A new kid on the block: Outcomes with Kcentra 1 year after approval

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BACKGROUND: As the population ages, more trauma patients are admitted with coagulopathy. Fresh frozen plasma is effective in reversing coagulopathy caused by warfarin; however, it is not appropriate for all patients. Prothrombin complex concentrates (PCCs) are an alternative for patients who require emergent reversal, minimal-volume administration and who have a supratherapeutic international normalized ratio (INR). A four-factor PCC initially approved in Europe is now available in the United States. We sought to review our experience with Kcentra (4F-PCC) in the first year following Food and Drug Administration approval.

METHODS: All trauma patients admitted to an academic Level 1 trauma center between July 15, 2013, and July 15, 2014, who received 4F-PCC for reversal of warfarin-induced coagulopathy were reviewed. 4F-PCC was given as per protocol. Univariate analysis was performed to examine patient demographics, injury characteristics, coagulation studies, 4F-PCC dose, vitamin K use, transfusions, response to reversal, duration of reversal, complications, and mortality.

RESULTS: Twenty-six patients met study criteria. Of these patients, 34.6% were reversed because of intracranial hemorrhage. The mean INR decreased from 5.7 ± 6.1 (range, 1.6–30) to 1.5 ± 0.4 (range, 1.2–2.6) after 4F-PCC administration. One patient (3.8%) received concurrent fresh frozen plasma. For patients with an initial INR greater than 5.0, the mean INR decreased from 12.0 ± 8.2 to 1.6 ± 0.5. Forty-eight hours following 4F-PCC administration, mean INR for all patients remained 1.4 ± 0.4 (range, 1.0–2.6). Of the patients, 80.8% received vitamin K over this period. Fourteen patients had a pre–4F-PCC thromboelastogram; four were hypocoagulable. Two patients had repeat thromboelastograms after 4F-PCC was given, which demonstrated normal coagulation. Of the patients with intracranial hemorrhage, 66.7% showed radiographic progression of the initial insult on post–4F-PCC head computed tomography, while only 11.1% progressed clinically. In-hospital mortality was 0%. There were no thromboembolic complications.

CONCLUSION: 4F-PCC effectively reverses elevated INRs in trauma patients with warfarin-induced coagulopathy, with results lasting more than 48 hours after administration. (*J Trauma Acute Care Surg*. 2015;79: 1004–1008.

LEVEL OF EVIDENCE: Therapeutic study, level V.

KEY WORDS: Prothrombin complex concentrate; warfarin; coagulopathy; intracranial hemorrhage; Kcentra.

Improvements in medical care together with the aging of the "Baby Boom" generation have led to an increasing number of active elderly persons and thus a well-documented rise in the number of geriatric patients admitted to trauma centers in the United States.[1,2] The risk of mortality after trauma rises sharply with increasing age.[3,4] This phenomenon is often complicated by medical comorbidities, including those that require anticoagulation. Warfarin is effective and widely prescribed for stroke prevention in atrial fibrillation as well as for the treatment of venous thromboembolic disease or thrombosis prevention in patients with mechanical heart valves. As recently as 2012, warfarin was the 24th most commonly dispensed prescription in the United States,[5] and the number of prescriptions for anticoagulants as a class continues to rise.[6] Accurate warfarin use remains difficult, however, with therapeutic dosing varying widely between patients based on both genetic factors and a multitude of drug-drug and food-drug interaction, leading to nontherapeutic or supratherapeutic international normalized ratios (INRs) in a significant number of patients.

The standard of care for the reversal of warfarin has long been transfusion of fresh frozen plasma (FFP), which directly replaces deficient clotting factors. Vitamin K (phytonadione) is often given as well, to spur the patient's own production of factors II, VII, IX, and X and provide more long-term anticoagulation reversal. However, effective reversal of therapeutic anticoagulation and treatment of coagulopathy with FFP is often significantly delayed because of the time required to thaw, cross-match, prepare, and transfuse each unit. Transfusion of blood products also carries known risks including infections (i.e., human immunodeficiency virus and hepatitis), transfusion-associated acute lung injury, and transfusion-associated circulatory overload. The last one may be especially problematic in patients with congestive heart failure or chronic renal disease, which are common comorbidities among elderly trauma patients.

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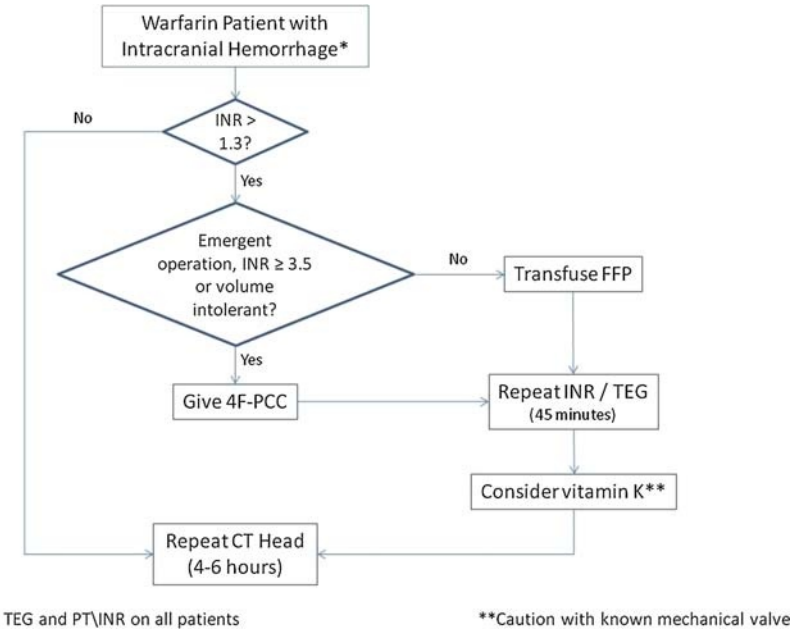

Figure 1. Standardized algorithm for warfarin reversal in trauma patients with ICH.

In addition, FFP is rarely able to fully reverse an abnormal INR, often leaving patients mildly anticoagulated despite ongoing transfusions.[7,8]

Prothrombin complex concentrates (PCCs) have recently emerged as an alternative to FFP for warfarin reversal. PCCs are human plasma-derived concentrates of the vitamin K–dependent clotting factors II, VII, IX, and X. Three-factor forms previously used in the United States contain very little factor VII, while four-factor concentrates (4F-PCC) were initially approved only in Europe. 4F-PCCs have demonstrated the ability to correct an elevated INR within minutes;[9–11] three-factor forms are also efficacious but may require a higher administered dose or the addition of other sources of factor VII to achieve equivalent reversal.[12–15] Both types of PCC are shelf-stable, can be reconstituted quickly, and are transfused in small volumes. Originally marketed in Europe as Beriplex P/N (CSL Behring, Marburg, Germany), the first nonactivated 4F-PCC for use in the United States was approved by the Food and Drug Administration in April of 2013, under the trade name Kcentra (CSL Behring). We sought to describe our first year of experience with Kcentra (4F-PCC) in trauma patients on warfarin.

PATIENTS AND METHODS

A case series with retrospective data collection was assembled following institutional review board approval. Our pharmacy database was queried for all trauma patients admitted to our Level 1 academic center between July 15, 2013, and July 15, 2014, who received 4F-PCC for warfarin reversal. All patients were included, regardless of trauma mechanism, injuries identified, or reason for warfarin reversal. Warfarin use was confirmed based on patient or family reported history. There were no exclusion criteria.

4F-PCC use is guided by a standardized hospital protocol in patients with warfarin-induced coagulopathy and intracranial hemorrhage (ICH) (Fig. 1), while patients with other reasons for warfarin reversal are treated in a patient-specific fashion at the discretion of the attending trauma surgeon. For ICH patients on warfarin, the INR is reversed to a goal of 1.3 or less to minimize hemorrhage progression. While FFP is appropriate for most patients, 4F-PCC is recommended in specific situations: (1) patients requiring emergent operative or procedural intervention, more quickly than the necessary volume of FFP could be transfused (usually those requiring transfer to the operating theater directly from the trauma bay or computed tomography (CT) scanner); (2) patients with a supratherapeutic INR of 3.5 or greater; and (3) patients unlikely to tolerate the large volumes of fluid often associated with FFP administration. The final decision for FFP versus 4F-PCC is at the discretion of the attending trauma surgeon. We do not yet have formal protocols for use in anticoagulated patients with non-ICH injury patterns, and 4F-PCC use in these situations is patient specific. Dosing of 4F-PCC is standardized for warfarin patients, based on INR and patient body weight (Table 1). We encourage the use of vitamin K only if ongoing INR reversal is desired, as the effects of 4F-PCC typically begin to wear off 24 hours to 48 hours after administration. Prolonged reversal should be avoided in patients at

TABLE 1. Suggested Kcentra Dosing Algorithm for Life-Threatening Bleeding Caused by Warfarin[16]

Pretreatment INR	2 to <4	4 to 6	>6
Dose* of Kcentra (units** factor IX) per kilogram of actual body weight	25	35	50
Maximum dose,† U	2,500	3,500	5,000

*Dosing is based on body weight. Dose based on actual potency as stated on the carton, which will vary from 20 to 31 factor IX U/mL after reconstitution. Nominal potency is 500 U or 1,000 U per vial, approximately 25 U/mL after reconstitution.

**Units refer to international units.

†Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

excessively high risk of thrombosis, such as those with a mechanical heart valve.

The first year of 4F-PCC use ending on July 15, 2014, was reviewed in the surgical intensive care unit pharmacy database. Additional information was collected on each patient from the institutional trauma registry and electronic medical record, including demographics, injury mechanism, injury severity, and outcomes. We also assessed laboratory values, thromboelastogram results, other hemostatic agents given, and blood product use over the time frame from admission to 48 hours after 4F-PCC administration.

By division protocol, we repeat head CT scans for all ICH patients after 4 hours to 6 hours, or with any decline in mental status. Patients with ICH were evaluated for progression of injury by comparing head CT scans before and after 4F-PCC administration. Radiographic injury progression was assessed in two distinct ways: (1) by the attending radiologist read of any increase in hemorrhage size or new hemorrhage development and (2) by calculating a modified Marshall score for each CT scan (Table 2). Modified Marshall scores were calculated by a trained neurosurgeon. Clinical progression was also evaluated based on recorded patient Glasgow Coma Scale (GCS) score.

Statistical Analyses

Statistical analysis was performed using SPSS version 21 (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, version 21.0, Armonk, NY). Normality of variables was assessed using the Shapiro-Wilk test, and significance testing for change in INR values was performed using the Wilcoxon signed-rank test. A $p < 0.05$ was considered significant.

RESULTS

A total of 26 patients receiving 4F-PCC for warfarin reversal met study criteria and were included for analysis. Mean patient age was 71.4 ± 14.8 years, with mean Injury Severity Score (ISS) 9.7 ± 6.1. Of the patients, 96.2% had a blunt mechanism of injury; 34.6% were reversed because of ICH (median Abbreviated Injury Scale [AIS] score, 3; median Marshall score, 2d) 15.4% for fractures, and 11.5% for soft tissue hematomas (Table 3). Of the patients, 38.5% were also on aspirin, none were on clopidogrel or other antiplatelet agents. The mean dose of 4F-PCC given was 28.4 U/kg, although three patients received a nonstandard dose of 6 U/kg to 10 U/kg (one vial of 4F-PCC).

TABLE 2. Modified Marshall CT Grade

I	Diffuse injury	No visible pathology	1
II	Diffuse injury (with present cisterns, midline shift 0–5 mm and/or small (<25 cc) high or mixed density lesions	No lesions	2a
		Only 1 lesion	2b
		≥2 unilateral lesions	2c
		Bilateral lesions	2d
III	Diffuse injury and swelling	I–II + compressed or absent cisterns	3
IV	Diffuse injury and shift	I–III + midline shift >5 mm	4
V	Evacuated mass lesion	Extradural	5a
		Subdural	5b
		Intracerebral	5c
		≥2 intracerebral + extracerebral	5d
VI	Nonevacuated mass lesion (>25 cc)	Extradural	6a
		Subdural	6b
		Intracerebral	6c
		≥ intracerebral + extracerebral	6d

TABLE 3. Patient Characteristics

Male	61.5%
Age, mean, y	71.4 ± 14.8
ISS, mean	9.7 ± 6.1
Mechanism	84.6% fall
	3.8% found down
	3.8% bicycle crash
	3.8% scooter crash
	3.8% gunshot wound
Bleeding source (reason 4F-PCC given)	34.6% ICH (median AIS score, 3; median Marshall score, 2d)
	15.4% fracture
	11.5% soft tissue hematoma
	7.7% surgical site
	3.8% gastrointestinal tract
	26.9% no hemorrhage (primarily reversed because of supratherapeutic INR)

A total of 30.7% of our patients also received FFP during the study time frame, although only one patient (3.8%) received FFP concurrently with 4F-PCC (between the pre–4F-PCC and post–4F-PCC INR values). The majority of these patients (19.2%) received FFP in the 24 hours following 4F-PCC administration. Subgroup analysis excluding patients who received FFP produced no significant change in study results. No patients received cryoprecipitate or platelet transfusions. A total of 80.8% of patients were given vitamin K, with a mean dose of 6.3 ± 2.5 mg. There was no significant difference in outcomes between the groups that did and did not receive vitamin K. No patients received tranexamic acid or desmopressin. No patients received a second dose of 4F-PCC.

For all patients receiving 4F-PCC, the mean INR decreased from 5.7 to 1.5 ($p < 0.001$; range, 1.6–30 to 1.2–2.6). For a subgroup of supratherapeutic patients with a starting INR greater than 5.0, the mean INR decreased from 12.0 to 1.6 ($p = 0.009$; range, 5.1–30 to 1.2–2.6). In both groups, the decrease was sustained over the subsequent 48 hours, with mean INR values of 1.4 and 1.6, respectively (Fig. 2). Four patients (15.4%) remained anticoagulated (INR ≥ 2.0) after 4F-PCC administration, a cohort we termed *partial responders*. The mean post–4F-PCC INR in this group was 2.3 (range, 2.0–2.6). Of the 14 patients who had a thromboelastogram obtained before 4F-PCC administration, 4 were found to be hypocoagulable (R time > 10 minutes or clotting index < −3). Two of these four patients had repeat TEGs obtained after 4F-PCC administration, both of which showed normal coagulation ability.

The subgroup analysis of patients with ICH showed progression of the initial injury in 66.7% (6 of 9 patients) when assessed using conservative radiographic criteria of any

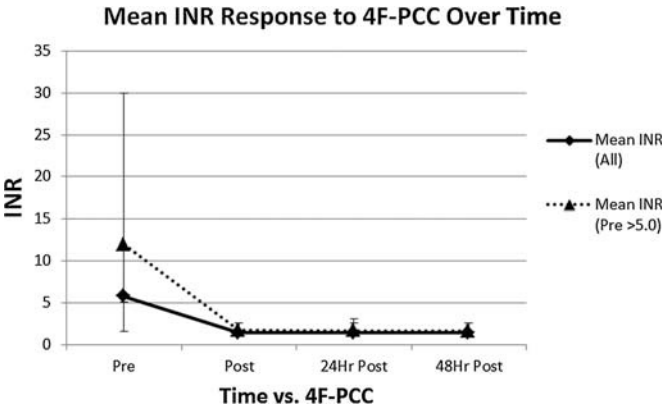

Figure 2. Mean INR response to 4F-PCC over time. *Vertical bars* represent minimum-maximum values at each time point.

increase in bleeding or new hemorrhage as read by the attending radiologist. Three of the six patients who progressed (50.0%) were on concurrent aspirin therapy. When assessed using modified Marshall scores, only three of nine patients showed progression of injury (Table 4). The median Marshall score was unchanged at a Category 2d. Only one of the nine ICH patients experienced a decline in GCS score; none required surgical intervention. A total of 88.9% (8 of 9) were at their baseline mental status by the time of discharge; 55.6% were discharged home, and 33.3% were discharged to a skilled nursing facility.

After ICH, the next largest subset of patients was those with fractures (four patients, 15.4%). All four patients had significant hematomas associated with their injuries—three pelvic fractures and one humerus fracture. All were treated nonoperatively and required no additional interventions for hemorrhage control other than coagulopathy reversal.

There was no in-hospital mortality in our study sample. No patients developed deep vein thromboses, pulmonary emboli, strokes, or myocardial infarctions. Two patients (7.7%) had an inferior vena cava filter placed. Median ± interquartile range hospital length of stay was 3 ± 3.42 days, with an intensive care unit length of stay of 1 ± 2.0 days and 0 ± 0 ventilator days.

DISCUSSION

Coagulopathy and trauma are a life-threatening combination, and patient outcomes are improved with rapid correction of bleeding diatheses. Our study demonstrates that a 4F-PCC or Kcentra effectively reverses coagulopathy caused by warfarin use. In conjunction with appropriate vitamin K use, results last at least 48 hours. 4F-PCC is effective even in patients with an initial INR greater than 5.0.

Although radiographic progression of ICH was frequent in this population, only three patients had an increase in hemorrhage significant enough to raise their Marshall score. More importantly, the majority of patients with radiographic progression did not have any clinical deterioration based on GCS. Only one patient demonstrated a decline in GCS score, a decrease from 14 to 13 that required no change in clinical management. No patients required operative intervention because of ICH. Our study sample did include four patients (15.4%) who remained anticoagulated after 4F-PCC administration (repeat INR ≥ 2.0). These "partial responders" started with a mean INR of 6.0 (range, 3.2–9.2). Two such patients received nonstandard doses of 4F-PCC (one vial or 6–10 U/kg), with INRs improving from 3.2 to 2.5 and 5.1 to 2.6; neither had a clinical source of hemorrhage. The third patient also had no clinical hemorrhage, and the INR decreased from 9.2 to 2.0 with a dose of 43 U/kg (recommended dose, 50 U/kg). The fourth patient presented with a right humerus fracture, associated hematoma, anemia, and an INR of 6.3, which decreased to 2.0 after a 4F-PCC dose of 35 U/kg (recommended dose, 50 U/kg). It seems that partial responders in this study were patients who had received a dose of 4F-PCC inappropriate for full anticoagulation reversal. Three of the patients had no clinical source of hemorrhage, and two of these were intentionally given a single vial of 4F-PCC with the goal of lowering their INR to a normal anticoagulated range of 2.0 to 3.0 rather than full reversal. The other two patients received an inappropriately low dose of 4F-PCC because of initial inaccurate estimations of patient weight. Although these patients would have been eligible for a second dose of 4F-PCC based on the new INR, none was given as the patients were clinically stable. Results were limited by these unusual doses, rather than limitations of the medication itself.

Concurrent FFP administration was rare in our study. Only one patient (3.8%) received FFP along with 4F-PCC between the pre–4F-PCC and post–4F-PCC INR assessments. An additional five patients (19.2%) received FFP in the 24 hours after 4F-PCC use. Reasons for FFP administration varied, including concurrent with packed red blood cell transfusion (two patients) and for progression of ICH despite appropriate INR reversal by 4F-PCC (two patients, INRs of 1.5 and 1.2). Only one patient received FFP for initial poor response to 4F-PCC, after receiving an inappropriate dose of 4F-PCC at 6.4 U/kg. A subgroup analysis excluding these patients from INR assessment had no impact on results, with a pre–4F-PCC INR of 4.4 decreasing to 1.4 after 4F-PCC use and remaining at 1.4 during the subsequent 48 hours.

TABLE 4. INR and Marshall Scores Before and After 4F-PCC Use

		Pre–4F-PCC		Post–4F-PCC	
Patient	Anticoagulation	INR	Marshall Score	INR	Marshall Score
5	Warfarin	1.6	2d	1.2	CT scan not repeated
11	Warfarin	2.2	2b	1.3	2d*
16	Warfarin	3.0	2c	1.4	2c
17	Warfarin	2.4	2d	1.2	6c*
19	Warfarin	5.3	1	1.5	2b*
23	Warfarin	4.7	2b	1.3	2b
24	Warfarin	2.7	2d	1.3	2d
30	Warfarin	12.7	2d	1.2	2d
31	Warfarin	2.5	2d	1.3	2d

*Progression of ICH by Marshall score.

One known adverse effect of the PCCs is thromboembolism formation, including deep venous thrombosis (DVT), pulmonary emboli, myocardial infarction, and embolic stroke.[12,17] Although our study size was too small to be definitive, we showed no increase in thrombotic events (0%). In our Level 1 trauma center, patients undergo aggressive DVT screening with routine weekly lower-extremity duplex studies, so we do not suspect that DVTs were underdetected.

Limitations of this study include small sample size and retrospective data collection. 4F-PCC use was protocol driven in patients with ICH, but use in other injury patterns was clinician dependent and so may suffer significantly from selection bias. Despite these limitations, we present encouraging initial data regarding 4F-PCC use in anticoagulated US trauma patients. In addition, we initially attempted to collect data on 4F-PCC use in patients with other etiologies for their coagulopathy, namely, cirrhosis and factor Xa inhibitor use. Unfortunately, the numbers in each group were small (two patients with cirrhosis, and three on the Xa inhibitor rivaroxaban), which precluded development of any meaningful conclusions, leading us to exclude these patients from our final results. We believe that further research in these patient populations is important but will likely require a multicenter trial to attain sufficient numbers.

In conclusion, 4F-PCC effectively reverses elevated INRs in trauma patients with warfarin-induced coagulopathy. With appropriate vitamin K use, effects last at least 48 hours. No increase in thrombotic complications was identified.

AUTHORSHIP

A.E.B., W.-T.H., K.B., L.K., L.N.G., and R.C. designed this study. A.E.B. conducted the literature search. A.E.B., W.-T.H., K.B., A.M.S., and D.W. performed data collection. All authors contributed to data analysis and interpretation. A.E.B. wrote the manuscript. A.E.B., W.-T.H., K.B., L.K., L.N.G., and R.C. contributed to critical revision.

DISCLOSURE

The authors declare no conflicts of interest.

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