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# Prothrombin complex concentrate: An effective therapy in reversing the coagulopathy of traumatic brain injury

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<b>BACKGROUND:</b>	Coagulopathy in patients with traumatic brain injury (TBI) is a well-studied concept. Prothrombin complex concentrate (PCC) has been shown to be an effective treatment modality for correction of TBI coagulopathy. However, its use and effectiveness compared with recombinant factor VII (rFVIIa) in TBI has not been established. The purpose of this study was to compare PCC and rFVIIa for the correction of TBI coagulopathy.
<b>METHODS:</b>	All patients with a TBI and an induced or acquired coagulopathy whom received rFVIIa or PCC at our Level I trauma center during a 4-year period were reviewed. Data collected included demographics, changes in international normalized ratio and blood products transfusion, craniotomy rates, and time to neurosurgical intervention, thromboembolic complications, and mortality differences.
<b>RESULTS:</b>	The study was composed of 85 TBI patients, of whom 64 patients received PCC while 21 patients received rFVIIa. PCC group were more likely to be on coumadin (44% vs. 14%, $p = 0.01$ ). There was a significant decline in packed red blood cell transfusion and fresh frozen plasma after PCC administration ( $p < 0.01$ ). There was no statistically significant difference in the craniotomy rate (28% vs. 10%, $p = 0.1$ ) or the mean time to intervention between the two groups (201 [33] vs. 230 [10], $p = 0.9$ ). Mortality rates were lower in the PCC group compared with rFVIIa (67% vs. 47%, $p = 0.02$ ). Subsequent thromboembolic event was seen in one patient on rFVIIa. Mean cost of treatment per patient on PCC was \$1,007 compared with \$5,757 for rFVIIa ( $p < 0.01$ ).
<b>CONCLUSION:</b>	PCC is safe and effective for treating coagulopathy in TBI patients, while reducing costs and resource use. PCC should be considered as an effective therapy to treat both acquired and induced coagulopathy in TBI with or without prehospital coumadin use. ( <i>J Trauma Acute Care Surg.</i> 2013;74: 248–253. Copyright © 2013 by Lippincott Williams & Wilkins)
<b>LEVEL OF EVIDENCE:</b>	Therapeutic study, level IV.
<b>KEY WORDS:</b>	Prothrombin concentrate complex; rFVIIa; traumatic brain injury; coagulopathy of trauma; craniotomy.

Traumatic brain injury (TBI) is one of the leading causes of death and disability in the United States.<sup>1,2</sup> While there are no therapeutic options to reverse the neuronal injury, there are treatment options for the sequelae that follows that injury. Adequate fluid resuscitation, reversal of coagulopathy, and maintenance of cerebral perfusion are the key to management.<sup>3–5</sup>

Coagulopathy in TBI patients may be caused by concomitant hemorrhage and crystalloid administration, prehospital use of anticoagulants, or the direct insult to the brain.<sup>6</sup> Regardless of the cause, coagulopathy in TBI patients is detrimental and precludes safe neurosurgical intervention.<sup>5–10</sup> Typical reversal of TBI coagulopathy is accomplished with the use of fresh frozen plasma (FFP); however, this method suffers from drawbacks for its inability to reliably fully reverse

traumatic coagulopathy.<sup>5</sup> Recombinant factor VII (rFVIIa) has been widely investigated as a safe and effective adjunctive hemostatic agent in the treatment of TBI coagulopathy.<sup>7–9</sup> rFVIIa is available at our institute for use in select coagulopathic trauma patients. Recently however, prothrombin complex concentrate (PCC) has been shown to be an effective treatment modality for correction of traumatic coagulopathy in patients with or without preinjury warfarin use.<sup>5</sup> Numerous studies have described the use of rFVIIa for reversal of TBI coagulopathy and in coagulopathic TBI patients requiring immediate neurosurgical intervention. The effectiveness of PCC in the reversal of coagulopathy associated with TBI is, however, yet to be determined.

The purpose of this study was to compare PCC and rFVIIa in the correction of TBI coagulopathy. A secondary aim was to document any changing trends in the use of rFVIIa and PCC in TBI patients at our institute and explore for differences in outcome.

## PATIENTS AND METHODS

After approval by the University of Arizona Institutional Review Board, the trauma registry at the University of Arizona Medical Center was used to identify all patients with TBI and an induced (preinjury anticoagulation) or acquired (coagulopathy of

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**TABLE 1.** Demographics

	rFVIIa	PCC	<i>p</i>
Age, mean (SD)	42 (22.6)	59 (23.7)	<0.01
Male, %	86	67	0.04
ISS, mean (SD)	40.9 (15.1)	27.8 (15.5)	<0.01
AIS score, mean (SD)			
Head	4.3 (0.7)	3.9 (1.2)	0.07
Face	3.2 (0.6)	2.1 (0.9)	<0.01
Thorax	3.9 (1.1)	2.9 (0.9)	<0.01
Abdomen	3.5 (1.0)	2.7 (0.9)	0.06
SBP, mean (SD)	118.7 (40.9)	129.4 (40.5)	0.31
GCS score, mean (SD)	8.0 (4.9)	8.8 (5.3)	0.53
Blunt injury, %	90	94	0.63
Coumadin, %	14	44	<0.01

systolic blood pressure.

trauma) coagulopathy, who received rFVIIa or PCC during a 4-year period (2007–2010). The selection of patients included those unable to tolerate the volume of FFP required for the correction of coagulopathy, those needing emergency craniotomy with immediate coagulopathy reversal, and those with worsening coagulopathy despite massive resuscitations. Patients with international normalized ratio (INR) refractory to the use of FFP were also included in the study.

Clinical guidelines for the transfusion of rFVIIa and PCC were followed during the period of this study. Decision for treatment of the coagulopathy with rFVIIa or PCC was at the discretion of the attending trauma physician or neurosurgeon.

All patients received PCC delivered as Profilnine SD (Grifols Biologicals; Los Angeles, CA). Our institution uses a three-factor PCC, Profilnine SD, which contains no more than 35 U of FVII. Dosage was based on weight, that is, 25 U/kg. rFVIIa was delivered as rFVIIa (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark), and the dosage used was 90 µg/kg.

Data that were obtained from the trauma registry included demographics (age and sex), Injury Severity Scale (ISS), Glasgow Coma Scale (GCS) score, systolic blood pressure, hospital and intensive care unit (ICU) lengths of stay (LOS), and mortality. The following data points were extracted from the electronic medical record: prehospital coumadin use, neurosurgical intervention, time to intervention, thromboembolic complications, GCS score at discharge, and INR before and after PCC and rFVIIa administration; all blood product administrations (red blood cells, FFP, cryoprecipitate, and platelets) 48 hours before and 48 hours after PCC and rFVIIa administration were also recorded. Neurosurgical intervention was defined as craniotomy or craniectomy. Time to intervention was defined as the difference in time from drug administration to the start of the surgical procedure.

Thromboembolic complications were defined by the presence of myocardial infarction, deep venous thrombosis, pulmonary embolism, cerebrovascular event, mesenteric artery infarction, inferior vena cava thrombosis, or peripheral venous thrombosis following administration of PCC or rFVIIa.

A subgroup analysis was also performed for patients with isolated head injuries, and no severe body area trauma, which

was defined as patients with chest, face, abdomen, and extremity Abbreviated Injury Scale (AIS) injury score of less than 3. Patients who died within 24 hours of admission were excluded from the study.

We examined the yearly changes in the use of rFVIIa and PCC in all TBI patients and compared the two groups with respect to baseline demographics and outcomes. Data are presented as mean or median ± SD. Comparison of the continuous data was performed by Wilcoxon rank-sum test and Student's *t* test. Pearson's  $\chi^2$  was used to explore differences within the distribution of descriptive categorical variables. Statistical analysis was performed using SPSS 18.0 statistical software. Statistical significance was defined as  $p \leq 0.05$ .

## RESULTS

The study was composed of 85 TBI patients; 60 patients having isolated brain injuries, while 25 had associated minor injuries to the face, chest, abdomen or extremities (AIS score < 3). Of the 85 patients enrolled in the study, 64 patients (75%) received PCC, while 21 patients (25%) received rFVIIa. Of the 85 patients enrolled in the study, 31 (36%) were on coumadin.

Differences between groups in demographics are seen in Table 1. PCC group patients were older (59.5[23.7] vs. 42 [22.6],  $p < 0.02$ ), had a lower ISS (27.8 [15.5] vs. 40.9 [15.1],  $p < 0.01$ ), and were more likely to be on coumadin (44% vs. 14%,  $p < 0.01$ ). The main type of intracranial hemorrhage found on initial head computed tomography (CT) was subdural hematoma (68%) in the PCC group and subarachnoid hemorrhage (64%) in the rFVIIa group. Table 2 highlights the head injury patterns on initial head CT in both groups.

PCC and rFVIIa both effectively normalized INR. There was no difference in the change in INR after administration of PCC in comparison with rFVIIa (0.7 [0.7] vs. 0.39 [2.4],  $p = 0.58$ ). (Table 2) There were significant reductions recorded in the number of units of packed red blood cells (PRBC), FFP, and platelets transfused after PCC administration. However, sub-analysis of isolated TBI patients showed no statistical significance in the reductions in the number of units of PRBC, FFP or platelets transfused after PCC administration (Table 3).

The mean (SD) hospital LOS in the PCC group was 8.3 (8.3) days compared with 9.6 (11.7) days in the rFVIIa group. There was no statistically significant difference in the craniotomy rate in patients who received PCC in comparison with the rFVIIa-treated group (28% vs. 10 %,  $p = 0.1$ ). The mean

**TABLE 2.** Findings on Initial Head CT

	rFVIIa, %	PCC, %	<i>p</i>
Skull fracture	7	18	0.44
ICH			
SDH	60	68	0.56
EDH	7	18	0.44
SAH	64	47	0.23
IPH	40	34	0.65
IVH	7	16	0.68

EDH, epidural hematoma; IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hematoma.

**TABLE 3.** Coagulation Profile and Blood Product Before and After FVIIa and PCC Administration

	rFVIIa	PCC	<i>p</i>
All patients			
INR			
Before therapy	2.6 (2.1)	2.2 (0.6)	0.44
After therapy	1.58 (1.9)	1.4 (0.3)	0.77
Change in INR	0.39 (2.4)	0.7 (0.7)	0.58
PRBC			
Before therapy	16.2 (12.7)	4 (6.5)	<0.01
After therapy	6.3 (6.5)	2.1 (3.6)	<0.01
FFP			
Before therapy	6.6 (7.3)	2.5 (3.5)	0.03
After therapy	8.3 (8.0)	2.1 (2.7)	<0.01
Platelets			
Before therapy	1.2 (1.4)	0.3 (0.7)	0.02
After therapy	1.4 (1.5)	0.5 (1.0)	0.03
Isolated TBI patients			
INR			
Before therapy	2.4 (2.1)	2.2 (0.8)	0.78
After therapy	1.0 (1.9)	1.4 (0.2)	<0.01
Change in INR	1.7 (2.4)	0.8 (0.7)	0.36
PRBC			
Before therapy	14.7 (12.7)	3.5 (6.5)	0.09
After therapy	4.0 (6.5)	1.7 (2.9)	0.11
FFP			
Before therapy	9.2 (8.8)	2.5 (3.5)	0.11
After therapy	2.0 (2.8)	2.1 (2.7)	0.93
Platelets			
Before therapy	1.2 (1.4)	0.3 (0.7)	0.13
After therapy	1.4 (1.5)	0.5 (1.0)	0.73

(SD) time to intervention in the PCC group was 201 (33) minutes compared with 230 (10) minutes in the rFVIIa group ( $p = 0.9$ ). The differences in outcomes between the two groups are presented in Table 4.

**TABLE 4.** Outcomes

	rFVIIa	PCC	<i>p</i>
All patients			
ICU LOS	6.4 (6.7)	6.0 (6.0)	0.81
Hospital LOS	9.6 (11.7)	8.3 (8.3)	0.65
Discharge GCS	12.8 (1.4)	13.09 (0.5)	0.9
Complications	5%	Nil	0.24
Craniotomy	10%	28%	0.1
Time to intervention	230 (10)	201 (33)	0.9
Mortality	67%	47%	0.02
Isolated TBI patients			
ICU LOS	5.8 (6.4)	5.8 (5.8)	0.93
Hospital LOS	12.1 (14.7)	8.1 (8.4)	0.45
Discharge GCS	12 (3)	12.87 (3.7)	0.9
Craniotomy	40%	27%	0.5
Time to intervention	230 (10)	207 (28)	0.2
Complications	Nil	Nil	NA
Mortality	44%	43%	0.03

**TABLE 5.** Cost Analysis

	rFVIIa	PCC	<i>p</i>
All patients			
Cost of therapy	5,757 (3,865)	1,007 (348)	<0.01
Hospital cost	62,491 (39,512)	31,694 (32,664)	<0.01
Hospital charges	197,928 (134,532)	120,594 (122,575)	0.02
Isolated TBI patients			
Cost of therapy	7,448 (3,865)	1,007 (4,176)	<0.01
Hospital cost	62,484 (39,512)	31,694 (44,834)	<0.01
Hospital charges	199,645 (15,677)	120,549 (122,575)	0.03

There was no difference in the functional outcome of the survivors as measured by discharge GCS score (12.8 [1.4] vs. 13.09 [0.5],  $p = 0.9$ ).

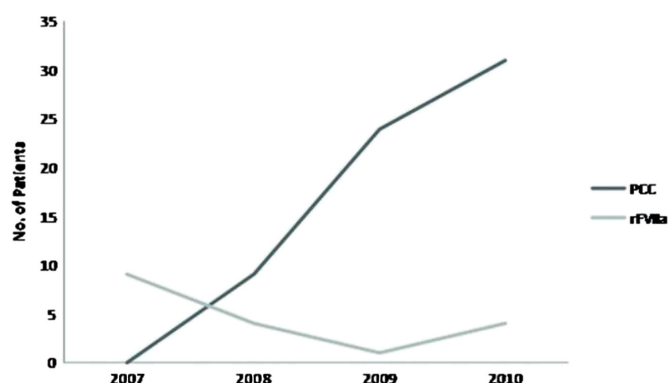
A single case of deep venous thrombosis was seen in a patient on rFVIIa. No thromboembolic complications were seen in patients on PCC; the difference in complications between the two groups was not statistically significant ( $p = 0.24$ ). The overall mortality was lower in the patient group that received PCC (47%) compared with 67% mortality rate in the patient groups receiving factor VIIa ( $p = 0.03$ ).

The mean cost of treatment per patient was significantly higher in the rFVIIa-treated group when compared with patients who received PCC (\$5,757 [\$3,865] vs. \$1,007 [4,176],  $p < 0.01$ ) (Table 5).

Figure 1 indicates a yearly decline in the use of rFVIIa and an increase in PCC use as a treatment option for traumatic coagulopathy at our institute.

## DISCUSSION

Coagulopathy and TBI are a deadly combination, and a rapid correction of coagulopathy in these patients may provide for better outcomes. In this study, we compared two treatment modalities—rFVIIa and PCC—for the treatment of TBI coagulopathy. We chose to examine the effects of PCC because of its established safety profile and significant cost reduction ability compared with rFVIIa. We found that both PCC and rFVIIa effectively normalized INR, and there was no difference in the change in INR after administration of PCC in comparison with rFVIIa. We did not find any statistically significant difference in

**Figure 1.** PCC and rFVIIa use in Coagulopathy of Traumatic Brain Injury.

outcomes in the form of neurosurgical intervention, time to intervention, or functional outcome measures (GCS score at discharge). In addition, we also documented a decline in the use of rFVIIa for reversal of coagulopathy at our institute. We concluded that PCC is as safe and effective as rFVIIa for treating coagulopathy in TBI patients, while reducing costs and resource use.

Coagulopathy in trauma patients is an undesirable event in the acute phase of injury.<sup>5</sup> Patients presenting with acute traumatic coagulopathy have a fourfold increase in mortality and are more likely to require massive transfusions and to develop multiple-organ failure.<sup>11</sup> Development of coagulopathy in patients with brain injury is well studied.<sup>5,7,8,10</sup> The published data regarding the incidence of coagulopathy in TBI patients are not consistent and may range from 8% to 86%.<sup>10</sup> Coagulopathy in TBI patients is associated with increasing morbidity, disability, and a 10-fold increase in death.<sup>12</sup> Piek et al.,<sup>13</sup> in a study involving 734 patients, found coagulopathy to be an independent predictor of unfavorable outcomes in patients with TBI. Early and rapid correction of traumatic coagulopathy may lead to reduced bleeding, lower transfusion requirements, and improved survival.<sup>3,11,14</sup>

The treatment options available for TBI coagulopathy included FFP, rFVIIa, and PCC.<sup>5,6,15</sup> FFP requires ABO compatibility and is typically available only after blood type has been established and the plasma has been thawed. Second, reversal with FFP in this patient population takes time and delays time toward neurosurgical intervention.<sup>6,15</sup>

rFVIIa is one of the most studied hemostatic agents used for the treatment of TBI coagulopathy.<sup>9</sup> rFVIIa was originally developed for bleeding control in hemophilia patients with inhibitors. However, recent studies have shown it to be successful in patients requiring neurosurgical intervention. Mayer et al.<sup>16</sup> concluded that rFVIIa given within 4 hours after the onset of symptoms of intracerebral hemorrhage significantly reduced growth of the hematoma compared with the placebo group. Numerous reports exist describing the successful use of rFVIIa for both traumatic and nontraumatic neurosurgical intervention. Coagulopathy precludes from safe neurosurgical intervention, which may result in poor outcomes if the primary injury is not taken care of. Stein et al.<sup>6</sup> concluded that the use of rFVIIa reduced the time to intervention in severe TBI patients when compared with FFP (144 minutes vs. 446 minutes). In our study the mean time to intervention in the PCC group was 207 minutes compared with 230 minutes in the rFVIIa-treated group. Although the time to intervention was faster in the PCC group, it was not statistically significant.

Although PCC was originally developed for hemophilia B treatment, recently, its indications have shifted toward replacement therapy of congenital or acquired deficiency of vitamin K–dependent clotting factors.<sup>17</sup> Small case series have suggested a potential role of PCC, for rapid reversal of warfarin induced coagulopathy.<sup>18</sup> Recently, our institute showed that PCC therapy leads to a significant correction in INR in all trauma patients, regardless of coumadin use, and concomitant reduction in blood product transfusion.<sup>5</sup> According to the American College of Chest Physicians recommendations, PCC is used as the first-line drug in the reversal of anticoagulation therapy and in patients with life-threatening bleeding and an increased INR.<sup>19</sup>

When compared with FFP, PCC has shown to reduce INR rapidly at lower volumes. FFP is often administered at the doses of 15 mL/kg, whereas the recommended doses of PCC required to achieve 50% to 100% levels of prothrombin complex factors can be delivered by the injection volumes of 1 to 2 mL/kg. The main advantages of coagulation factor concentrates are related to their immediate availability, which facilitates early and prompt correction of coagulopathy while avoiding further dilution.<sup>20</sup> The dosing scheme for PCC is well studied, with 25 U/kg being the standard dose. PCC dosage is calculated according to body weight, degree of INR prolongation, and desired level of correction, and preparations vary in the ratio of their coagulation factor components.<sup>21</sup> Pabinger et al.<sup>22</sup> used PCC doses of 25, 35, and 50 IU/kg in accordance with the baseline INR. These dosing schedules achieve normalization of INR in 93% of the patients. Safaoui et al.<sup>23</sup> developed a protocol of using 2,000 U for patients weighing less than 90 kg and 3,000 U for patients weighing more than 90 kg for rapid reversal of warfarin coagulopathy in traumatic intracranial hemorrhage.

The indications, safety profile and optimal doses of rFVIIa are not known.<sup>24</sup> Many of the early case series used a mean dose of 120 mg/kg, but in a randomized control trial, Boffard et al.<sup>25</sup> used a much larger dose of 200 mg/kg followed by two additional doses of 100 mg/kg. Another limitation in the use of rFVIIa is that, for effective functioning, it requires pH greater than 7.2, platelets of greater than 100,000 and an adequate body temperature.<sup>12</sup>

Clinically, there is a lack of evidence for the use of PCC in place of rFVIIa. However, animal studies have shown PCC to be more effective than rFVIIa in maintaining hemostasis. PCC along with fibrinogen has shown to reduce blood loss and time to hemostasis in a porcine model for dilutional coagulopathy. Dickneite et al.<sup>26</sup> compared PCC with rFVIIa in a porcine trauma model and concluded that PCC is more effective than rFVIIa in reducing INR and maintaining hemostasis. The PCC however used in these studies is Beriplex B/N, which is currently only available in the European market and differs from the Profilnine SD, which is used at our institution. The Profilnine SD PCC used at our institution contains no more than 35 U of FVII per 100 U of PCC. This relatively low concentration classifies this PCC as a three-factor PCC.<sup>27</sup>

Dickneite et al.<sup>26</sup> showed increased survival after use of PCC. Boffard et al.<sup>25</sup> also showed that factor VIIa use is not associated with a decline in mortality. In our study, the overall mortality in the PCC group was lower than that of the patients who received rFVIIa. However, our study was not powered or designed to compare outcomes. We do note that the overall mortality rate at our institution remained constant over the change from rFVIIa to PCC for the reversal of both acquired and induced traumatic coagulopathy. Lower ISS in patients who received PCC might be also attributed to this difference in mortality.

We recorded a difference in PRBC administered before the administration of PCC or rFVIIa. Patients in the rFVIIa received 16 U of PRBC before administration of rFVIIa as compared with 4 U in the PCC group. This difference can be explained by the fact that patients who received rFVIIa were more injured as indicated by the higher ISS. Second, the most

common indication for PCC use was to reverse warfarin. Finally, the difference may also be attributed to the high costs of rFVIIa, which was under the control of a “gate keeper” at our institution resulting in a delayed release of the drug.<sup>6</sup>

A single complication, deep vein thrombosis, was seen in our study in a patient on rFVIIa. Given the potent procoagulant activity of rFVIIa administered in pharmacologic doses, there has been concern regarding the potential for thromboembolic complications.<sup>8,28</sup> A retrospective review of thromboembolic complications in an otherwise unselected consecutive series of trauma patients receiving rFVIIa off-label at a single major trauma center revealed that in 285 patients receiving the drug, 27 (9%) had a subsequent thromboembolic event.<sup>24</sup>

Boffard et al.<sup>25</sup> demonstrated a total of 12 thromboembolic events in a randomized clinical trial—6 in rFVIIa-treated patients and 6 in placebo-treated patients. In our study we did not encounter any thromboembolic complications in patients receiving PCC. The overall complication rates were low in the study, similar to other studies.<sup>5,22</sup> Pabinger et al.<sup>22</sup> recorded a 6.7% incidence of thromboembolic complication in patients treated with PCC. In a previous study at our institute, we recorded two cases of deep venous thrombosis and one case of mesenteric thrombosis in trauma patients receiving PCC.<sup>5</sup>

Questions regarding the cost and safety profile of rFVIIa have been raised. In our study, the mean cost for treatment per patient on PCC was calculated to be \$1,007 compared with \$5,757 for rFVIIa. Stein et al.<sup>7</sup> reported that factor VIIa is an expensive homeostatic agent with a cost ranging from \$3,240 for a 50 µg/kg to \$12,960 for a 200-µg/kg dose. Stein et al.<sup>8</sup> however concluded significant economic benefits with the use of rFVIIa in TBI coagulopathy because of a decline in the LOS and decrease in the need of mechanical ventilation. Our findings differ from this study because we did not find any difference in hospital or ICU LOS between the two groups.

Although the use of rFVIIa has revolutionized trauma resuscitations, one of the greatest hurdles has been its extremely high costs. For this reason, there has been a push to find products with the same safety and efficacy. PCC can be concluded as an effective alternate to rFVIIa and FFP in the reversal of both induced (warfarin) and acquired (coagulopathy of trauma) coagulopathy in TBI patients. The findings of this study must be interpreted within the contexts of its limitations. The results are limited by the single-center, retrospective design and small sample size, which reduce the power necessary to draw conclusions regarding efficacy and safety of PCC. Second, a well-defined protocol for the indications and use of PCC and rFVIIa was not in place. The two groups were not evenly matched as the patients on PCC were older and more likely to be on prehospital coumadin, while patients who received rFVIIa had a higher ISS. We did not calculate the difference or the amount of crystalloids that were used in these patients. Our data did not include a cohort of injured patients managed without PCC. One of the limitations of our study is the use of INR to assess for coagulopathy. While the INR did reduce after therapy, it is impossible for us to accurately assess the effect of PCC on in vitro coagulation function. Thrombelastography, although seems to be fast and a more accurate measure for in vitro coagulation, was not available to us during the study period. Our study lacks the power to determine

whether reported negative results are indeed significant. The complication rates and the difference in mortality should be interpreted keeping in mind these limitations.

We conclude that PCC is as safe, effective, and a much more cost-effective option than rFVIIa for the correction of TBI coagulopathy. A prospective randomized trial comparing PCC with rFVIIa is needed to confirm the findings.

## CONCLUSION

PCC is safe and effective for treating coagulopathy in TBI patients, while reducing costs and resource use. PCC should be considered as an effective therapy to treat both acquired and induced coagulopathy in TBI with or without prewarfarin use. Our study adds to the emerging literature regarding the role of PCC in both induced and acquired trauma coagulopathy.

Further prospective studies examining TBI outcomes comparing PCC and rFVIIa are needed.

## AUTHORSHIP

B.J., P.H., H.A., R.S.F., and P.R. conducted the literature search, designed the study, collected the data, and performed the statistical analyses. All authors contributed to the article preparation and final revision.

## DISCLOSURE

The authors declare no conflicts of interest.

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