the prevention of stroke in patients with nonvalvular atrial fibrillation [2]. Although coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa; Alexion Pharmaceuticals, Inc., Boston, MA) is a US Food and Drug Administration-approved agent for the reversal of apixaban and rivaroxaban, prothrombin complex concentrates (PCCs) are commonly used off-label treatments for factor Xa inhibitor-associated life-threatening hemorrhage. Two of the most commonly used PCCs are four-factor PCC (4F-PCC) and activated PCC (aPCC). In the United States, the only commercially available 4F-PCC is Kcentra (CSL Behring, King of Prussia, PA) and the only available aPCC is FEIBA (Takeda Pharmaceutical Company Limited, Lexington, MA). The use of 4F-PCC has been previously described for the treatment of factor Xa inhibitor-associated bleeding [3, 4]. In a study by Panos et al. [5], 4F-PCC was effective at achieving good or excellent hemostasis with few thrombotic events when used for the treatment of apixaban- or rivaroxaban-associated ICH. Similar results have been seen with aPCC [6–8]. In addition, the Neurocritical Care Society guidelines suggest 4F-PCC or aPCC at 50 units/kg for factor Xa inhibitor reversal in spontaneous ICH [9].

Despite growing evidence concerning the use of PCC for the treatment of spontaneous ICH, there is no consensus regarding appropriate indication, target dose, or anticipated effects of PCC administration for factor Xa inhibitor reversal in patients presenting with a traumatic ICH. The purpose of our study was to describe the effects of PCC as treatment of factor Xa inhibitor-associated intracerebral hemorrhage in patients with TBI.

Methods

This was a retrospective cohort study of patients who were taking a preinjury factor Xa inhibitor and presented with an acute TBI to a tertiary academic medical center between September 1, 2016, and September 1, 2019. This study was conducted at a 700-bed academic medical center and level I trauma center in the southeastern United States, and it was approved by the local institutional review board with waiver of consent. Patients were identified from the institutional Trauma Quality Improvement Program database and screened for inclusion in the study on the basis of the following criteria: age ≥ 18 years, presenting with an acute TBI of any severity, and taking apixaban or rivaroxaban prior to injury. Acute TBI was defined as radiographic evidence of ICH secondary to head trauma and/or treatment via the institutional TBI pathway. Factor Xa inhibitor use was identified via documented home medication list, pharmacy record, refill history, prescription bottles, and/or patient or family member report. Patients with a spontaneous ICH or known coagulopathy were excluded. Included patients were grouped into reversal or no reversal (NR) groups. The reversal group was defined as any included patent who received either aPCC (FEIBA; Takeda Pharmaceutical Company Limited), 4F-PCC (Kcentra; CSL Behring), or both aPCC and 4F-PCC. All other included patients were in the NR group.

Baseline demographics, including age, sex, race, weight, comorbidities, anticoagulant and antiplatelet use, time from last factor Xa inhibitor dose, factor Xa inhibitor indication, source of admission (i.e., transfer or initial presentation), need for mechanical ventilation, and injury characteristics, were collected at the time of admission. Admission Glasgow Coma Scale (GCS) scores, injury severity scores, and Abbreviated Injury Scale scores were collected to characterize severity of illness. Radiographic findings (type of hemorrhage, presence and size of midline shift, progression of hemorrhage, and intracerebral hemorrhage size and change in size) were classified according to radiology reports and were verified by the study investigator (JHG). Discharge disposition was taken directly from the medical record and classified as either in-hospital mortality, home, home with services, long-term care facility, skilled nursing facility, or other. Data were collected from the electronic medical record using a secure standardized case report form via

Research Electronic Data Capture and hosted on secure internal servers. Research Electronic Data Capture is a secure Web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources [10, 11].

The primary outcome of hemorrhage stability was defined as no new or worsening hemorrhage identified on repeat head computed tomography (CT) scans within 48 h of admission. Hemorrhage stability was determined through evaluation of radiologist reports and confirmed through inspection of scans by JHG. If multiple head CT scans were obtained during the 48 h following admission, the initial and next head CT scan was used for evaluation of this outcome. If the patient had a neurosurgical procedure between the initial head CT scan and follow-up scan, this patient was not included in the hemorrhage expansion calculation. Secondary outcomes included evaluating the degree of hemorrhage progression from baseline, in-hospital mortality, discharge disposition, intensive care unit length of stay, and incidence of thromboembolic events during hospitalization. Additionally, we sought to identify if reversal was associated with a good outcome, which was defined as discharge to home or inpatient rehabilitation.

Continuous variables were evaluated for normality through a holistic evaluation of the Shapiro–Wilk test, the Kolmogorov–Smirnov test, histograms, and Q–Q plots. Continuous numeric variables found to have a normal distribution were presented as mean and standard deviation. Between-group comparisons were made with a *t*-test. If the variable's distribution violated the assumption of normality, it was presented as median and interquartile range. Between group comparisons of such variables were made with a Mann–Whitney *U*-test. Categorical variables, reported as count and proportion of group, were analyzed using χ^2 or Fisher's exact test, as appropriate.

Propensity score matching of the included cohort was conducted. Matching variables included age, Abbreviated Injury Scale (head) score, and Charlson Comorbidity Index score. The matching was conducted using a greedy nearest neighbor 1:1 matching method with a caliper of 0.25. All statistical analyses were conducted using SAS (version 9.4 [TS1M4]; SAS Institute, Inc., Cary, NC).

Results

Of the 593 patients screened for inclusion, 478 were excluded because there was no evidence of an acute TBI, they were not taking apixaban or rivaroxaban, or they had a nontraumatic ICH (Fig. 1). Eighty-four of the 115 patients (demographic information for the unmatched cohort is in Table 1) who met inclusion criteria were included in the propensity score matched data set. Of those 84 patients included in the propensity score matched cohort, 42 were in the reversal group (38 received aPCC, 2 received 4F-PCC, and 2 received both) and 42 were in the NR group. Baseline characteristics and comorbidities were similar between groups (Table 2). The majority of patients in the reversal group (35 [83.3%]) and the NR group (40 [95.2%]) experienced a mild TBI (admission GCS score of 14 to 15), and two (4.8%) patients in each group experienced a severe TBI (admission GCS score of 8 or less). Atrial fibrillation was the most common indication for factor Xa inhibitor therapy, with 34 (81%) in the NR group and 33 (78.6%) in the reversal group reporting this indication. In addition, apixaban was the most commonly used factor Xa inhibitor, with 31 (73.8%) in the NR group and 27 (64.3%) in the reversal group reporting it as their prior-to-admission prescribed anticoagulant. In patients with a known time from last dose of anticoagulation (reversal 45.3%, NR 50%), 17 (41.5%) in the NR group and 20 (48.8%) in the reversal group reported having taken it within 24 h of admission.

There was no significant difference in the primary mechanisms of injury ($p > 0.999$). The most prevalent mechanisms of injury were fall from standing (35 [83.3%] NR vs. 35 [83.3%] reversal) and motor vehicle collision (4 [9.5%] NR vs. 4 [9.5%] reversal). As compared with the NR group, a higher incidence of mechanical ventilation was observed in the reversal group (7 [16.7%] vs. 3 [7.1%]), but this did not reach statistical significance ($p = 0.1778$). However, the median intensive care unit length of stay was significantly longer in the reversal group (2 [0–3] vs. 2 [1–3] days; $p = 0.0392$).

As shown in Table 2, baseline hemorrhage classifications included subdural (61.9% NR vs. 71% reversal), subarachnoid (47.6% NR vs. 38.2% reversal), intraparenchymal (9.5% NR vs. 19.1% reversal), intraventricular (4.8% NR vs. 9.5% reversal), and epidural (2.4% NR vs. 4.8% reversal). Although not statistically significant, a higher incidence of midline shift was observed in the reversal group (9.5% NR vs. 23.8% reversal; $p = 0.79$). Management of TBI was consistent, with few patients receiving hyperosmolar therapy (1 [2.4%] NR vs. 2 [4.8%] reversal) or neurosurgical intervention (1 [2.4%] NR vs. 4 [9.5%] reversal) with craniotomy or burr holes. No intracranial pressure monitors or external ventricular devices were placed in either group.

Of the 82 matched patients, 77 patients had at least one repeat head CT scan within 48 h of admission: 40

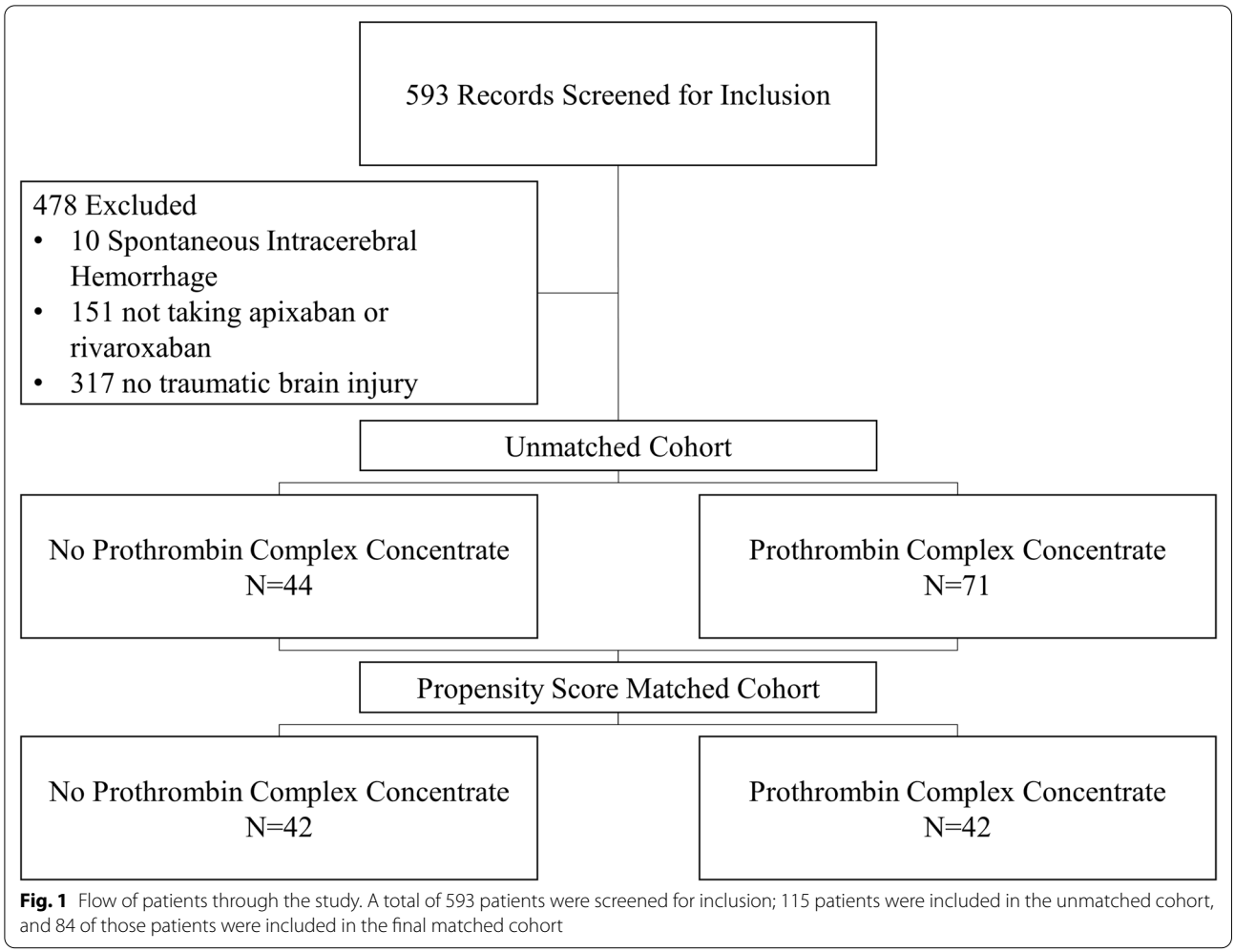

Fig. 1 Flow of patients through the study. A total of 593 patients were screened for inclusion; 115 patients were included in the unmatched cohort, and 84 of those patients were included in the final matched cohort

patients in the reversal group and 37 patients in the NR group. The median time to repeat head CT scan was not statistically different when comparing the NR and reversal groups (8.9 [5.9–12.8] vs. 7.1 [4.4–10.2] hours; $p=0.1150$). There was no difference observed in the incidence of hemorrhage progression (10.8% NR vs. 15.0% reversal; $p=0.739$) or in the median change in ICH volume (0 [0–0] mL NR vs. 1 [0–1] mL reversal; $p=0.2199$) between groups. Additionally, the use of reversal did not affect in-hospital mortality (3 [7.1%] NR vs. 4 [9.5%] reversal; $p>0.999$) or discharge disposition (Table 3). When comparing those who did not receive reversal with those who did, there was no difference in the proportion of patients who had a good outcome (25 [59.5%] NR vs. 19 [45.2%] reversal; $p=0.189$), which was defined as patients with a discharge disposition of home or inpatient rehabilitation.

Among patients in the reversal group, 38 (90.5%) received aPCC (FEIBA; Takeda Pharmaceutical Company Limited), 2 (4.8%) received 4F-PCC (Kcentra; CSL Behring), and 2 (4.8%) received both (Table 4) within 1.75 h (2.25) of admission on average. If given alone, the mean dose of aPCC was 34.3 units/kg (13.6 units/kg) and the mean dose of 4F-PCC was 30.5 units/kg (15.3 units/kg); however, a higher total dose was observed in patients who received both aPCC and 4F-PCC (54.9 units/kg [23.4 units/kg]). Pharmacologic deep vein thrombosis (DVT) prophylaxis was initiated during the hospital stay in approximately half of the patients in both groups (19 [45.2%] NR vs. 24 [57.1%] reversal; $p=0.275$). One patient in the reversal group (patient received aPCC) developed a DVT during the hospitalization; however, this did not result in a statistically significant difference in the occurrence of DVT ($p>0.999$).

Discussion

This study demonstrated that PCC used for the treatment of factor Xa inhibitor-associated ICH related to mild TBI did not significantly impact the incidence or degree of hemorrhage progression, and PCC treatment did not

Table 1 Unmatched patient demographics

Variable	No reversal ($n=44$)	Reversal ($n=71$)	p value
Age, years, mean (SD)	78.5 (7.7)	76.3 (10.6)	0.1969
Female sex, *n* (%)	26 (59.1)	37 (52.1)	0.4649
Black race, *n* (%)	1 (2.3)	3 (4.2)	> 0.05
Actual body weight, kg, mean (SD)	77.5 (17.7)	79.8 (25.8)	0.5720
Admission GCS score, median (IQR)	15 (14–15)	15 (14–15)	0.6086
Injury severity score, median (IQR)	11.5 (9–17)	16 (10–24)	0.0879
AIS (head) score, median (IQR)	3 (2–4)	3 (3–4)	0.0212
Charlson Comorbidity Index score, median (IQR)	2 (1–3)	2 (1–3)	0.7142
Comorbidities, *n* (%)			
Ventricular arrhythmia	0 (0)	1 (1.4)	> 0.999
Coronary artery disease	13 (29.6)	31 (43.7)	0.1301
Ischemic stroke	5 (11.4)	8 (11.3)	< 0.999
Hemorrhagic stroke	0 (0)	0 (0)	–
Hypertension	36 (81.8)	52 (73.2)	0.2915
Active cancer	3 (6.8)	5 (7.0)	> 0.999
Hormone replacement	2 (4.6)	1 (1.4)	0.5572
Substance use disorder	7 (15.9)	12 (16.9)	0.8892
Blunt cerebrovascular injury	1 (2.3)	0 (0)	0.3826
None	6 (13.6)	4 (5.6)	0.1782
Mechanical ventilation, *n* (%)	3 (6.8)	14 (19.7)	0.0582
Mechanism of trauma, *n* (%)			0.8552
Fall from standing	37 (84.1)	61 (85.9)	–
Fall from height	2 (4.6)	3 (4.2)	–
Motor vehicle collision	4 (9.1)	5 (7.0)	–
Knife or gun shot wound	0 (0)	1 (1.4)	–
Other	0 (0)	1 (1.4)	–
Substance use, *n* (%)			
Tobacco	3 (6.8)	9 (12.7)	0.3676
Alcohol	5 (11.4)	6 (8.5)	0.7463
Prescription opioid	0 (0)	1 (1.4)	> 0.999
Prescription benzodiazepines	0 (0)	1 (1.4)	> 0.999
Rivaroxaban, *n* (%)	12 (27.3)	24 (33.8)	0.4630
DOAC indication, n (%)			
Atrial fibrillation	36 (81.8)	51 (71.8)	0.2252
History of DVT	4 (9.1)	20 (28.2)	0.0144
History of PE	2 (4.6)	10 (14.1)	0.1268
VTE prophylaxis	1 (2.3)	0 (0)	0.3826
Other/unknown	3 (6.8)	2 (2.8)	0.3691
Antiplatelet prior to admission, *n* (%)	14 (31.8)	26 (36.6)	0.5993
Hemorrhage type, *n* (%)			
Subdural	26 (59.1)	53 (74.7)	0.0804
Epidural	1 (2.3)	3 (4.2)	> 0.999
Subarachnoid	22 (50.0)	27 (38.0)	0.2070
Intraparenchymal	4 (9.1)	13 (18.3)	0.1758
Intraventricular	2 (4.6)	8 (11.3)	0.3132
Midline shift size ($n=4$ no reversal, $n=24$ reversal), median (IQR)	9 (4.5–17.5)	8 (4–11.5)	0.7941

AIS, Abbreviated Injury Scale, DOAC, direct oral anticoagulant, DVT, deep vein thrombosis, GCS, Glasgow Coma Scale, IQR, interquartile range, PE, Pulmonary embolism, VTE, venous thromboembolism

Table 2 Matched patient demographics

Variable	No reversal ($n=42$)	Reversal ($n=42$)	p value
Age, years, mean (SD)	78.4 (7.8)	76.4 (10.6)	0.3275
Female sex, *n* (%)	24 (57.1%)	23 (54.8%)	0.8260
Black race, *n* (%)	1 (2.4%)	2 (4.8%)	> 0.999
Actual body weight, kg, mean (SD)	78.4 (17.5)	82.4 (27.7)	0.4309
Admission GCS score, median (IQR)	15 (14–15)	15 (14–15)	0.7444
Injury severity score, median (IQR)	13.5 (9–17)	13.5 (10–17)	0.7763
AIS (head) score, median (IQR)	3 (2–4)	3 (3–4)	0.7099
Source of admission			0.1082
Initial presentation	18 (42.9%)	11 (26.2%)	
Transfer from outside facility	24 (57.1%)	31 (73.8%)	
Charlson Comorbidity Index score, median (IQR)	2 (1–3)	2 (1–3)	0.7142
Comorbidities, *n* (%)			
Coronary artery disease	13 (31.0%)	21 (50.0%)	0.0754
Ischemic stroke	4 (9.5%)	6 (14.3%)	0.5004
Hemorrhagic stroke	0 (0%)	0 (0%)	–
Hypertension	34 (81.0%)	30 (71.4%)	0.3055
Mechanical ventilation, *n* (%)	3 (7.1%)	7 (16.7%)	0.1778
Mechanism of trauma, *n* (%)			> 0.999
Fall from standing	35 (83.3%)	35 (83.3%)	
Fall from height	2 (4.8%)	2 (4.8%)	
Motor vehicle collision	4 (9.5%)	4 (9.5%)	
Substance use, *n* (%)	7 (16.7%)	5 (11.9%)	0.5329
Tobacco	3 (7.1%)	4 (9.5%)	> 0.999
Alcohol	5 (11.9%)	2 (4.8%)	0.4326
Rivaroxaban, *n* (%)	11 (26.2%)	15 (35.7%)	0.3451
Factor Xa inhibitor indication, *n* (%)			
Atrial fibrillation	34 (81.0%)	33 (78.6%)	0.7860
History of DVT	4 (9.5%)	10 (23.8%)	0.0790
History of PE	1 (2.4%)	4 (9.5%)	0.3597
VTE prophylaxis	1 (2.4%)	0 (0%)	> 0.999
Other/unknown	3 (7.1%)	1 (2.4%)	0.6158
Time of last factor Xa inhibitor dose, *n* (%)			0.9035
Less than 12 h	9 (21.4%)	10 (23.8%)	
12 to 24 h	8 (19.1%)	10 (23.8%)	
24 to 48 h	2 (4.8%)	1 (2.4%)	
Unknown	23 (54.8%)	21 (50%)	
Antiplatelet prior to admission, *n* (%)	14 (33.3%)	19 (45.2%)	0.2640
Hemorrhage type, *n* (%)			
Subdural	26 (61.9%)	30 (71.4%)	0.3545
Epidural	1 (2.4%)	2 (4.8%)	> 0.999
Subarachnoid	20 (47.6%)	16 (38.2%)	0.3778
Intraparenchymal	4 (9.5%)	8 (19.1%)	0.2123
Intraventricular	2 (4.8%)	4 (9.5%)	0.6758
Midline shift present, *n* (%)	4 (9.5%)	10 (23.8%)	0.0790
Midline shift size, mm, median (IQR)	9 (4.5–17.5)	8 (4–10)	0.8348
Hemorrhage progression, *n* (%)	4/37 (10.8%)	6/40 (15.0%)	0.739
Initial ICH size ($n=20$ no reversal, $n=33$ reversal), mL, median (IQR)	5.5 (3.5–8)	8 (4–12)	0.2514
ICH volume change ($n=20$ no reversal, $n=33$ reversal), mL, median (IQR)	0 (0–1)	1 (0–1)	0.2199

AIS, Abbreviated Injury Scale, DOAC, direct oral anticoagulant, DVT, deep vein thrombosis, GCS, Glasgow Coma Scale, ICH, intracranial hemorrhage, PE, pulmonary embolism, VTE, venous thromboembolism

Table 3 Discharge disposition

Variable, *n* (%)	No reversal (*n* = 42)	Reversal (*n* = 42)	*p* value
In-hospital mortality, *n* (%)	3 (7.1%)	4 (9.5%)	> 0.999
Home, *n* (%)	19 (45.2%)	12 (28.6%)	0.1135
Home with services, *n* (%)	6 (14.3%)	7 (16.7%)	0.7629
Long- term care facility, *n* (%)	0 (0%)	1 (2.4%)	> 0.999
Skilled nursing facility, *n* (%)	13 (31.0%)	18 (42.9%)	0.2582
Other, *n* (%)	1 (2.4%)	0 (0%)	> 0.999

Table 4 Prothrombin complex concentrates dose

Type of reversal	*n* (%) (*N* = 42)	Total dose, units, mean (SD)	Total dose per kg, units/kg, mean (SD)
Activated prothrombin complex concentrates	38 (90.5%)	2650.8 (1224)	34.3 (13.6)
Four-4 factor prothrombin complex concentrates	2 (4.8%)	2243.4 (1063.4)	30.5 (15.3)
Both	2 (4.8%)	6125 (2174)	54.9 (23.4)

result in increased thromboembolic events. Administration of PCC for factor Xa inhibitor reversal is suggested for spontaneous ICH by the Neurocritical Care Society guidelines and is recommended as an alternative to andexanet alfa for critical site or life-threatening bleeding by the American College of Cardiology expert consensus [9, 12]. Although PCC is commonly used in clinical practice for factor Xa inhibitor-associated ICH related to TBI, there is limited guidance on the optimal dose and indication for treatment. This study increases the evidence that the use of PCC is safe for the treatment of factor Xa inhibitor-associated ICH related to TBI even at reduced dosages.

The results of this trial are similar to those of a recent multicenter retrospective cohort study of 433 patients with traumatic or spontaneous ICH that found that 4F-PCC administration exhibited good or excellent hemostatic efficacy in 81.8% of patients with only a 3.8% thrombosis rate [5]. Although the study by Panos and colleagues [5] did not have a comparator group, the proportion of patients with hemorrhage progression was similar to that in the current study. In this study there was no statistical difference in the proportion of patients with ICH progression; 10.8% of patients in the NR group and 15% in the reversal group demonstrated hemorrhage progression, meaning that approximately 85% of the patients in the reversal group did not have hemorrhage progression in this study despite treatment with PCC. In another study by Dybdahl and colleagues [13], 4F-PCC was compared with supportive care in patients with TBI; however, because it only included patients with an international normalized ratio (INR) of 1.5 or greater, patients with additional coagulopathies might have been preferentially included in the trial. There was no observed difference in mortality, functional recovery, or thrombosis only after accounting for higher baseline injury severity scores in the reversal group [13]. This study corroborated the findings of Dybdahl and colleagues [13]; we found no difference in the incidence of hemorrhage progression or in-hospital mortality with the administration of PCC for factor Xa inhibitor-associated ICH related to TBI. Although PCC is thought to be thrombogenic, we observed no increase in the incidence of venous thromboembolism. One patient in the reversal group developed a DVT during hospitalization. This finding may be clinically meaningful given that most patients received aPCC and only about half received pharmacologic DVT prophylaxis during their hospitalization.

This study was not without limitations. A major limitation of this study is the relatively small sample size. A total of 77 patients of the included 84 had information concerning the primary outcome. In addition, some secondary outcomes had relatively large numeric differences when comparing groups. Although not statistically significant, this may represent a type II error and may indicate that a sicker subset of patients received reversal despite the use of propensity score matching. Because our patient population primarily consisted of those with mild TBIs, we cannot rule out that PCC administration may be beneficial in patients with moderate or severe TBIs. This study was conducted at a single academic medical center, limiting external validity; however, our findings are likely still applicable to similar institutions that admit patients with TBI with preinjury factor Xa inhibitor usage. At the time of this study, only aPCC was on formulary at our institution. Additionally, our institutional anticoagulant reversal guideline does not require objective monitoring of hemostasis for factor Xa inhibitor reversal, such as anti-factor Xa levels or thromboelastography; therefore,

we do not know if PCC actually reversed their coagulopathy secondary to factor Xa inhibitor usage or if it caused hypercoagulability. Because of the retrospective nature of the study, the use of reversal could have been affected by selection bias based on provider preference or illness severity. However, our study used propensity score matching to account for potential differences between groups at baseline and to ensure they were well balanced.

Conclusions

Although we found no difference in hemorrhage progression or in-hospital mortality with the administration of PCC for factor Xa inhibitor-associated ICH related to mild TBI, this study also found no significant increase in the incidence of thromboembolic events. This pragmatic study was unable to identify any impact of PCC administration on hemorrhage stability; however, this factor Xa inhibitor reversal strategy demonstrated safety when compared with supportive care in this patient population.

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Author contributions
Authors GEC, LAH, JCM, JHG, and ASR contributed to the initial design, data collection, drafting, and review of the final manuscript. Authors ASR and GEC were also involved with data analysis.

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Conflicts of interest
Author JCM is currently employed by Amgen. At the time of study development and conduct, JCM was not affiliated with Amgen. Amgen does not have a role in this project.

Ethical approval/informed consent
This project is institutional review board approved and complies with ethical guidelines.

Publisher's Note

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References

1. Centers for Disease Control and Prevention. Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2014: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2019. https://www.cdc.gov/traumaticbraininjury/pdf/TBI-Surveillance-Report-FINAL_508.pdf.
2. Scotti P, Seguin C, Lo BWY, de Guise E, Troquet JM, Marcoux J. Antithrombotic agents and traumatic brain injury in the elderly population: hemorrhage patterns and outcomes. J Neurosurg 2019:1–10.
3. Allison TA, Lin PJ, Gass JA, et al. Evaluation of the use of low-dose 4-factor prothrombin complex concentrate in the reversal of direct oral anticoagulants in bleeding patients. J Intensive Care Med. 2020;35(9):903–8.
4. Sheikh-Taha M. Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate. Intern Emerg Med. 2019;14(2):265–9.
5. Panos NG, Cook AM, John S, Jones GM, Neurocritical Care Society Pharmacy Study. Factor Xa inhibitor-related intracranial hemorrhage: results from a multicenter, observational cohort receiving prothrombin complex concentrates. Circulation 2020;141(21):1681–9.
6. Castillo R, Chan A, Atallah S, et al. Treatment of adults with intracranial hemorrhage on apixaban or rivaroxaban with prothrombin complex concentrate products. J Thromb Thrombolysis. 2021;51(1):151–8.
7. Engelbart JM, Zepeski A, Galet C, Policeni B, Skeete DA, Faine BA. Safety and effectiveness of Factor Eight Inhibitor Bypassing Activity for direct oral anticoagulant-related hemorrhage reversal. Am J Emerg Med. 2019;37(2):214–9.
8. Sheikh-Taha M, Crawley RM. Reversal of apixaban and rivaroxaban using activated prothrombin complex concentrates in patients with major bleeding. Am J Cardiovasc Drugs. 2020;20(3):295–9.
9. Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the neurocritical care society and society of critical care medicine. Neurocrit care. 2016;24(1):6–46.
10. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.
12. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution set oversight committee. J Am Coll Cardiol. 2020;76(5):594–622.
13. Dybdahl D, Walliser G, Chance Spalding M, Pershing M, Kincaid M. Four-factor prothrombin complex concentrate for the reversal of factor Xa inhibitors for traumatic intracranial hemorrhage. Am J Emerg Med. 2019;37(10):1907–11.