

Utility of 4-Factor Prothrombin Complex Concentrate in Trauma and Acute-Care Surgical Patients

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Context: Since 2013, prothrombin complex concentrate (PCCs) have been approved in the United States for the reversal of anticoagulation induced by vitamin K antagonists. However, there has been limited investigation into their use in trauma and acute-care surgery (ACS).

Objective: To investigate the role that 4-factor PCC may have in reversing anticoagulation in the setting of trauma and ACS.

Methods: All trauma and ACS patients who presented between March 14, 2014, and August 1, 2015, were included in this retrospective descriptive analysis. Patients receiving 4-factor PCC were compared with patients receiving fresh frozen plasma (FFP) alone. The following data were collected from medical records: age, sex, race, international normalized ratio (INR) at admission (baseline) and after reversal, blood products given, dosing of medication, injury severity score, length of stay, thromboembolic event, death during admission, and death within 90 days after admission.

Results: There were 188 trauma and ACS patients who required reversal of anticoagulation. Of these, 98 patients received FFP and 90 received PCC. Patients who received PCC were at increased risk for death during admission (20% vs 9.2% for FFP group) or within 90 days (39% vs 15%, respectively). Patients in the PCC group had a higher median baseline INR (2.9 vs 2.5 in the FFP group) and a lower postintervention INR (1.4 vs 1.8); consequently, the decrease in INR was greater in the PCC group than in the FFP group (1.5 vs 0.7, respectively). The number of total units of packed red blood cells transfused was significantly higher in patients receiving PCC.

Conclusion: Patients receiving PCC had worse outcomes than those who received FFP. Given that these differences may have resulted from baseline differences between groups, these results mandate further prospective analysis of the use of PCC in trauma and ACS patients.

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Since 1954, when the Food and Drug Administration first approved warfarin, an oral vitamin K antagonist, physicians have been challenged by the prospect of reversing therapeutic anticoagulation. This concern is especially true in the setting of hemorrhage, trauma, and emergency surgery. Since 2013, a new category of

reversal agents, prothrombin complex concentrates (PCCs), has been approved for the reversal of acquired coagulation factor deficiency induced by warfarin. However, there has been limited investigation into their role in trauma and acute-care surgery (ACS).¹

Coagulopathy in trauma and ACS patients is a common and potentially hazardous scenario. The lethal triad of coagulopathy, hypothermia, and acidosis is a well-described phenomenon that prevents the body from self-regulation and self-healing. It is vitally important for the osteopathic physician to correct this coagulopathy and allow the body to return to homeostasis and limit further hemorrhage. Factors attributing to coagulopathy include dilution secondary to intravenous fluid administration, blood transfusion, hypothermia, and acidosis. Furthermore, brain and long bone injuries have been shown to lead to coagulopathy, owing to factors released that interfere with hemostatic mechanisms.² Patients who present to the trauma bay already anticoagulated by warfarin are especially prone to coagulopathy and massive hemorrhage.

In the setting of traumatic hemorrhage, it is vital to ensure hemostasis by reversing any preexisting coagulopathy. Standard reversal agents have included fresh frozen plasma (FFP) and vitamin K. However, vitamin K can take up to 6 hours to take effect so is of little value when used alone in the acute setting,³ and FFP transfusion puts patients at risk for transmission of infectious agents, can lead to volume overload, requires cross-matching, and takes time to thaw and administer.⁴⁻⁷ These limitations make the potential use of PCCs in trauma appealing; PCCs do not require cross-matching, are virally inactivated, do not cause volume overload, and are rapidly infused.⁸ The most important advantage of PCC use is more rapid reversal of anticoagulation leading to increased speed of hemostasis. In theory, PCCs should lead to decreased blood loss and, therefore, decreased rates of packed red blood cell (pRBC) transfusions, transfusion-related complications, and mortality.^{9,10}

In a new protocol (**Figure 1**) implemented in March 2014 at our institution, 4-factor PCC became available for reversal of warfarin in the setting of major traumatic

bleeding or before emergency invasive procedures. Laboratory tests at admission included prothrombin time/international normalized ratio (INR), activated partial thromboplastin time, complete blood cell count, fibrinogen, soluble fibrin monomer, and type and screen. In patients in whom the physician chose to follow the new PCC protocol, 10 mg of vitamin K was administered along with 4-factor PCC. The dose of 4-factor PCC administered was 25 U/kg (maximum dose, 2500 U), 35 U/kg (maximum, 3500 U), or 50 U/kg (maximum, 5000 U), respectively, in patients with an INR less than 4, between 4 and 6, or greater than 6. Laboratory tests were repeated at 1 and 24 hours after 4-factor PCC administration. If 4-factor PCC was unavailable or ineffective, 2 U of FFP was administered.

This protocol was a guideline for physicians, who were ultimately free to deviate from the protocol based on their clinical judgment. During this same period there were patients in whom the physicians chose to not administer 4-factor PCC; these patients received only FFP and constituted the comparison group. The goal of the current study was to examine the effectiveness of this new protocol, evaluate adherence to the protocol, and compare clinical outcomes between patients given 4-factor PCC and all other trauma and ACS patients who required correction of anticoagulation.

Methods

We performed a retrospective review of trauma and ACS patients who required reversal of anticoagulation caused by vitamin K antagonists. The study focused on the 17 months (from March 14, 2014, to August 1, 2015) of a new protocol at our institution that used 4-factor PCC to reverse anticoagulation. We examined adherence to the new protocol and attempted to determine the factors that contributed to deviation from it. Trauma and ACS patients who received 4-factor PCC in accordance with the protocol (PCC group) were compared with those who required reversal of anticoagulation but received only FFP (FFP group). Patients were identified in multiple ways. Those treated with FFP

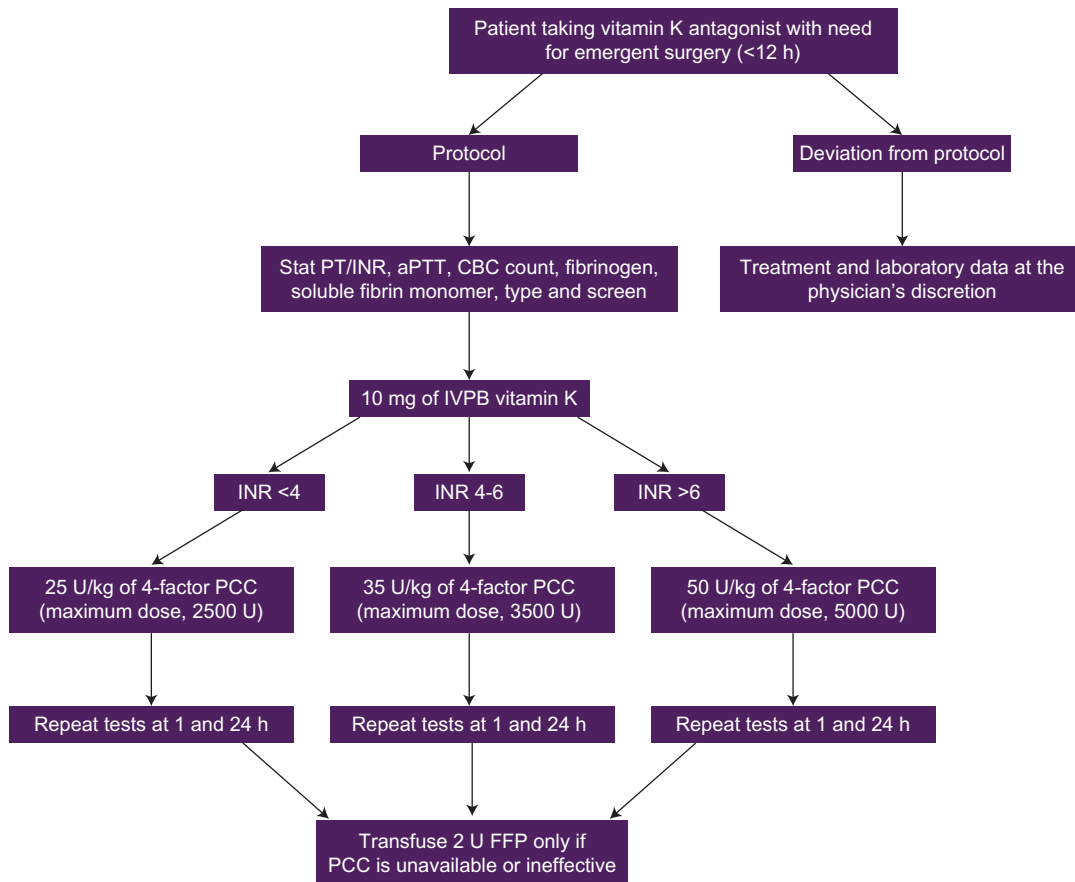


Figure 1.

Prothrombin complex concentrate (PCC) protocol for trauma and acute-care surgical patients. *Abbreviations:* aPTT, activated partial thromboplastin time; CBC, complete blood cell; FFP, fresh frozen plasma; INR, international normalized ratio; IVPB, intravenous piggyback; PT, prothrombin time.

were directly identified through the trauma registry, those treated with PCC were identified through the pharmacy records, and those treated with FFP who required emergency surgery were identified using blood bank records.

All trauma and ACS patients admitted from March 14, 2014, to August 1, 2015, were considered in this descriptive analysis. The criteria for inclusion were age 18 years or older, warfarin treatment, elevated baseline INR (≥ 1.8), and receipt of a reversal agent. The exclusion criteria were age less than 18 years, prisoner status, pregnancy, and any failure to meet the inclusion criteria. The following data were collected: age, sex, race,

indication for anticoagulation, diagnosis at admission, INR at admission and after administration of reversal agent, blood products given during admission, adherence to protocol, dosing of medication, injury severity score (ISS) in trauma patients, length of stay, thromboembolic events, death during admission, and death within 90 days after admission. The primary outcomes examined were change in INR and pRBCs administered. Secondary outcomes included length of stay, thromboembolic events, death during admission, and death within 90 days.

Means with SDs, medians with interquartile ranges, and frequencies were calculated, as appropriate, for all

patient characteristic variables, for trauma and ACS patients (combined and separately and also by adherence vs nonadherence to the PCC protocol). Adherence and nonadherence groups were compared using Wilcoxon rank sum tests and Pearson χ^2 tests for continuous and categorical variables, respectively. Logistic models were used to assess the association between pRBC transfusion and the risk factors. An α level of .05 was used to determine statistical significance. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc). This study was approved by the Geisinger Medical Center Institutional Review Board with a waiver of the need for consent.

Results

Baseline Characteristics

Overall, 188 trauma and ACS patients required reversal of anticoagulation; 98 received FFP, and 90 received

PCC. No patients who met inclusion criteria were directly excluded. Patients in the PCC group had a higher median baseline INR than those in the FFP group (2.9 vs 2.5, respectively; $P=.003$). The majority of patients were white, and more men than women were included in the study. When grouped as ACS or trauma patients, the patients receiving PCC were again noted to have higher baseline INRs. Analysis of trauma patients included assessment of their ISSs. The trauma patients receiving PCC had a higher median ISS than those receiving FFP (11 vs 9; $P=.007$) (Table).

Change in INR

Comparing outcomes between patients in the PCC and FFP groups, we observed a higher median baseline INR in the PCC group (2.9 vs 2.5 in the FFP group), a lower median posttreatment INR (1.4 vs 1.8) and, therefore, a significantly larger median decrease in INR (1.3 vs 0.7; $P<.001$). Similar results were also seen in both ACS and trauma subgroups (Figure 2).

Table.
Baseline Characteristics of Study Group Receiving FFP or 4-Factor PCC

Characteristic	All Patients			ACS Patients			Trauma Patients		
	FFP (n=98)	PCC (n=90)	P Value	FFP (n=70)	PCC (n=72)	P Value	FFP (n=28)	PCC (n=18)	P Value
Age, mean (SD), y	74 (13)	73 (14)	.020 ^a	71 (13)	71 (14)	.853	77 (9)	78 (12)	.743
Race, No. (%)									
White	97 (99)	85 (94)	.132	69 (97)	67 (93)	.238	28 (100)	18 (100)	.999
Black	0	3 (3)		0	3 (4)		0	0	
Hispanic	1 (1)	2 (2)		1 (3)	2 (3)		0	0	
Sex, No. (%)									
Male	59 (60)	56 (62)	.550	44 (63)	45 (63)	.965	15 (54)	11 (61)	.615
Female	39 (40)	34 (38)		26 (37)	27 (38)		13 (46)	3 (39)	
Baseline INR, median (IQR)	2.5 (2.2-3.2)	2.9 (2.3-4.1)	.003 ^a	2.5 (2.1-3.4)	2.8 (2.3-4.4)	.002 ^a	2.6 (2.3-3.0)	3 (2.4-4.1)	.044 ^a
ISS, median (IQR)	...	...	...	...	...	...	9 (5.0-9.0)	11 (6.0-22.0)	.007 ^a

^a Significant at $P<.05$.

Abbreviations: ACS, acute-care surgery; FFP, fresh frozen plasma; INR, international normalized ratio; IQR, interquartile range; ISS, injury severity score; PCC, prothrombin complex concentrate.

Length of Stay

The PCC group had a median length of stay of 9 days, compared with 6 days in the FFP group. This significant difference was also seen in both the ACS (10 days for PCC vs 7 days for FFP) and trauma (6.5 vs 5.5 days) subgroups ($P=.007$) (Figure 3).

Thromboembolic Events

There was a higher rate of thromboembolic events in the PCC group, although this did not reach significance. Overall, thromboemboli developed in 10% in the PCC vs 5.1% in the FFP group ($P=.2013$). Similar results were seen in the trauma and ACS subgroups (trauma, 5.6% for PCC vs 0% for FFP; $P=.2073$; ACS, 11% vs 7.1%; $P=.412$) (Figure 4).

Transfusion Requirements

Patients in the PCC group were significantly more likely than those in the FFP group to receive blood transfusions (57% vs 45%, respectively) or to receive a massive transfusion of more than 10 U of pRBCs (8.9% vs 4.8%; $P=.001$). As expected, FFP use was lower in the PCC group than in the FFP group (40% vs 100%; $P<.001$) (Figure 4).

Mortality Rates

Mortality rates were significantly higher in the PCC than in the FFP group, both during admission (20% for PCC vs 9% for FFP) and within 90 days after admission (39% vs 15%) ($P<.05$). When trauma and ACS patients were considered separately, mortality rates were still significantly higher with PCC treatment, both during admission (trauma, 39% for PCC vs 11% for FFP; ACS, 15% vs 9%) and within 90 days (trauma, 50% vs 21%; ACS, 36% vs 13%) ($P<.05$ for all comparisons) (Figure 4).

Protocol Adherence

In the PCC group, we compared patients in whom the protocol was followed with patients in whom there was any deviation from protocol. Among the 90 patients receiving PCC, the protocol was properly

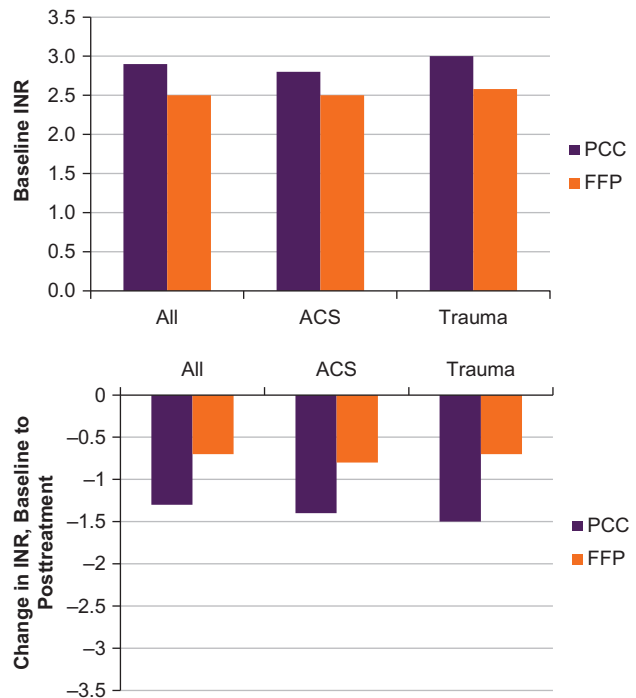


Figure 2.

Baseline international normalized ratio (INR) and change in INR by treatment group—fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC)—among all patients and in the acute-care surgical (ACS) and trauma patients.

followed in 59, and 31 patients were treated outside the protocol guidelines. The most common deviation was not coadministering vitamin K with 4-factor PCC. Other nonadherence issues included failure to monitor

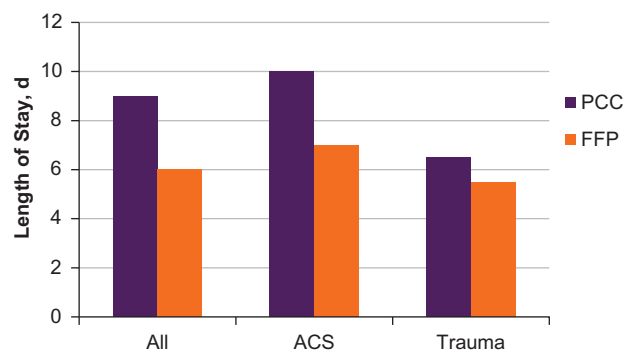


Figure 3.

Baseline length of stay (LOS) by treatment group—fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC)—among all patients and in the acute-care surgical (ACS) and trauma patients.

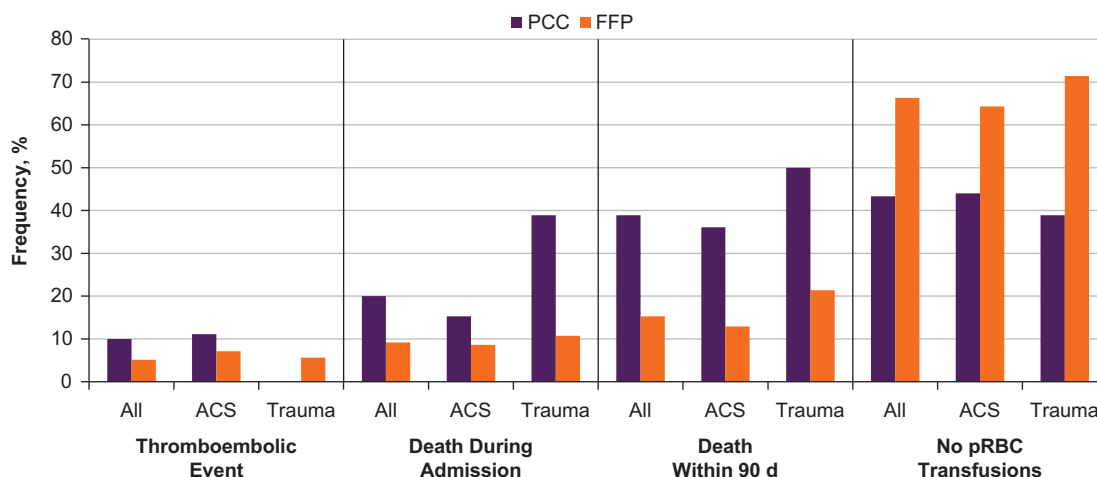


Figure 4.

Percentages of patients with thromboembolic events, death during admission or within 90 days after admission, and no packed red blood cell (pRBC) transfusions, by treatment group (fresh frozen plasma [FFP] or prothrombin complex concentrate [PCC]), among all patients and in the acute-care surgery (ACS) and trauma patients.

post-PCC laboratory values, incorrect dosing, and off-label use. The adherence PCC group had a significantly higher median baseline INR than the nonadherence group (4.2 vs 3.1, respectively; $P<.0001$), a greater decrease in INR (2.8 vs 1.5; $P<.0001$), and a higher incidence of pRBC transfusion (64.6% vs 42.9%; $P<.005$). To eliminate the effect of nonadherence to the PCC protocol, we compared the adherence PCC group with the FFP group. Results were similar to those for the comparison with the whole PCC group; the adherence PCC group had a significantly higher baseline INR, a larger decrease in INR, and a higher mortality rate than the FFP group.

Discussion

Prothrombin complex concentrates were first developed as a source of factor IX for the management of hemophilia B, but they have since been replaced by recombinant factor IX.¹¹ Most PCCs include the 4 vitamin K-dependent coagulation factors (II, VII, IX, and X), although some 3-factor PCCs do not include factor VII. Each PCC includes a different concentration of factors and at least 1 anticoagulant (heparin,

antithrombin III, or protein C, S, or Z). Although PCCs have been used successfully in Europe for many years for the reversal of oral vitamin K antagonists, until 2013 their use in the United States was limited to the management of hemophilia. There were concerns over the safety profile of the original PCCs because of the risks of pathogenicity and thrombogenesis.¹² In 2013, the first 4-factor PCC was approved by the Food and Drug Administration for the reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients who have acute major bleeding or require urgent surgical intervention.

Four-factor PCCs are plasma-derived products that include all 4 vitamin K-dependent factors (II, VII, IX, and X), as well as anticoagulants, such as heparin, antithrombin III, and proteins C and S. They undergo a rigorous pathogen inactivation and removal process that includes heat treatment and virus filtration. However, because they are derived from human blood, there remains a theoretical risk of transmission of infectious bacteria, viruses, and prions.¹³ Furthermore, patients requiring a 4-factor PCC for the reversal of warfarin have underlying conditions that predispose

them to thromboembolic events. Reversing anticoagulation in these patients exposes them to the thromboembolic risk of their underlying disease. Both fatal and nonfatal thromboembolic complications have been reported.¹³ It is important to monitor patients and inform them of the signs and symptoms of thromboembolic events. In clinical trials, such events occurred more frequently after administration of 4-factor PCC than with plasma treatment.¹³ Four-factor PCCs are contraindicated in patients with known anaphylactic or severe systemic reactions to them or any of their components and in patients with disseminated intravascular coagulation or heparin-induced thrombocytopenia.¹³

In clinical trials, 4-factor PCC decreased the INR from a median of 3.0 to 1.3 or lower within 30 minutes. In contrast, the median INR 30 minutes after FFP administration was 2.4.¹⁴ Further studies revealed that effective hemostasis was obtained in 90% of patients who received PCC compared with 75% in the control group.¹⁴ The results of the current study support the findings of previous clinical trials that PCC is effective in reversing coagulopathy. Patients receiving PCC had a greater change in their INR and a lower postintervention INR than the FFP group. However, in the patients receiving PCC, we found higher mortality rates during hospital admission and within 90 days after admission; we also noted an increased number of thromboembolic events, though this difference was not significant. These poorer outcomes may reflect the fact that patients in the PCC group had more severe baseline coagulopathy and may also have had worse baseline physiologic status or more severe injuries. The median ISS in the PCC group was higher than that in the FFP group, which suggests the possibility of selection bias, with physicians favoring the PCC protocol in sicker patients.

Multiple previous studies have linked the use of blood products with worse clinical outcomes, and there has consequently been a nationwide push to limit the use of blood products.¹⁵⁻²² One of the proposed advantages of PCCs is their smaller volume and decreased risk of fluid overload and pulmonary compli-

cations.²³ Given these benefits, coupled with a more rapid and pronounced reversal of coagulopathy, one would expect a decrease in the use of blood products. However, patients in the PCC group were more likely to receive blood transfusions and more likely to receive massive transfusion of more than 10 U of pRBCs. Thus, the proposed benefit of decreased blood transfusion with PCCs was not realized in our study, again possibly because of differences in baseline physiologic status or severity of injury.

Thromboembolic events have long been the most alarming complication of PCCs.²⁴⁻³⁰ There were 14 thromboembolic events during the study period, with 6 occurring in patients who died within 90 days. Four of these events occurred in patients receiving PCCs, 3 in the ACS PCC and 1 in the trauma PCC group. There were no recorded pulmonary emboli; all events were deep vein thromboses. Our data seem to be approaching statistical significance, but there were too few events overall, limiting our conclusions.

This study was designed as a retrospective review of one institution's new protocol for reversal of anticoagulation. Several practices led to nonadherence. The most common was the failure to coadminister vitamin K with PCC. Other examples included failure to monitor post-PCC laboratory values and inaccurate weight-based dosing. Of note, patients in whom the protocol was followed had a higher baseline INR, a greater decrease in INR, and a greater number of pRBCs transfused. This finding suggests that the PCC protocol was more likely to be followed in patients with more severe baseline coagulopathy. Regardless, there were no significant differences in mortality rates between adherence and nonadherence groups.

Our study has multiple limitations. As with any retrospective study, there is an element of selection bias. We compared patients receiving PCC with patients receiving primarily FFP and vitamin K. If the protocol was followed universally by all physicians, then all patients would have received PCC, and there would not be an FFP group. One could postulate that the physicians used PCC more liberally in sicker

patients with higher INRs, which may have led to poorer outcomes in the PCC group.

Certainly, this argument is aided by the fact that the trauma patients who received PCC had higher INRs and higher ISSs. This study was not designed to collect similar data in ACS patients or to compare their relative levels of acuity and comorbid conditions. Future studies on ACS patients should include a Charlson index, APACHE (Acute Physiologic Assessment and Chronic Health Evaluation) score, or other means to assess and compare functional status and surgical risk. Our data collection started from the onset of the new protocol. Awareness, knowledge, and experience with the protocol will continue to increase with time and may affect selection of and adherence to the protocol.

Although our research showed statistical significance for many variables and outcomes, another limitation of our study is a sample too small to allow examination of rare events, such as thromboembolism. The small sample may have led to an underpowered analysis of these rare events and to a type II error. Several other nonrandomized studies have indicated an advantage of PCC over FFP, but randomized control trials have been inadequately powered to assess the clinical impact of PCC compared with FFP, particularly with regard to infrequent complications and mortality rates.¹

Prospective randomized trials are needed. In addition, as the use of 4-factor PCC continues to increase, outcomes should be collected in international databases to enable retrospective analysis and meta-analysis of rare outcomes, such as thromboembolic events. Only then will we be able to determine the safety of PCC for the reversal of coagulation in trauma and emergency surgery.

Conclusion

This retrospective analysis of a new anticoagulation reversal protocol found an increase in mortality rates, transfusion requirements, and thromboembolic events with the use of 4-factor PCCs. Given the gravity of

our results, further investigation is necessary. There is no value in treating a patient's coagulopathy if doing so increases that patient's risk of death. Improving laboratory results without a corresponding improvement in clinical outcomes is of little consequence in these critically ill patients. Although limited by possible selection bias, our data mandate further prospective randomized research into the role of 4-factor PCCs in these patients.

Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Drs Sellers, Bendas, and Becker drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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