Comparison of outcomes in patients with intracranial hemorrhage on factor Xa inhibitors versus vitamin K antagonists treated with 4-factor prothrombin complex concentrate

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ABSTRACT

The relative clinical efficacy of 4-factor prothrombin complex concentrate (4F-PCC) in oral anticoagulant-associated intracranial hemorrhage is unknown, especially for factor Xa-inhibiting anticoagulants. We report short-term outcomes of patients with oral anticoagulant-associated intracranial hemorrhage on vitamin K antagonists and factor Xa inhibitors who were treated with 4F-PCC. This multicenter, observational study involved patients presenting to the emergency department in nine hospitals in an integrated health care delivery system in Texas between July 2013 and December 2015. Forty-two patients diagnosed with oral anticoagulant-associated intracranial hemorrhage—24 taking a vitamin K antagonist and 14 taking a factor Xa inhibitor—were treated with 4F-PCC as part of usual care. Study patients had similar baseline demographics, with the exception of suspected etiology of hemorrhage. Outcomes of the vitamin K antagonist group were similar to those of the factor Xa inhibitor group, with no significant differences in overall in-hospital mortality (32.1% vs 14.2%, respectively), length of stay, or rates of hemorrhagic expansion, thromboembolism, or discharge to home. In conclusion, this small sample of patients with oral factor Xa inhibitor and vitamin K antagonist-associated intracranial hemorrhage treated with 4F-PCC had similar mortality and neurological outcomes, with no venous thromboembolic events.

KEYWORDS 4-factor prothrombin complex concentrate; emergent reversal; fresh frozen plasma; intracranial hemorrhage; oral anticoagulation

Current guidelines recommend the use of 4-factor prothrombin complex concentrate (4F-PCC) over fresh frozen plasma for the emergent correction of coagulopathy in patients with vitamin K antagonist (VKA)-associated major bleeding.¹ Based upon animal studies, *ex vivo* trials, and trials in healthy human volunteers, it appears that 4F-PCC may have similar efficacy in correcting laboratory measurements of coagulopathy associated with the factor Xa inhibitors apixaban and rivaroxaban.^{2,3} Although at this time there are no Food and Drug Administration–approved agents for reversal of coagulopathy from factor Xa inhibitors, in our health care system, 4F-PCC is used off label at physician discretion for intracranial hemorrhage (ICH) in patients taking factor Xa inhibitors. The objective of this study was to compare outcomes, including mortality rates, of patients with factor Xa inhibitor anticoagulant-associated ICH who were treated with 4F-PCC to those of similar patients with VKA-associated

ICH. A secondary aim was to evaluate the incidence of hematoma expansion, venous thrombotic complications, and length of stay in the hospital and intensive care unit (ICU).

METHODS

Patients were included as part of a multicenter registry of patients with oral anticoagulant-associated ICH admitted to 9 hospitals in our system from January 2013 to December 2015. The protocol for the registry was approved by the Baylor Scott and White Health institutional review board.

The system's pharmacy utilization database and electronic health record order codes were queried to identify patients who received 4F-PCC. Patients were included in the study if they were 18 years or older and were admitted with traumatic or nontraumatic oral anticoagulant-associated ICH. Patients who received 4F-PCC without traumatic or nontraumatic oral anticoagulant-associated ICH were excluded from the study.

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Additionally, patients who were anticoagulated with direct thrombin inhibitors or received alternative coagulation factors or fresh frozen plasma as reversal agents were excluded from the study. All chart abstractions were done by the primary author (SKH) utilizing a standardized form. Chart reviews were then audited by additional authors (KNK, JSG).^{4,5} We considered 4F-PCC to be administered regardless of dose used, although the recommended dose at our institution is 50 units/kg to a maximum of 5000 units for reversal of apixaban and rivaroxaban. We defined oral anticoagulation as requiring documented evidence of prescription for an oral anticoagulant; we did not require proof of when the patient last took an oral anticoagulant, only that the drug was prescribed.

The baseline characteristics collected for both groups included age, gender, weight, height, serum creatinine, and past medical history of stroke and/or coagulopathy. Information on oral anticoagulation was also collected, including medication, indication, dose, dosing regimen, and appropriateness assessed based on the patient's age, indication, and renal function. Initial coagulation parameters were recorded and included initial international normalized ratio, postreversal international normalized ratio, initial activated partial thromboplastin time, postreversal activated partial thromboplastin time, initial prothrombin time, and postreversal prothrombin time. Suspected etiology was categorized as spontaneous or traumatic, based upon physician documentation. Other data collected included time and date of the event as well as time between diagnosis and reversal, whether the patient was transferred from another institution and the institution the patient was admitted to, Glasgow Coma Scale category on presentation, ICH scale, National Institutes of Health Stroke Scale, and withdrawal of treatment and resuscitation status.^{6,7} The Glasgow Coma Scale category, ICH, and National Institutes of Health Stroke Scale were recorded as documented in source records by care providers or based upon extraction of component variables and insertion into published scoring systems. Initial hematoma location, size (estimated as part of standard radiologist assessment using simple ellipsoid measurements), and volume were documented. Treatment initiated, including vitamin K dose and route and 4F-PCC dose, was collected.

Outcome information collected included in-hospital mortality, total hospital and ICU length of stay, evaluation of neurological function at discharge based on disposition, thromboembolic events (myocardial infarction, deep venous thromboembolism, pulmonary embolism, and ischemic stroke), and hemorrhagic expansion. Because death was the unambiguous primary outcome, no interobserver agreement statistic was performed. Secondary outcomes evaluated were postreversal international normalized ratio, activated partial thromboplastin time, and prothrombin time.

All data analyses were performed using JMP 10 (SAS Institute Inc., Cary, NC). Presentation characteristics and demographic data were analyzed using frequencies and percentages for categorical variables such as gender, race, and method of arrival; means and standard deviations were used for

continuous variables. Where appropriate, tests for differences in population characteristics were performed using chi-square analysis or *t* tests.

RESULTS

Of the 61 patients who received 4F-PCC, 42 met the inclusion criteria. Four patients were excluded due to anticoagulation with direct thrombin inhibitor and 15 for receiving fresh frozen plasma. Of the remaining 42 patients who received 4F-PCC, 28 were taking a VKA, and 14 were taking a factor Xa inhibitor. *Table 1* compares demographic and outcomes data. Overall, the two groups were well matched for age, comorbidity, type of hemorrhage, size of hematoma, and initial Glasgow Coma Scale score. However, ICH etiology differed among the two groups. Patients receiving factor Xa inhibitors were more likely to have a spontaneous ICH (85.7% vs 35.7%, $P = 0.002$), whereas those receiving VKA were more likely to have a traumatic ICH (60.7% vs 14.2%, $P = 0.004$). Vitamin K was administered systemically in 25 (89%) VKA patients. The international normalized ratio and prothrombin time were prolonged at diagnosis in both groups and were significantly shortened after 4F-PCC administration in both groups. Mortality was not statistically different, with 9 deaths in the VKA group and 2 in the factor Xa inhibitor group treated with 4F-PCC ($P = 0.21$). Likewise, ICU and hospital lengths of stay and the rate of clinically significant hematoma expansion were similar between groups (*Table 2*). No patients had venous thromboembolic disease within 30 days. The distribution of the discharge disposition (home, rehabilitation, skilled nursing facility, or long-term acute care facility) was similar between groups.

DISCUSSION

This study evaluated the comparative efficacy of 4F-PCC in emergent reversal of factor Xa inhibitors and VKA in the setting of ICH. We found no salient differences in mortality, neurological outcome, or expansion rate of hematoma size. We acknowledge a possible trend toward lower mortality for patients with factor Xa inhibitor-associated ICH (14.2%) compared to VKA-associated ICH (32.1%, $P = 0.21$). Our work adds to the literature, because little evidence has been presented to allow any inference about the efficacy of 4F-PCC in factor Xa inhibitor-associated ICH. The current literature describing the use of 4F-PCC for emergent correction of coagulopathy from factor Xa inhibitors is limited to animal models and healthy humans.^{2,3} Indeed, the evidence used by the American Heart Association/American Stroke Association to recommend the use of 4F-PCC for correction of VKA-associated coagulopathy for ICH was based upon very limited data in patients with ICH.^{1,8,9}

The limitations of this study include a small patient population, uncontrolled design (use of 4F-PCC was at the discretion of the provider), and higher rates of spontaneous ICH vs traumatic ICH in the factor Xa inhibitor group compared to the VKA group. Of interest, in contrast to

Table 1. Comparison of clinical characteristics and outcomes of patients with intracranial hemorrhage

Variable	VKA (n = 28)	Factor Xa inhibitors (n = 14)	P value
Age (years)	73 ± 14	74 ± 8	0.74
Men	10 (35.7%)	6 (42.8%)	0.65 ^a
Body mass (kg)	76 ± 18	79 ± 18	0.56
Creatinine clearance (mL/min)	53 ± 23	65 ± 18	0.056
Prior ischemic stroke	7 (25%)	2 (14.2%)	0.42 ^a
Prior hemorrhagic stroke	2 (7.1%)	0	0.30 ^a
Indication for anticoagulation ^b			
Atrial fibrillation	18	12	0.14 ^a
Venous thromboembolic disease	6	3	1 ^a
Mechanical valve	4	0	0.13 ^a
Factor V Leiden	1	0	0.47 ^a
Cerebrovascular accident	2	2	0.45 ^a
Left ventricular assist device	1	0	0.47 ^a
ICH etiology			
Spontaneous	10 (35.7%)	12 (85.7%)	0.002 ^a
Trauma	17 (60.7%)	2 (14.2%)	0.004 ^a
Conversion	1 (3.5%)	0	0.47 ^a
Hematoma size (mL)	15.89 (45.38)	13.44 (13.72)	0.81
	n = 23	n = 12	
Hematoma volume (mL)	43.65	12.07 (9.08)	0.25
	n = 4	n = 7	
Time from diagnosis to 4F-PCC administration (h)	2.21 (2.07)	6 (13.61)	0.32
Initial Glasgow Coma Scale			
13–15	20 (71%)	11 (79%)	0.61 ^a
9–12	5 (18%)	2 (14%)	0.76 ^a
3–8	3 (11%)	1 (7%)	0.71 ^a
ICH scale (range)	2.2 (1.72)	1.6 (0.89)	0.50
	n = 6	n = 5	
Initial NIH Stroke Scale (range)	10.8 (11.32)	7.2 (5.82)	0.44
	n = 8	n = 10	
Initial INR (sec)	4.35 (3.19)	1.26 (0.26)	<0.001
	n = 28	n = 13	
Repeat INR (sec)	1.37 (0.31)	1.07 (0.08)	<0.001
	n = 26	n = 8	
Initial activated PTT (sec)	35.00 (8.08)	32.39 (5.93)	0.27
	n = 25	n = 12	
Repeat activated PTT (sec)	23.19 (2.78)	29.3 (2.67)	<0.001
	n = 11	n = 7	

(Continued on next column)

Table 1. Comparison of clinical characteristics and outcomes of patients with intracranial hemorrhage (Continued)

Variable	VKA (n = 28)	Factor Xa inhibitors (n = 14)	P value
Kcentra dose (units/kg)			
25	20	2	<0.001 ^a
35	5	2	0.76 ^a
50	3	10	<0.001 ^a

VKA indicates vitamin K antagonist; ICH, intracranial hemorrhage; 4F-PCC, 4-factor prothrombin complex concentrate; NIH, National Institutes of Health; INR, international normalized ratio; PTT, partial thromboplastin time. Unless otherwise indicated, data shown as means and standard deviation.

^aDetermined by chi-square test; all others were determined by *t* test.

^bPatients may have more than one indication.

our study results, spontaneous ICH has been associated with a higher mortality rate than traumatic ICH.¹⁰ Although other baseline characteristics including Glasgow Coma Scale score were similar between the two groups, the lack of a controlled design allows little inference into causation. Nonetheless, the mortality and outcome data and lack of venous thromboembolic complications suggest that 4F-PCC is unlikely to worsen outcomes with factor Xa inhibitor-associated ICH.

In conclusion, our data demonstrate similar mortality and neurological outcomes and no venous thromboembolic events for patients with factor Xa inhibitor- and VKA-associated ICH treated with 4F-PCC. These findings suggest no clear evidence of benefit or harm with 4F-PCC for patients with factor Xa inhibitor-associated ICH.

Table 2. Outcomes in patients treated with 4F-PCC while on VKA or factor Xa inhibitors

Outcome	VKA (n = 28)	Factor Xa inhibitors (n = 14)	P value
In-hospital mortality	9 (32.1%)	2 (14.2%)	0.21
Total length of stay, days: mean (SD)	7 (7.05)	7.06 (3.85)	0.84 ^a
ICU length of stay, days: mean (SD)	4.25 (5.10)	4.43 (3.39)	0.89 ^a
Hemorrhagic expansion	3 (10.7%)	1 (7.14%)	0.71
Thromboembolism	0	0	0
Disposition ^b			
Home	8	6	0.35
Rehabilitation center	8	3	0.61
Skilled nursing facility	4	2	1
Long-term acute care facility	1	1	0.6

4F-PCC indicates 4-factor prothrombin complex concentrate; VKA, vitamin K antagonist; ICU, intensive care unit. Unless otherwise indicated, data shown are *n* or *n* (%).

^aDetermined by *t* test; all others were determined by chi-square test.

^bBased on total number of patients.

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1. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032–2060. doi:10.1161/STR.0000000000000069.
2. Martin AC, Le Bonniec B, Fischer AM, et al. Evaluation of recombinant activated factor VII, prothrombin complex concentrate, and fibrinogen concentrate to reverse apixaban in a rabbit model of bleeding and thrombosis. *Int J Cardiol*. 2013;168:4228–4233. doi:10.1016/j.ijcard.2013.07.152.
3. Marlu R, Hodaj E, Paris A, Albaladejo P, Crackowski JL, Pernod G. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomized crossover ex-vivo study in healthy volunteers. *Thromb Haemost*. 2012;108:217–247.
4. Kaji AH, Schriger D, Green S. Looking through the retrospectroscope: reducing bias in emergency medicine chart review studies. *Ann Emerg Med*. 2014;64:292–298. doi:10.1016/j.annemergmed.2014.03.025.
5. Lowenstein SR. Medical record reviews in emergency medicine: the blessing and the curse. *Ann Emerg Med*. 2005;45:452–455. doi:10.1016/j.annemergmed.2005.01.032.
6. Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score, a simple, reliable grading scale intracerebral hemorrhage. *Stroke*. 2001;32:891–897. doi:10.1161/01.STR.32.4.891.
7. Brott T, Adams HP, Olinger CP, et al. Measurement of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864–870. doi:10.1161/01.STR.20.7.864.
8. Sarode R, Milling TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding. *Circulation*. 2013;128:1234–1243.
9. Tazarourte K, Riou B, Tremey B, Samama CM, Vicaut E, Vigue B. Guideline-concordant administration of prothrombin complex concentrate and vitamin K is associated with decreased mortality in patients with severe bleeding under vitamin K antagonist treatment (EPAHK study). *Crit Care*. 2014;18:R81. doi:10.1186/cc13843.
10. Siddique MS, Gregson BA, Fernandes HM, et al. Comparative study of traumatic and spontaneous intracerebral hemorrhage. *J Neurosurg*. 2002;96:86–89. doi:10.3171/jns.2002.96.1.0086.