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Reversal of warfarin associated coagulopathy with 4-factor prothrombin complex concentrate in traumatic brain injury and intracranial hemorrhage

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Abstract

Warfarin-associated intracranial hemorrhage is associated with a high mortality rate. Ongoing coagulopathy increases the likelihood of hematoma expansion and can result in catastrophic hemorrhage if surgery is performed without reversal. The current standard of care for emergency reversal of warfarin is with fresh frozen plasma (FFP). In April 2013, the USA Food and Drug Administration approved a new reversal agent, 4-factor prothrombin complex concentrate (PCC), which has the potential to more rapidly correct coagulopathy. We sought to to determine the feasibility and outcomes of using PCC for neurosurgical patients. A prospective, observational study of all patients undergoing coagulopathy reversal for intracranial hemorrhage from April 2013 to December 2013 at a single, tertiary care center was undertaken. Thirty three patients underwent emergent reversal of coagulopathy using either FFP or PCC at the discretion of the treating physicians. Intracranial hemorrhage included subdural hematoma, intraparenchymal hematoma, and subarachnoid hemorrhage. FFP was used in 28 patients and PCC was used in five patients. International normalized ratio at presentation was similar between groups (FFP 2.9, PCC 3.1, $p = 0.89$). The time to reversal was significantly shorter in the PCC group (FFP 256 minutes, PCC 65 minutes, $p < 0.05$). When operations were performed, the time delay to perform operations was also significantly shorter in the PCC group (FFP 307 minutes, PCC 159 minutes, $p < 0.05$). In this preliminary experience, PCC appears to provide a rapid reversal of coagulopathy. Normalization of coagulation parameters may prevent further intracranial hematoma expansion and facilitate rapid surgical evacuation, thereby improving neurological outcomes.

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Keywords

Fresh frozen plasma; Intracranial hemorrhage; Prothrombin complex concentrate; Subdural hematoma; Warfarin

1. Introduction

Oral anticoagulation therapy associated intracranial hemorrhage (ICH) carries a nearly 60% 30 day mortality rate, compared to 40% for non-anticoagulated patients[1,2]. Poor outcome in ICH is associated with expansion in hematoma size after admission[3]. While the zone of normal hemostasis can be considered below an international normalized ratio (INR) of 1.7[4], data in the neurosciences literature suggest that an INR > 1.2 is associated with worse outcomes in ICH[5]. 4-factor prothrombin complex concentrates (4F-PCC) are shown to reduce INR to < 1.4 within 30 minutes of administration[6]. Specifically, INR was reduced to ≤ 1.3 in 93% of patients within 30 minutes in the European prospective multinational clinical trial[6] compared to < 10% for fresh frozen plasma (FFP). On average, it takes 8 hours to achieve the same effect with FFP[7]. This is supported by the recent USA-European randomized prospective trial[8]. 4F-PCC, when used with Vitamin K, maintains INR < 1.4 for 48 hours without the administration of other products[6]. Reversal with 4F-PCC has been associated with overall fewer adverse events (death, stroke, myocardial infarction, heart failure, venous thromboembolism, or peripheral arterial thromboembolism) compared to FFP −9.7% for 4F-PCC *versus* 19.5% for FFP ($p = 0.014$)[9].

4F-PCC contains Factors II, VII, IX and X, and antithrombotic Proteins C and S as a lyophilized concentrate. Kcentra (CSL Behring, King of Prussia, PA, USA) is the only approved 4F-PCC in the USA. It was approved by the Food and Drug Administration on 30 April 2013. Kcentra is produced from human plasma that is purified, heat-treated, nanofiltered and lyophilized into a reconstitutable powder. One mL of reconstituted Kcentra contains approximately the same factor activity as 10 mL of FFP. According the manufacturer, common adverse events with Kcentra include headache, nausea/vomiting, arthralgia, and hypotension. Contraindications to Kcentra use include known anaphylactic or severe systemic reactions to heparin, human albumin, or any of the clotting factors, disseminated intravascular coagulation, and heparin-induced thrombocytopenia.

2. Methods

Following institutional board approval, we assessed 1400 consecutive emergency department neurosurgery consults at our institution, isolated the consults for intracranial and spinal hemorrhage, and categorized them by type (Table 1). Three point one percent of consultations from the emergency department involved reversal of warfarin in the setting of acute neurosurgical pathology. We then assessed the number of each category that required operative intervention. Forty five percent of these patients ultimately required operative or procedural (external ventricular drain, intracranial pressure monitor) intervention within the first 24 hours of hospitalization. On this basis, we have devised general recommendations on intracranial pathology types for which PCC should be used (Table 2).

3. Results

Five patients with acute ICH were treated with 4F-PCC since its approval, comprising one operative acute subdural hematoma, one non-operative posterior fossa hematoma, one non-operative subdural hematoma, and two non-operative intraventricular hemorrhages (Table 3). All patients had an initial INR > 2.0, which was corrected to ≤ 1.2 in all patients. In the operative cases, the average time from patient arrival in the emergency department to correction of INR (defined as INR < 1.6) was 161 minutes and time to anesthesia induction in the operating room was 159 minutes. The average time from administration of 4F-PCC to corrected INR was 65 minutes. With FFP, the average time to correction of INR to < 1.6 was 256 minutes and time to operating room was 307 minutes. Long-term outcomes remain to be determined in several of these patients.

4. Discussion

There is ample evidence in the literature that warfarin-associated ICH is associated with worse outcomes and the rapidity of intervention may be an important ultimate predictor of outcome. As previously outlined, oral anticoagulation therapy associated ICH carries a nearly 60% 30 day mortality rate, compared to 40% for non-anticoagulated patients[1,2], and indeed poor outcome in ICH is associated with expansion in hematoma size after admission[3].

The literature strongly suggests and our initial findings support the notion that 4F-PCC more rapidly corrects INR and allows neurosurgeons to take patients with acute intracerebral hemorrhage for surgery in a more timely fashion. While PCC appears effective in specifically reversing warfarin-associated coagulopathy, it has no role in the reversal of newer oral anticoagulants, such as dabigatran[10]. While there are no data to show that 4F-PCC improves outcomes in patients with acute ICH in the setting of warfarin-associated coagulopathy, study is underway.

On this preliminary basis, we have devised general recommendations on the use of PCC (Table 2). The general guiding principle in formulating these guidelines was the use of PCC in patients with a high potential to require operative intervention, in an attempt to facilitate rapid and safe surgical intervention. Alternatively, we consider the use of PCC in situations where rapid coagulopathy reversal may avert surgical intervention by arresting the growth of an intracerebral hemorrhage.

To our knowledge, there are two major prospective randomized clinical trials in the literature regarding the use of PCC. In addition, there are several retrospective trials. In evaluating these studies, it is important to identify the rate and degree of warfarin-related coagulopathy reversal, maintenance of coagulopathy reversal, cost, and if applicable, neurological or surgical outcomes.

In a study by Sarode et al., 36 sites across the USA and Europe were enrolled in a prospective, randomized, open-label, non-inferiority phase IIIb trial; this was supported by CSL Behring (the company that produces Kcentra). There were a total of 216 patients (mean age 69.8 [range 26–96]), 103 in the 4F-PCC group and 109 in the FFP group; all had an INR

≥ 2.0 within 3 hours prior to treatment. Weight-based 4F-PCC was administered at a maximum infusion rate of 3 international units [IU]/kg/minute. A total dose of 25 IU/kg, 35 IU/kg, and 50 IU/kg were used for patients with an initial INR of 2–3.9, 4–6, and > 6, respectively. Weight-based FFP was administered with a total dose of 10 mL/kg, 12 mL/kg, and 15 mL/kg for patients with an initial INR of 2–3.9, 4–6, and > 6, respectively. All patients were concomitantly administered intravenous Vitamin K. There were two primary endpoints. (1) Hemostatic efficacy as defined in the case of ICH with three tiers: effective (≤ 35% increase in hematoma volume compared to baseline CT scan at 3 and 24 hours) *versus* ineffective (> 35%); of note the study was not powered adequately to examine the ICH population in isolation – other definitions exist for gastrointestinal bleeds and musculoskeletal hemorrhages. (2) INR correction to ≤ 1.3 at 30 minutes after the end of infusion. They had a 24 hour follow-up period and conducted a non-inferiority analysis with intention-to-treat efficacy analysis, with secondary superiority analysis if non-inferiority was demonstrated. Results of this trial were promising. Aggregate effective hemostasis (gastrointestinal, musculoskeletal, ICH) was achieved in 72.4% of patients receiving 4F-PCC and 65.4% of patients receiving FFP ($p = 0.50$). A *post hoc* analysis of musculoskeletal hemorrhage demonstrated 4F-PCC superiority at 4 hours compared to FFP ($p = 0.02$). Similar analysis could not be performed with the study data for ICH due to insufficient data. INR was corrected to ≤ 1.3 at 30 minutes in 62.2% of patients receiving 4F-PCC, compared to 9.6% receiving FFP ($p < 0.02$), demonstrating superiority of 4F-PCC in the rapidity of INR correction. In this study, there were similar rates of adverse events, serious adverse events, thromboembolism, and mortality. This study provided some of the first evidence that 4F-PCC is significantly faster than correcting INR than FFP.

In another study by Pabinger et al., 15 sites across Europe were enrolled in a single-arm prospective trial supported by CSL Behring. It involved a total of 43 patients (mean age 69.8 [range 26–96]); all had an INR ≥ 2.0 prior to treatment. Weight-based 4F-PCC was administered at a maximum infusion rate of 3 IU/kg/minute. A total dose of 25 IU/kg, 35 IU/kg, and 50 IU/kg were used for patients with an initial INR of 2–3.9, 4–6, and > 6, respectively. Eighty eight percent (38/43) of patients were concomitantly administered Vitamin K in intravenous, intramuscular, or oral formulation. The primary endpoints included (1) INR correction to ≤ 1.3 at 30 minutes after the end of infusion and (2) INR maintenance at ≤ 1.3 for 48 hours after the end of infusion without further intervention. They had a 24 hour follow-up period and conducted single-arm descriptive statistical analysis. INR was corrected to ≤ 1.3 at 30 minutes in 93% of patients receiving 4F-PCC. Furthermore, the median INR remained between 1.2 and 1.3 in all corrected study participants for the entire 48 hour follow-up. This study provided further evidence that 4F-PCC rapidly reduced INR to normal levels and maintained it for 48 hours without further intervention in the majority of patients.

Another recent important study is a retrospective series by Hickey et al., involving two institutions in Canada (The Ottawa Hospital and University of Ottawa). They assessed 314 patients (mean age 76 [range 24–83]), 165 in the 4F-PCC group and 1149 in the FFP group; all had an INR ≥ 1.5 prior to treatment. 4F-PCC 1000 IU was administered to all patients

regardless of weight and initial INR. A variable amount of FFP was administered in order to correct INR.

Vitamin K was variably given to patients. The primary endpoint was the incidence of serious adverse events (taken in aggregate, including death, ischemic stroke, myocardial infarction, heart failure, venous thromboembolism, and peripherial arterial thromboembolism). Secondary endpoints included time to INR reversal (measurement of INR after administration of 4F-PCC and FFP were highly variable) and hospital length of stay. They conducted a two-sample *t*-test for continuous variables (time to INR reversal, hospital length of stay) or χ^2 test for categorical variables (incidence of serious adverse events). Taken in aggregate, serious adverse events occurred in 19.5% of FFP patients compared to 9.7% of 4F-PCC patients ($p = 0.016$). The median time to INR reversal was 11.8 hours in the FFP group compared to 5.7 hours in the 4F-PCC group ($p < 0.0001$). The average hospital length of stay was 5 days in the FFP group compared to 4 days in the 4F-PCC group ($p = 0.245$). From this study 4F-PCC appears to be safer than FFP in terms of serious adverse events. However, while patients were reasonably matched ($p > 0.05$ for over 20 demographic variables), there were several inconsistencies in dosage of administered 4F-PCC and FFP, measurement time points, and patient outcome recording. Within these caveats, there is certainly a suggestion that 4F-PCC may be safer than FFP with respect to serious adverse events. Furthermore, there is a trend in this study towards a shorter hospital length of stay with the use of 4F-PCC compared to FFP.

5. Conclusion

4F-PCC is faster than FFP in reversing INR in patients who have warfarin-associated coagulopathy and may allow neurosurgeons to intervene in cases of critical patients in a more timely fashion. Utilization of this agent may lead to better outcomes in ICH, although its cost effectiveness and clinical effectiveness remain to be determined.

References

1. Lavoie A, Ratte S, Clas D, Demers J, Moore L, Martin M, et al. Preinjury warfarin use among elderly patients with closed head injuries in a trauma center. J Trauma. 2004; 56:802–807. [PubMed: 15187746]
2. Mina AA, Bair HA, Howells GA, Bendick PJ. Complications of preinjury warfarin use in the trauma patient. J Trauma. 2003; 54:842–847. [PubMed: 12777897]
3. Radberg JA, Olsson JE, Radberg CT. Prognostic parameters in spontaneous intracerebral hematomas with special reference to anticoagulant treatment. Stroke. 1991; 22:571–576. [PubMed: 2028484]
4. Rossi, EC.; Simon, TL. Rossi's principles of transfusion medicine. 4. Chichester, UK; Hoboken, NJ: Wiley-Blackwell/AABB Press; 2009.
5. Bershad EM, Farhadi S, Suri MF, Feen ES, Hernandez OH, Selman WR, et al. Coagulopathy and inhospital deaths in patients with acute subdural hematoma. J Neurosurg. 2008; 109:664–669. [PubMed: 18826353]
6. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H, et al. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. J Thromb Haemost. 2008; 6:622–631. [PubMed: 18208533]

7. Zubkov AY, Mandrekar JN, Claassen DO, Manno EM, Wijdicks EF, Rabinstein AA. Predictors of outcome in warfarin-related intracerebral hemorrhage. Arch Neurol. 2008; 65:1320–1325. [PubMed: 18852345]

8. Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding: A Randomized, Plasma-Controlled, Phase IIIb Study. Circulation. 2013; 128:1234–1243. [PubMed: 23935011]

9. Hickey M, Gatien M, Taljaard M, Aujnarain A, Giulivi A, Perry JJ. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. Circulation. 2013; 128:360–364. [PubMed: 23770745]

10. Awad AJ, Walcott BP, Stapleton CJ, Yanamadala V, Nahed BV, Coumans J-V. Dabigatran, intracranial hemorrhage, and the neurosurgeon. Neurosurgical focus. 2013; 34:E7. [PubMed: 23634926]

Table 1

Emergency consults requiring the reversal of warfarin

Diagnosis	Total number	Number immediately operative
Traumatic brain injury		
Subarachnoid hemorrhage, GCS 13–15	17	0
Subarachnoid hemorrhage, GCS 9–12	2	0
Subarachnoid hemorrhage, GCS < 9	2	2
Contusion, GCS 13–15	5	2
Contusion, GCS 9–12	3	3
Contusion, GCS < 9	2	2
Acute subdural hematoma < 5 mm thick	4	0
Acute subdural hematoma 5–10 mm thick	2	1
Acute subdural hematoma > 10 mm thick	2	2
Cerebellar hematoma		
< 1 cm without hydrocephalus	1	0
>1 cm with hydrocephalus	2	2
Chronic subdural hematoma	8	0
Aneurysmal subarachnoid hemorrhage	2	2
Intraparenchymal hematoma (supratentorial)	9	2
Spinal epidural hematoma	1	1
Other neurosurgical emergencies		
Ventricular shunt failure	2	2
Hydrocephalus requiring external ventricular drain placement	1	1
Total	44	20

GCS = Glasgow Coma Scale.

Table 2

General recommendations for use of 4-factor prothrombin complex concentrate for intracranial hemorrhage with warfarin-associated coagulopathy

1	Any patient suffering from head trauma with an initial or current GCS < 9 (severe TBI) with an abnormal head CT scan (e.g. skull fracture, hydrocephalus, intracranial hemorrhage of any size).
2	Any patient suffering from head trauma with intracranial hemorrhage of any size and initial or current GCS < 13 (moderate or severe TBI).
3	Any patient suffering form intracranial hemorrhage that meets, or is at risk of meeting, criteria for urgent or emergent neurosurgical intervention, regardless of presenting or current GCS. Examples: ○ Acute subdural hematoma ≥ 3 mm in size ○ Epidural hematoma of any size ○ Cerebellar hematoma of any size ○ Cerebral intraparenchymal hematoma or hemorrhagic contusion > 1 cm in diameter in any plane or > 30 cc in volume ○ Fourth ventricle hemorrhage ○ Aneurysmal subarachnoid hemorrhage ○ Multifocal traumatic subarachnoid hemorrhage
4	Any patient scheduled to undergo an emergency neurosurgical procedure within a 4 hour time period.

cc = cubic centimeter, GCS = Glasgow Coma Scale, TBI = traumatic brain injury.

Table 3

Patients from the current study with acute intracranial hemorrhage who received 4-factor prothrombin complex concentrate

Patient	Diagnosis	Initial INR	Other relevant medication	PCC dose	Final INR	Time from initial onsite INR to INR < 1.6	Time from administra tion of PCC to INR <1.6
1	Intraparenchymal supratentorial hemorrhage, intraventricular hemorrhage, hydrocephalus	2.5 (referring hospital), 1.9 (onsite)	Vitamin K, FFP en route from referring hospital; FFP onsite	2500 U	1.1	110 minutes	30 minutes
2	Intraventricular hemorrhage	3.7 (referring hospital), 2.0 (onsite)	Vitamin K, FFP prior to transfer	2000 U	1.1	241 minutes	113 minutes
3	Acute traumatic subdural hematoma (unilateral)	2.9 (onsite)	Vitamin K	2500 U	1.2	9 hours 18 minutes	123 minutes
4	Acute traumatic subdural hematoma (bilateral)	4.0 (onsite)	FFP	2500 U	1.1	157 minutes	28 minutes
5	Intraparenchymal cerebellar hemorrhage	2.6 (onsite)	None	1500 U	1.1	160 minutes	35 minutes

FFP = fresh frozen plasma, INR = international normalized ratio, PCC = prothrombin complex concentrate.