

Assessing the Efficacy of Prothrombin Complex Concentrate in Multiply Injured Patients With High-Energy Pelvic and Extremity Fractures

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Objectives: Prothrombin complex concentrate (PCC) is being increasingly used for reversing induced coagulopathy of trauma. However, the use of PCC for reversing coagulopathy in multiply injured patients with pelvic and/or lower extremity fractures remains unclear. The aim of our study was to assess the efficacy of PCC for reversing coagulopathy in this group of patients.

Design: Two-year retrospective analysis.

Setting: Our level I trauma center.

Patients/Participants: All coagulopathic [International normalized ratio (INR) ≥ 1.5] trauma patients. Patients with femur, tibia, or pelvic fracture were included. Patients were divided into 2 groups: PCC (single dose) and fresh frozen plasma (FFP). Patients in the 2 groups were matched using propensity score matching.

Main Outcome Measurements: Time to correction of INR, time to intervention, development of thromboembolic complications, mortality, and cost of therapy.

Results: A total of 81 patients (PCC: 27, FFP: 54) were included. Patients who received PCC had faster correction of INR and shorter time to surgical intervention in comparison to patients who received FFP. PCC therapy was also associated with lower overall blood product requirement ($P = 0.02$) and lower transfusion costs ($P = 0.0001$).

Conclusions: In a matched cohort of multiply injured patients with pelvic and/or lower extremity fractures, administration of a single dose of PCC significantly reduced the time to correction of INR and time to intervention compared with patients who received FFP therapy. This may allow orthopaedic surgeons to more safely proceed with early, definitive fixation strategies.

Key Words: extremity fractures, PCC, traumatic coagulopathy, prothrombin complex, coagulopathy reversal

Level of Evidence: Therapeutic level III. See Instructions for Authors for a complete description of levels of evidence.

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INTRODUCTION

Acute traumatic coagulopathy is associated with increased risk of mortality after major trauma. Nearly one-quarter of all trauma patients present to an emergency department with clinically significant coagulopathy.^{1–3} The coagulopathy of trauma is multifactorial and caused by tissue trauma, hypoperfusion, hemodilution, and inflammation.⁴ Femur, tibia, and pelvic fractures are commonly observed in polytraumatized patients who present with acute traumatic coagulopathy. These musculoskeletal injuries have few physiologic consequences when occurring in isolation but in constellation may be an important source of hemorrhage. For example, in severely injured individuals with pelvic fracture, hemorrhage is an important, but potentially preventable, source of mortality.^{5–7} Pelvic ring and acetabular injuries infrequently occur in isolation. Associated musculoskeletal injuries may be sources of continued hemorrhage and contribute to the development or continuation of hypocoagulable states which may complicate resuscitative efforts. Additionally, the thrombogenic elements released after significant extremity trauma can augment the other proposed cascades of coagulopathy of trauma.^{8,9}

Recent developments in trauma resuscitation have established damage control resuscitation (DCR) as an effective strategy to counter the coagulopathy of trauma. DCR advocates liberal use of blood products, minimization of crystalloid, and replacement of coagulation factors.^{3,10} The use of fresh frozen plasma (FFP) as a component of DCR serves the dual purpose of volume support and coagulation factor replacement. However, the correction of coagulopathy using FFP alone requires considerable time.^{11–13} The use of recombinant factor VIIa in conjunction with FFP has been shown to reduce the time to correction of coagulopathy, but its higher cost limits its utility.^{13–15}

An alternative approach to this problem is concomitant use of prothrombin complex concentrates (PCCs). PCC can effectively correct acute traumatic coagulopathy at a much lower cost compared with rFVIIa.¹³ However, the role of PCC

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in reversing acute traumatic coagulopathy in multiply injured patients with pelvic and lower extremity fractures has not previously been described. The aim of this study was to assess the efficacy of PCC for reversing coagulopathy in polytrauma patients with high-energy pelvic and lower extremity fractures. We hypothesize that PCC can reduce the time to correction of coagulopathy compared with FFP.

PATIENTS AND METHODS

After approval by the University of Arizona Institutional Review Board, we performed a 2-year (2012–2013) retrospective analysis of a prospectively maintained database of all coagulopathic trauma patients presenting to our level I trauma center. We defined coagulopathy as an admission International normalized ratio (INR) of ≥ 1.5 that is associated with hypocoagulable state. Patients presenting with high-energy femur, tibia, or pelvic fracture were included in the study. Fractures of the femur, tibia, pelvic ring, and/or acetabulum were identified through review of radiographs, radiologist report, and orthopaedic consultation and operative reports. We excluded patients on preinjury warfarin therapy, patients who received multiple doses of PCC, and those who received PCC in conjunction with FFP during the initial resuscitation in the trauma department.

The following data points were recorded after review of the electronic medical records: patient demographics (age, sex, race, and ethnicity); mechanism and type of injury; vitals [systolic blood pressure, heart rate, temperature, and Glasgow Coma Scale (GCS) score] and laboratory parameters on presentation (INR, prothrombin time, partial thromboplastin time, and platelet count); time of initial INR and subsequent INR obtained as soon as reasonably practical after infusion completion; initial computed tomography and/or x-ray findings; units of blood products transfused, dosage of PCC, time of initiation of PCC or FFP transfusions, hospital and intensive care unit length of stay, thromboembolic complications, hospital costs and charges, cost of PCC therapy, cost of transfusions, and in-hospital mortality. The Injury Severity Score (ISS) and Abbreviated Injury Score were obtained from the trauma registry. Time of initiation of therapy was defined as the time from admission to the first dose of PCC or FFP. Blood products were defined as transfusion of packed red blood cells (PRBCs), FFP, and platelets.

We stratified our study population into 2 groups based on the type of therapy administered: those who received PCC therapy, and those who received FFP therapy. In PCC group, all patients received Profilnine SD (Grifols Biologicals, Inc, Los Angeles, CA), which is a 3-factor PCC. The dose of PCC administered was 25 units/kg, and we followed clinical guidelines for the transfusion of PCC. FFP was administered as the standard dose (15 mL/kg) based on the patient's weight. The decision to use PCC and/or FFP therapy was at the discretion of the attending surgeon. Patients who received PCC during initial resuscitation and required subsequent FFP transfusion during hospitalization were evaluated in the PCC group.

Patients of both groups (PCC and FFP therapy) were then matched using propensity score matching in a 1:2 (PCC:

FFP) ratio for age, sex, mechanism of injury, systolic blood pressure on admission, ISS, and INR on presentation.¹⁶ Propensity matching is an analog to the process of randomization that is commonly used in observational studies. The propensity score denotes the conditional probability of an individual to receive a certain treatment. A propensity score was generated for each patient based on all confounding factors using a logistic regression model. In our study, patients who received PCC therapy were matched to patients who received FFP therapy based on their propensity scores to obtain a similar cohort of patients.

The primary outcome measures were correction of INR, time to correction of INR, thromboembolic complications, and blood product utilization. Secondary outcome measures were mortality, cost of therapy, and cost of total blood products transfused. Time to correction of INR was defined as time between initial INR and subsequent INR < 1.5 after initiation of therapy (PCC or FFP). Thromboembolic complications were defined as pulmonary embolism, deep venous thromboembolism (DVT), mesenteric infarction, or myocardial infarction. Blood product utilization was defined as the total amount of blood products (PRBC, FFP, and platelets) transfused during the hospital stay. Cost of therapy was defined as cost of PCC or FFP required for reversal of coagulopathy. Cost of transfusion was defined as the cost of therapy plus the cost of blood products used for the reversal of coagulopathy. The cost of therapy and transfusion and also hospital costs and charges were obtained from the trauma registry.

Data are reported as mean \pm SD for continuous descriptive variables, median (range) for ordinal descriptive variables, and as proportions for categorical variables. We performed Mann–Whitney *U* and Student *t* test to explore for differences in the 2 groups (PCC and FFP) for continuous variables. We used χ^2 test to identify differences in outcomes between the 2 groups for categorical variables. For our study, we considered *P* value ≤ 0.05 as statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS, version 20; IBM Inc, Armonk, NY).

RESULTS

A total of 5146 trauma patients were reviewed, of which 26% ($n = 1318$) presented with high-energy fractures of the femur, tibia, pelvic ring, or acetabulum. Of the total number of patients with fractures ($n = 1318$), 43% ($n = 570$) had an INR ≥ 1.5 on admission. Among the coagulopathic patients, 35 patients received PCC therapy alone. After propensity score matching, a total of 81 patients (27 PCC:54 FFP, in a 1:2 ratio) were included in the analysis.

Table 1 highlights the demographics and presenting INR between the patients receiving PCC and FFP therapy. The mean age was 49 ± 26 years; 76.5% ($n = 62$) were male, mean INR was 2.2 ± 0.8 , and the median (interquartile range) ISS score was 25 (15–31). Blunt injury was the most commonly observed mechanism occurring in 81.5% ($n = 66$) of the patients. Motorcycle collision ($n = 43$) followed by fall ($n = 19$) were the most common modes of injury. Eighty-four percent ($n = 68$) of the patients had a femur fracture, 51.8%

TABLE 1. Demographics

Variables	PCC (N = 27)	FFP (N = 54)	P
Age, mean ± SD	48.3 ± 23.2	51.4 ± 28.4	0.61
Male, % (n)	74 (20)	77.8 (42)	0.78
ED GCS, median (IQR)	15 (13–15)	15 (13–15)	0.84
Initial INR, mean ± SD	2.3 ± 0.8	2.2 ± 0.9	0.61
Serum lactate, mean ± SD	3.1 ± 1.4	2.8 ± 1.2	0.31
Crystalloids, mean ± SD	4.2 ± 2.8	4.6 ± 2.9	0.56
ED SBP, median (IQR)	124 (106–141)	126 (110–141)	0.35
ED heart rate, median (IQR)	97 (82–116)	99 (84–113)	0.75
Pelvic fracture, % (n)	37 (10)	42.6 (23)	0.23
Femur fracture, % (n)	85.2 (23)	83.4 (45)	0.99
Tibia fracture, % (n)	48.1 (13)	53.7 (29)	0.64
Pelvic and femur, % (n)	11 (3)	2 (10)	0.52
Femur and tibia, % (n)	15 (4)	22 (12)	0.55
Blunt injury, % (n)	77.8 (21)	83.4 (45)	0.99
Mechanism of injury			
MVC, % (n)	44.5 (12)	57.4 (31)	0.34
Falls, % (n)	26 (7)	22.2 (12)	0.78
ISS, median (IQR)	24 (14–31)	25 (15–31)	0.52
AIS			
Extremity, median (IQR)	4 (4–5)	4 (4–5)	0.89
Head, median (IQR)	2 (1–2)	2 (1–2)	0.94
Chest, median (IQR)	1 (1–2)	1 (1–2)	0.81
Abdomen, median (IQR)	1 (1–2)	1 (1–2)	0.79

AIS, Abbreviated Injury Score; ED, emergency department; GCS, Glasgow Coma Scale; IQR, interquartile range; SBP, systolic blood pressure; MVC, Motor vehicle collision.

(n = 42) of the patients had a tibia fracture, and 40.7% (n = 33) of the patients had a pelvic fracture. There was no difference in age (P = 0.61), vital parameters on presentation, initial INR (P = 0.6), serum lactate (P = 0.31), crystalloids (P = 0.56), mechanism of injury (P = 0.54), injury severity (P = 0.52), and type of fractures (P = 0.63) between the 2 groups.

Table 2 highlights the correction of INR and blood product utilization between the 2 groups. INR was ultimately corrected in 91.3% (n = 74) of the patients. There was no difference in the proportion of patients with corrected INR (P = 0.99) between the 2 groups. Time to initiation of therapy (PCC or FFP) was similar in both groups (P = 0.06). The mean time to correction of INR was 374 ± 195 minutes. Patients receiving PCC had a faster correction of INR (P = 0.0001), and had a lower overall PRBC (P = 0.009) and FFP (P = 0.005) requirements compared with patients who received FFP therapy. Figure 1 demonstrates the proportion of patients with INR corrected and time to correction of INR in both groups (PCC and FFP).

All patients underwent surgical fixation of their fractures. Patients who received PCC had faster time to surgical intervention compared with patients who received FFP alone (P = 0.0002). 11.1% (n = 9) developed in-hospital thromboembolic complications. There was no difference in the development of DVT (P = 0.68) and mesenteric infarction (P = 0.99) between the 2 groups. The overall mortality rate was 25.9% (n = 21). There was no difference in

TABLE 2. Outcomes

Variables	PCC (N = 27)	FFP (N = 54)	P
Time to initiation of therapy, min	55 ± 26	70 ± 36	0.06
INR			
Correction of INR	92.6 (25)	90.7 (49)	0.99
Time to correction, min	285 ± 161	490 ± 208	0.0001
Blood products			
PRBC, units	3.2 ± 1.9	5.4 ± 4.1	0.009
FFP, units	5.1 ± 3.6	7.8 ± 4.1	0.005
Platelets, units	1.4 ± 2.3	1.6 ± 2.4	0.72
Time to surgical intervention, min	324 ± 192	702 ± 481	0.0002
Thromboembolic complications			
DVT	11.1 (3)	7.4 (4)	0.68
Mesenteric infarction	3.7 (1)	1.8 (1)	0.99
Mortality	22.3 (6)	27.8 (15)	0.78

Results are reported in mean ± SD or % (n). Values in bold represent statistically significant values.

mortality rate between the patients who received PCC therapy in comparison with patients who received FFP (P = 0.78). Table 2 highlights the complications and mortality between the 2 groups.

Table 3 highlights the differences in length of stay and costs between the patients receiving PCC and FFP therapy. The cost of therapy was higher (P = 0.02) in patients who received PCC therapy compared with patients who received FFP therapy. However, the total cost of transfusion was lower (P = 0.0001) in the patients who received PCC compared with the patients who received FFP for correction of their coagulopathy. There was no difference in the hospital (P = 0.34) and intensive care unit length of stay (P = 0.15), the hospital costs (P = 0.73), and hospital charges (P = 0.84) between the 2 groups.

DISCUSSION

The correction of coagulopathy remains an important component of initial resuscitation of trauma patients. In

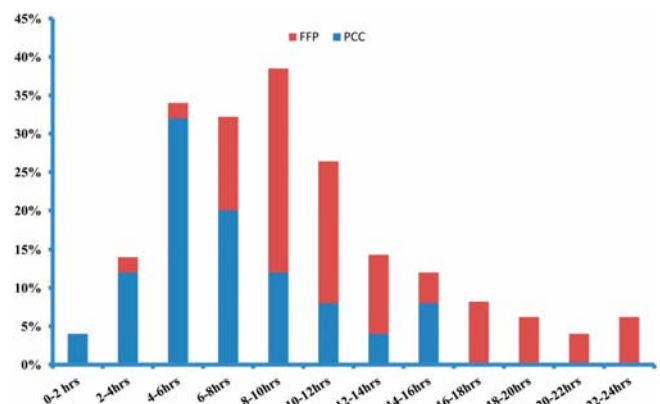


FIGURE 1. Proportion of patients with INR corrected and time to correction of INR in both the groups (PCC and FFP). **Editor's Note:** A color image accompanies the online version of this article.

TABLE 3. LOS and Cost Analysis

Variables	PCC (N = 27)	FFP (N = 54)	P
LOS			
Hospital LOS, mean ± SD	4 (2–9)	5 (2–10)	0.34
ICU LOS, median (IQR)	1 (0–3)	1 (0–3)	0.15
Cost analysis			
Cost of therapy, mean ± SD	1871 ± 1189	1295 ± 942	0.02
Cost of transfusion, mean ± SD	6334 ± 1576	8169 ± 1858	0.0001
Hospital costs, mean ± SD	54,976 ± 48,147	51,204 ± 45,683	0.73
Hospital charges, mean ± SD	204,614 ± 151,628	197,962 ± 138,451	0.84

LOS is represented in days; cost is represented in US dollar. Values in bold represent statistically significant values.
LOS, length of stay.

patients with high-energy pelvic and lower extremity fractures, it is even more important as it may affect the time to definitive surgical intervention and development of thromboembolic complications. However, the role of factor replacement in this group of patients remains unknown. The results of our study indicate a promising role for PCC as a suitable therapy to correct coagulopathy of trauma in patients with high-energy pelvic and lower extremity fractures.

Early operative fixation is an important determinant of in-hospital and long-term functional outcomes after high-energy pelvic and lower extremity fractures. The literature suggests a trend toward higher mortality, thromboembolic complications, and malunion in cases in which fixation is performed after 24 hours.¹⁷ However, in patients presenting with acute coagulopathy of trauma, operative intervention may be delayed. Conventionally, coagulopathy is corrected using FFP; however, with the advent of DCR, factor replacement therapy is gaining favor. During the acute resuscitation of trauma patients, FFP is often given owing to its ability to provide volume support as well as coagulation factor replacement. However, FFP administration requires ABO compatibility screening and thawing process before it can be transfused. This may add significant delay before the initiation of therapy.^{18–20} In contrast, PCC is a pooled plasma product available in 3- and 4-factor preparations containing varying concentrations of factors II, IX, X and, in 4-factor preparations, VII. It is available in ready-to-use packaging and can be administered immediately without the need for compatibility screening. Recently, a 4-factor preparation has been made available in the United States; this preparation provides normal levels of factor VII along with factors II, IX, and X.²¹ Compared with 3-factor PCC, 4-factor preparations are extremely expensive.

We observed shorter time to initiation of therapy in the PCC group; however it did not reach statistical significance. As most of our population was hemodynamically stable, this time to initiation of therapy might not reflect the true utility of PCC as an immediately available alternative to FFP. Our institutional experience has shown that in situations where coagulation factor replacement is immediately warranted, PCC is a safe and effective alternative to FFP.

Several studies have questioned the ability of FFP to rapidly reverse coagulopathy in trauma patients. In a study comparing the use of PCC and FFP for the reversal of coagulopathy in a porcine animal model, Dickneite et al showed that PCC more effectively normalizes prothrombin time, bleeding time, peak thrombin generation, and better controls bleeding. Their experiment demonstrated that time to hemostasis and blood loss after femur or spleen injury was significantly reduced by PCC treatment in comparison with FFP.²⁰ Demeyere et al²² showed that patients undergoing cardiac surgery had faster INR correction after receiving PCC compared with patients who received FFP. In a previous study, we assessed the effects of combined PCC and FFP therapy for the correction of coagulopathy of trauma. The result of that study indicated that combination therapy leads to earlier correction and better outcomes after coagulopathy of trauma.¹¹ Consistent with these reports and additionally published literature, we observed earlier correction of coagulopathy in patients who received PCC. In this series, the PCC group achieved normal INR in 2–7 hours compared with more than 11 hours in FFP group.

Several studies have assessed different factor replacement strategies for the correction of coagulopathy including recombinant factor VIIa (rVIIa) and PCC. Factor rVIIa has consistently outperformed FFP; however, outcomes are equivalent compared with PCC. A previous study conducted at our institution compared outcomes of patients treated with rVIIa to those treated with PCC. This study indicated that both strategies effectively normalized INR; there was no difference in the change in INR despite improved cost effectiveness in the PCC group.¹³ In the context of the emerging literature in favor of PCC, we strongly believe that PCC can provide similar, if not better results, as compared with rVIIa but at a much lower cost.

Time to operative intervention was significantly shorter in PCC group compared with FFP group. Earlier correction of coagulopathy seems to be the most plausible argument in favor of this observation as both groups are propensity score matched for injury severity, presenting vitals, and injury patterns. The presence of coagulopathy in trauma patients precludes safe surgery and in patients who are hemodynamically stable, surgery is often deferred until

appropriate correction of coagulopathy is obtained. We observed that in most patients, correction of coagulopathy was ultimately obtained using FFP but required significantly longer time compared with PCC.

Several animal studies have indicated that standard doses of PCC lead to 2–4 times higher levels of coagulation factors compared with standard doses of FFP.^{20,23} This discrepancy in factor levels may be responsible for the significant delays in INR correction and could also be responsible for the higher blood product requirement observed.²⁴ The group of patients who received PCC required significantly lower amounts of PRBCs compared with FFP group. Although we initially excluded patients from PCC group who also required FFP during the initial resuscitation phase, we later found that these patients required fewer units of FFP over the course of their hospitalizations. Increased concentration of factor provided by both 3-factor and 4-factor PCC may decrease the overall blood product transfusion requirements and ultimately lead to shorter time to correction of INR.

One major concern regarding the use of PCC or any other concentrated factor replacement is the increased risk of the development of thromboembolic complications. However, this concern may be unfounded as numerous authors have shown that standard doses of PCC do not increase the risk of developing thromboembolic complications.^{12,25–27} Our own work has shown that there was no difference in thromboembolic complications between patients receiving PCC and FFP versus solely FFP.⁵ Similarly, our study shows no difference in the development of DVT and mesenteric infarction between the 2 groups. Two patients who developed mesenteric infarction during the study period had independent risk factors predisposing them to these complications. One of the patients had a history of atrial fibrillation but was found to be noncompliant with medications, and the second patient presented with prolonged hypotension resulting in a low flow state in an already compromised blood supply due to significant atherosclerosis.

We observed no significant difference in mortality rate between the 2 groups. The published literature comparing PCC with FFP and other concentrated factor replacement therapies remains divided as far as survival advantage of PCC is concerned.^{11,13,23,28} Nonetheless, our previous studies comparing PCC and other therapies for correction of coagulopathy have demonstrated survival advantage of PCC over rVIIa and FFP.^{13,28} This finding was not repeated in this study as we found no significant difference in mortality between the groups.

A secondary additional concern related to the use of PCC is its associated costs. Although PCC is less costly compared with other concentrated factor replacement therapies, it costs more than FFP. Intuitively, we found higher cost of therapy in PCC group compared with FFP. However, the results of our study indicate that overall cost of transfusion was significantly lower in PCC group.^{29,30} This reduction in cost can be attributed to reduced amount of transfusion in PCC group. During the study period, our institution exclusively used 3-factor preparations but has since transitioned to a 4-factor preparation owing to recent regulatory approval in the United States. Unfortunately, the present data do not

address issues of cost with 4-factor preparations. Nonetheless, we observed no statistically significant difference in overall hospital costs between the groups. The results of this study are consistent with the results of our previous studies in which significant transfusion related cost reduction in PCC groups was observed.^{11,28}

The results of our study should be interpreted within the context of its limitations. First, its nonrandomized, retrospective nature is associated with certain, inherent inaccuracies of data collection. This study is a single-center study with relatively small sample size, and caution should be practiced before generalizing the results beyond similar population groups. Furthermore, a detailed analysis of coagulopathy using thromboelastogram was not available for this study, which could have provided more insight into coagulation profile. One additional source of error is the absence of a standardized protocol for obtaining posttransfusion blood draws; however, it is a standard practice at our institution to administer PCC or FFP at the time of subsequent blood sampling. This lack of standardization may introduce considerable variability in the timing of subsequent blood sampling; presumably, both groups were affected equally and, in isolation, this potential source of error is unlikely to explain the observed results. Additionally, our previous work and the work of others have failed to demonstrate an increased risk of thromboembolic complications in appropriately dosed patients; however, this study is underpowered to evaluate this claim. Judicious use of PCC is recommended until more robust data are available to address concerns regarding safety. Nevertheless and to our knowledge, this is the first study to discuss the utility of PCC for correction of traumatic coagulopathy in patients with high-energy femur, tibia, and/or pelvic fractures.

CONCLUSIONS

In a matched cohort of patients with extremity fractures, the use of a single dose of PCC significantly reduced the time to correction of INR and time to intervention compared with patients who received FFP therapy. A further investigation for the utility of PCC as a therapy of choice for the correction of coagulopathy after significant extremity injuries is required.

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Invited Commentary

Joseph et al continue their commendable work regarding the efficacy and safety of prothrombin complex concentrate (PCC) products for the urgent reversal of trauma coagulopathy.^{1,2} During the 2-year period 2012–2013, the authors did not impose the use of PCC for elevated international normalized ratio (INR) correction, but rather surgeons were free to choose the new PCC product or to use the time-honored standard of fresh frozen plasma. There is no mention of the use of thromboelastography. Instead, an INR ≥ 1.5 was chosen as a surrogate measure of trauma coagulopathy, a teleological error that the authors acknowledge, but this can be excused because the INR is what most of us are measuring in day-to-day practice anyway. The authors found through propensity matching that using PCC instead of fresh frozen plasma led to faster correction of INR, shorter time to surgical intervention, lower blood product usage, and lower transfusion costs.

PCC products contain various concentrations of the clotting factors II, IX, and X, with or without VII, and can be administered immediately in a weight-based dose without the need for screening. The products are already in common use for the reversal of warfarin-induced coagulopathy and toxicity. Trauma surgeons are accustomed to using similar products to rapidly reverse elevated INRs in patients with hemorrhagic brain injuries.³ The use of PCC in the acute management of trauma coagulopathy in multiply injured patients is not new⁴ but has been slow to acceptance because of concerns of efficacy and safety. This study, combined with several others, will help bring the use of PCC to the “prime time”. PCC products have an enviable safety and efficacy record, as well as a reproducible association with faster surgical intervention, lower blood product usage, and lower transfusion costs. I highly recommend this article and this practice to the readers of the Journal of Orthopaedic Trauma.

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