The role of four-factor prothrombin complex concentrate in coagulopathy of trauma: A propensity matched analysis

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BACKGROUND: Coagulopathy is a common complication after severe trauma. The efficacy of four-factor prothrombin complex concentrate (4-PCC) as an adjunct to fresh frozen plasma (FFP) in reversal of coagulopathy of trauma (COT) has not been studied. The aim of our study is to compare 4-PCC + FFP versus FFP alone for the treatment of COT.

METHODS: We reviewed all trauma patients older than 18 years who received PCC + FFP or FFP alone at our Level I trauma center from 2015 to 2016. We excluded patients on preinjury oral anticoagulants. Patients were divided into two groups (4-PCC + FFP: FFP alone) and were matched in a 1:2 ratio using propensity score matching for demographics, vital and injury parameters, and initial international normalized ratio (INR). COT was defined as admission INR > 1.5. Corrected INR was defined as an INR of 1.5 or less. Outcome measures were time to correction of INR, packed red blood cells units transfused, thromboembolic complications, and mortality.

RESULTS: We analyzed 516 trauma patients, of which 120 patients (4-PCC + FFP: 40, FFP: 80) were matched. Mean age was 58 ± 20 years; 60% were male, median Injury Severity Score was 29 (14–38). Mechanism of injury was blunt in 87% patients. 4-PCC + FFP was associated with an accelerated correction of INR (373 minutes vs. 955 minutes; p = 0.001), a decrease in packed red blood cells units (7 units vs. 9 units; p = 0.04), and FFP units (5 units vs. 7 units; p = 0.03) trans fus ed compared to FFP alone. 4-PCC + FFP was associated with a lower mortality (25% vs. 33% p = 0.04) compared with FFP alone; however, there was no difference in the thromboembolic complications (2.5% vs. 1.2%, p = 0.5) between the two groups. Administration of PCC + FFP led to an earlier correction of the INR compared with FFP alone.

CONCLUSION: Results of our study demonstrated that the use of 4-PCC in conjunction with FFP is associated with the rapid reversal of INR and reduction in transfusion requirements as compared with FFP alone. Four-factor PCC as a component therapy along with FFP is superior to FFP alone for the reversal of COT. (J Trauma Acute Care Surg. 2018;85: 18–24. Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic studies, level IV.

KEY WORDS: PCC, FFP, coagulopathy of trauma.

Trauma is one of the leading causes of morbidity, mortality, and disability in the United States. The most common cause of preventable death in trauma patients is hemorrhage. The primary tissue injury, blood loss, consumption of coagulation factors in an attempt to prevent bleeding, hypoperfusion of organs, and the resulting acidemia all lead to a vicious cycle called the coagulopathy of trauma. The situation may be further worsened by injudicious use of crystalloids leading to dilution of the available factors. It is estimated that every third trauma patient in combat casualties and every fourth patient in civilian trauma who receives transfusion has coagulopathy of trauma on presentation to the emergency department (ED). Replacement of factors is deemed pivotal in the correction of coagulopathy of trauma and the fresh-frozen plasma (FFP) has been traditionally used for this purpose as it not only replaces the coagulation factors but also provides volume support as these patients are often hypovolemic. However, the use of concentrated factor products like the prothrombin complex concentrates (PCCs), either alone or in conjunction with FFP for the correction of coagulopathy is increasing in trauma patients. While initially developed for the treatment of hemophilia, the indications for the use of PCC have progressively shifted and they are now used for the rapid reversal of elevated international normalized ratio (INR).

The use of PCC is well established and is now the standard of care for the reversal of INR in patients taking warfarin. Prothrombin complex concentrate is considered superior to FFP, as it can be used more rapidly, and it does not require thawing or blood group testing and matching. In addition, PCC is also a cost-effective alternative to recombinant factor VIIa (rVIIa) for the replacement of factor VII. There are two different types of PCC available, the three-factor PCC (3-PCC) and the four-factor PCC (4-PCC). Compared with the 3-PCC, the 4-PCC has higher concentrations of factor VII in addition to some anticoagulant proteins (protein C, protein C, antithrombin, and heparin). Recently the Food and Drug Administration approved the first 4-PCC for warfarin reversal in the United States. Since its approval, its use has been progressively increasing in the reversal of coagulopathy in trauma patients.
Previous studies in the literature have compared factor replacement therapy (rVIIa or 3-PCC) with FFP therapy in the reversal of coagulopathy of trauma. However, there is a scarcity of data on the use of 4-PCC in combination with FFP for the reversal of coagulopathy. The aim of our study was to compare the outcomes in coagulopathy trauma patients receiving 4-PCC + FFP versus those receiving FFP alone. We hypothesized that the use of 4-PCC in combination with FFP is associated with the rapid reversal of INR and decrease in the blood products requirements without an increase in thromboembolic complications compared with FFP alone.

METHODS

We performed a 2-year (2015–2016) retrospective analysis of our prospectively maintained database of coagulopathic trauma patients. The database contains all trauma patients with deranged INR on admission, or those receiving blood products (FFP or PCC). The institutional review board at the University of Arizona, College of Medicine approved this study.

Study Population; Inclusion and Exclusion Criteria

We analyzed all adult (age ≥ 18 years) trauma patients admitted to our Level I trauma center with coagulopathy on admission. All patients with admission INR greater than 1.5 who received 4-PCC + FFP or FFP alone were included. Patients with documented bleeding diathesis, chronic liver disease, on preinjury anticoagulant (vitamin K antagonists, direct thrombin inhibitors & factor Xa inhibitors), who died in the ED and those who received only PCC (without FFP) were excluded.

At our institution, in 2015, we started using the 4-PCC in trauma patients. Four-factor PCC is now the gold standard and first-line agent for the reversal of INR in patients on warfarin. In addition, patients with significant bleeding who are coagulopathic, 4-PCC is used as an adjunct to the FFP based on the discretion of the trauma surgeon. Four-factor PCC was delivered as Kcentra (CSL Behring, Germany). The dose of PCC administered was 25 units/kg, and we followed the clinical guidelines for the transfusion of PCC. Fresh frozen plasma was administered as part of the massive transfusion protocol based on clinical presentation of the patient.

Data Points

We recorded the following data points for each patient: demographics included patient age, sex, and race; mechanism of injury; vitals on presentations, including systolic blood pressure, heart rate, temperature, and Glasgow Coma Scale (GCS) score; laboratory parameters on presentation, including hematocrit/hemoglobin levels, platelet count, INR prothrombin time, partial thromboplastin time; time of initial INR, and all the subsequent INRs; blood product transfusion details, which included packed red blood cells (pRBC), FFP, and platelet, hospital, and intensive care unit (ICU) length of stay, thromboembolic complications, and in-hospital mortality. The dosage of PCC and tranexamic acid (TXA) and the time of initiation of therapy was extracted from the pharmacy registry. The Injury Severity Score (ISS) and head Abbreviated Injury Scale (h-AIS) score were obtained from the Trauma Registry.

Outcomes

Our primary outcome measures were correction of INR, time to correction of INR, the rate of correction of INR, blood and blood products utilization (pRBC, FFP, and platelets), and thromboembolic complications (deep venous thrombosis, pulmonary embolism, and mesenteric ischemia). Our secondary outcome measures were hospital length of stay, ICU length of stay, and mortality.

Coagulopathy was defined as INR of 1.5 or greater. We defined the time of initiation of therapy as a time of the first dose of PCC in the PCC + FFP group or the first dose of FFP in the other group. Correction of INR was defined as final INR less than 1.5. Time to correction of coagulopathy was defined as the timing of the first dose of PCC to the correction of INR. The rate of INR correction was calculated as the difference in the admission INR and corrected INR divided by the time.

Statistical Analysis

Patients were divided into two groups based on the therapy they received: patients who received PCC + FFP and those who received FFP alone. In our analysis, we calculated the probability of receiving PCC in our patient population using the logistic regression with PCC as the dependent variable. We used all the confounding variables that were hypothesized to be associated with both treatment and outcome (age, sex, race, mechanism of injury, admission vitals, admission INR and hemoglobin, TXA use, and ISS). We obtained the propensity score for the predicted probability to receive the treatment. We then analyzed that the propensity score was balanced across treatment and comparison groups, and checked that covariates are balanced across treatment and comparison groups within strata of the propensity score. We used standardized differences to examine the distributions. We then matched the PCC group with two patients in the FFP alone group using the nearest neighbor matching. We finally verified that covariates are balanced across the treatment and comparison groups in the matched sample. We then used the area under the receiver operator characteristic curve to quantify the accuracy of our model.

All the data in our study are reported as a mean with standard deviation for continuous parametric data and as median with interquartile range for the nonparametric data. Categorical variables are calculated as proportions. We performed the Student’s t test and the Mann-Whitney U test to explore the differences between parametric and nonparametric data in our two groups. Similarly, we used the χ² test for evaluating differences in categorical variables. We considered a p value less than 0.05 as statistically significant in our study. All statistical analyses including the propensity scoring were performed using the R Integration Package for IBM, SPSS (Statistical Package for Social Sciences, Version 24; SPSS, Inc., Chicago, IL).

RESULTS

We analyzed a total of 4,285 patients, of which 1,056 patients had an admission INR greater than 1.5. After exclusion, a total of 516 patients were included in our study (PCC + FFP = 210 and FFP alone = 306). Using propensity score in 1:2 ratio and matching for demographics, injury parameters, laboratory values, and comorbidities, we got a final cohort of 120 patients (PCC + FFP = 40 and FFP alone = 80) as shown in Figure 1. Overall, mean age was 58 ± 20 years, 60% were males, and median ISS was 29 (14–38). Motor vehicle collision (n = 185) followed by pedestrian struck (n = 177) was the most common
mechanism of injury. The demographics of the two unmatched groups are demonstrated in Table 1. Patients in the PCC + FFP group had lower ED SBP, higher heart rate, and had higher ISS compared with the patients who received FFP only.

After propensity score matching in a 1:2 ratio, there was no difference between the age \( (p = 0.91) \), sex \( (p = 0.82) \), race \( (p = 0.70) \), comorbidities \( (p = 0.6) \), mechanism of injury \( (p = 0.85) \), injury severity \( (p = 0.12) \), and admission laboratory values \( (p = 0.13) \) between patients who received PCC + FFP compared with those who received FFP alone as shown in Table 2. The mean dose of PCC was 2,397 ± 989 units. Patients who received PCC + FFP had a shorter time to correction of INR (373 minutes vs. 955 minutes; \( p < 0.001 \)) and faster rate of INR correction (0.31 vs. 0.08; \( p = 0.01 \)) compared with FFP alone as shown in Table 3. Moreover, patients who received PCC + FFP have lower pRBC (7 units vs. 9 units; \( p = 0.04 \)) and FFP (5 vs. 7; \( p = 0.03 \)) requirements with no difference in platelet transfusion (3 units vs. 3 units; \( p = 0.72 \)) compared with the FFP alone. Similarly, there was no difference in thromboembolic complication (2.5% vs. 1.2%; \( p = 0.5 \)) between the two groups.

Patients who received PCC + FFP also had lower mortality (25% vs. 33%; \( p = 0.04 \)) and hospital length of stay (5 days vs. 7 days; \( p = 0.03 \)) compared with FFP alone as shown in Table 4. However, there was no difference in the ICU length of stay (1 day vs. 1 day; \( p = 0.01 \)) and the adverse discharge disposition (15% vs. 17%; \( p = 0.56 \)) between the two groups. Figure 2 demonstrates the proportion of patients with corrected INR and the time from initiation of therapy (PCC + FFP or FFP alone). The time to achieve corrected INR in 75% of the patients was 6 to 8 hours in the PCC + FFP group and 16 to 18 hours in the FFP alone group.

DISCUSSION

In this study, we evaluated the outcomes of patients receiving PCC + FFP compared with those who received FFP alone for the reversal of coagulopathy of trauma. We performed propensity scoring and matched for all the patient characteristics and presentation to have two similar groups between which we can compare the efficacy and thromboembolic complications between the two groups. Our study demonstrated that the use of PCC + FFP for the reversal of coagulopathy of trauma is associated with the decrease in time to correction of INR, decreased blood products transfusions (pRBC and FFP), and mortality without an increase in thromboembolic complications when compared with patients who received FFP alone.

Hemorrhage and the subsequent coagulopathy are common after trauma and is the leading cause of preventable death. The development of acute coagulopathy is a result of complex interplay between multiple processes and is associated with high

| TABLE 1. Demographics and Injury Parameters for the Unmatched Data |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Characteristics             | PCC + FFP \( (n = 210) \)     | FFP \( (n = 306) \)       | \( p \)         |
| Age: mean ± SD, y           | 57 ± 20.9                   | 58 ± 19                    | 0.91                     |
| Male, % (n)                 | 65% (136)                   | 58% (178)                  | 0.82                     |
| Whites, % (n)               | 70% (147)                   | 71% (217)                  | 0.70                     |
| BMI, mean ± SD              | 24.6 ± 7.2                  | 25.7 ± 11.2                | 0.52                     |
| Blunt injury, % (n)         | 80% (168)                   | 87% (266)                  | 0.76                     |
| Injury severity, % (n)      | 28% (59)                    | 25% (76)                   | 0.35                     |
| Vital parameters            |                             |                            |                          |
| ED SBP, mean ± SD           | 100 ± 20                    | 109 ± 23                   | 0.02                     |
| SBP < 90, % (n)             | 51% (107)                   | 42% (128)                  | 0.04                     |
| ED HR, mean ± SD            | 102 ± 15                    | 95 ± 12                    | 0.03                     |
| Injury parameters           |                             |                            |                          |
| ISS, median [IQR]           | 29 [16–39]                  | 26 [16–35]                 | 0.02                     |
| ISS > 15, % (n)             | 76% (160)                   | 75% (230)                  | 0.83                     |
| Head, AIS                   | 3 [2–3]                     | 3 [2–3]                    | 0.53                     |
| Chest, AIS                  | 3 [1–3]                     | 3 [1–3]                    | 0.91                     |
| Abdomen, AIS                | 3 [2–4]                     | 2 [2–4]                    | 0.03                     |
| Mechanism of injury, % (n)  |                             |                            |                          |
| MVC                         | 30% (63)                    | 40% (122)                  | 0.85                     |
| Pedestrian struck           | 35% (73)                    | 34% (104)                  | 0.63                     |
| Falls                       | 15% (32)                    | 13% (40)                   | 0.25                     |
| Hematologic parameters, mean ± SD |                        |                            |                          |
| Initial HB                  | 13 ± 3                      | 12 ± 4                     | 0.13                     |
| Initial INR                 | 1.9 ± 2                     | 1.8 ± 2                    | 0.15                     |
| Comorbidities               |                             |                            |                          |
| Hypertension                | 30% (63)                    | 26% (80)                   | 0.04                     |
| Diabetes                    | 22% (46)                    | 16% (49)                   | 0.03                     |
| COPD                        | 12% (25)                    | 10% (30)                   | 0.08                     |
| TXA, % (n)                  | 60% (126)                   | 50% (153)                  | 0.34                     |

BML, body mass index; SBP, systolic blood pressure; HR, heart rate; MVC, motor vehicle collision; HB, hemoglobin; COPD, chronic obstructive pulmonary disease.
TABLE 2. Demographics and Injury Parameters for the Matched Data

| Characteristics          | PCC + FFP (n = 40) | FFP (n = 80) | p  
|--------------------------|--------------------|-------------|----
| Age: mean ± SD, y        | 57 ± 20.9          | 58 ± 19     | 0.91
| Male, % (n)              | 65% (26)           | 62% (50)    | 0.82
| Whites, % (n)            | 70% (28)           | 71% (57)    | 0.70
| BMI, mean ± SD           | 24.6 ± 9.2         | 25.7 ± 11.2 | 0.52
| Blunt injury, % (n)      | 83% (33)           | 87% (69)    | 0.76
| Antiplatelet use, % (n)  | 25% (10)           | 26.5% (21)  | 0.35

Primary Parameters

| Characteristics          | PCC + FFP (n = 40) | FFP (n = 80) | p  
|--------------------------|--------------------|-------------|----
| GCS, median [IQR]        | 10 [3–13]          | 10 [3–12]   | 0.21
| ED SBP, mean ± SD        | 105 ± 20           | 109 ± 23    | 0.30
| SBP < 90, % (n)          | 50% (20)           | 50% (40)    | 1.00
| ED HR, mean ± SD         | 99 ± 15            | 95 ± 12     | 0.21

Injury Parameters

| Characteristics          | PCC + FFP (n = 40) | FFP (n = 80) | p  
|--------------------------|--------------------|-------------|----
| ISS > 15, % (n)          | 75% (30)           | 75% (60)    | 1.00
| Head, AIS                | 2 [2–3]            | 2 [2–3]     | 0.91
| Chest, AIS               | 3 [1–3]            | 3 [1–3]     | 0.91
| Abdomen, AIS             | 3 [2–4]            | 3 [2–4]     | 0.91

Hematologic Parameters, mean ± SD

| Characteristics          | PCC + FFP (n = 40) | FFP (n = 80) | p  
|--------------------------|--------------------|-------------|----
| Initial HB               | 13 ± 3             | 12 ± 4      | 0.13
| Initial INR              | 1.9 ± 2            | 1.8 ± 2     | 0.15

Comorbidities

| Characteristics          | PCC + FFP (n = 40) | FFP (n = 80) | p  
|--------------------------|--------------------|-------------|----
| Hypertension             | 27% (11)           | 26% (21)    | 0.89
| Diabetes                 | 15% (6)            | 19% (15)    | 0.56
| COPD                     | 7% (3)             | 8% (6)      | 0.78
| TXA, % (n)               | 58% (23)           | 52% (42)    | 0.34

Surgical intervention, % (n)

| Characteristics          | PCC + FFP (n = 40) | FFP (n = 80) | p  
|--------------------------|--------------------|-------------|----
| Mortality                | 25% (10)           | 33% (26)    | 0.04

SNF, skilled nursing facility.

There is a linear relationship between the degree of hypoperfusion and development of coagulopathy. The recent era has seen a paradigm shift in trauma resuscitation from aggressive use of crystalloids to blood products. Volume resuscitation using crystalloids was previously used to restore the intravascular volume and prevent hypoperfusion; however, injudicious use of crystalloids in trauma patients worsens the coagulopathy due to the dilution of coagulation factors and is associated with increased mortality. Fresh-frozen plasma has been used for the correction of coagulopathy of trauma because it not only replaces the volume but also provides coagulation factors. However, it requires thawing and crossmatching before administration that limits its readily availability for use in trauma patients. This has led to the use of concentrated factor products that have a high concentration of coagulation factors, leading to a rapid reversal of INR and does not require crossmatching and thawing unlike the FFP. Some institutes have also incorporated thawed plasma in their massive transfusion protocols. Thawed plasma in contrast to the conventional FFP plasma does not require thawing, and centers using thawed plasma have demonstrated reductions in time to first plasma transfusion and reduction in the overall number of blood and components transfused. The use of thawed plasma avoids up to a 30-minute delay that is seen in FFP transfusion. Unfortunately, we do not have thawed plasma at our institution, and we have to rely on factor concentrates like PCC for the rapid reversal of INR before the first pack of FFP is available.

We have evaluated the role of 3-PCC in trauma patients at our institution and have shown that 3-PCC either alone or in combination with FFP is superior to FFP alone in a number of studies. In 2015, we started using 4-PCC in trauma patients. Four-factor PCC has a higher concentration of factor VII compared with the 3-PCC in addition to several other anticoagulant compounds. Although 4-PCC is superior to FFP and is the standard therapy for the reversal of INR in patients on warfarin, the clear role of 4-PCC in trauma patients has not been clearly defined yet. Hemorrhage management has changed significantly over the last decade. Now, prompt hemorrhage control along with adequate resuscitation using platelets, plasma, and pRBC in 1:1:1 ratio along with factor replacement is key component of trauma care. One of the adjuncts to the massive transfusion is the use of 4-PCC. The decision to use PCC as an adjunct was at the discretion of the attending trauma surgeon. Generally, patients who are coagulopathic and hypotensive on presentation will usually receive FFP and PCC together, because FFP in these patients will expand the volume thus mitigating the hypotension. Our study results demonstrated that 4-PCC in conjunction with FFP decreases the time to correction of INR, and pRBC and FFP transfusion requirements. The longer time to correction of INR in both groups

TABLE 3. Primary Outcomes

| Variables       | PCC + FFP (n = 40) | FFP (n = 80) | p  
|-----------------|--------------------|-------------|----
| INR             | 373 ± 211          | 955 ± 524   | 0.001
| Correction of INR, % (n) | 95% (38) | 92% (74) | 0.62
| Rate of INR correction | 0.31 ± 0.1 | 0.08 ± 0.1 | 0.01

Blood products

| Characteristics          | PCC + FFP (n = 40) | FFP (n = 80) | p  
|--------------------------|--------------------|-------------|----
| pRBC transfused, units   | 7 ± 3              | 9 ± 5       | 0.04
| FFP, units               | 5 ± 2              | 7 ± 3       | 0.03
| Platelets, units         | 3 ± 3              | 3 ± 3       | 0.72

Thromboembolic complications

| Characteristics          | PCC + FFP (n = 40) | FFP (n = 80) | p  
|--------------------------|--------------------|-------------|----
| DVT                       | 2.5% (1)           | 1.2% (1)    | 0.51
| PE                        | 0%                 | 0%          | 0.95
| Mesenteric infarction     | 0%                 | 1.2% (1)    | 0.84

DVT, deep venous thrombosis; PE, pulmonary embolism.
compared with the reported time for the reversal of INR in patients on warfarin can be attributed to the severe injured patients in our cohort as shown by the median ISS of 28. Most of these patients had active hemorrhage, were coagulopathic, and required massive transfusion with multiple units of pRBC, platelets and PCC and/or FFP to correct the coagulopathy and achieve hemostasis. However, still the time to correction of INR was lower in the PCC + FFP group compared with the FFP alone group. Dickneite and Pragst demonstrated that 4-PCC was an effective superior to FFP in correcting the dilutional coagulopathy and controlling bleeding in a porcine trauma model. In their study, the coagulation factors were restored to normal levels with 4-PCC but not with FFP. Greater restoration of coagulation factor levels with FFP is further discouraged by the risk of fluid overload. In addition, freezing and thawing and dilution with citrate for clinical use further decrease the concentration of coagulation factors in the FFP.

One of the feared complications of concentrated factor replacement therapy is the risk of developing thromboembolic complications. Although the true estimate of the incidence of thromboembolic complications following PCC administration remains unknown, because most studies are limited by sample size to detect a difference. However, studies have reported up to a 4% risk of thromboembolic complications with the use of 4-PCC. Our study showed no difference in the risk of thromboembolic complications between the 4-PCC + FFP and FFP alone group. Similarly, a multicenter open-label randomized control trial also did not show an increased risk of thromboembolic complications in patients receiving 4-PCC compared with FFP for the rapid reversal of vitamin K antagonist in patients requiring surgery. Another study by Joseph et al. showed no difference in thromboembolic complications in trauma patients receiving 3-PCC + FFP compared with FFP alone group. Although the 4-PCC has higher concentrations of some anticoagulant proteins (protein C, protein S, antithrombin, and heparin) compared with the 3-PCC; however, the risk of thrombosis may be high due to the high concentration of factor VII in 4-PCC. However, this has not been evaluated in vivo in patients.

Our study has certain limitations. First, being a retrospective, single-center study, it may lack generalizability. Second, we did not randomize patients into FFP alone versus PCC + FFP groups, and it was based on the discretion of the trauma attending. In addition, we used INR to assess the coagulopathy in our patient population, which does not depict the overall picture of the coagulation status of the picture. Due to the retrospective nature of our study, we were not able to assess accurately the effect of PCC on in vitro coagulation function. Moreover, at this current time, we do not use thromboelastography or rotational thromboelastometry in our institution that may be a more accurate measure of in vitro coagulation. Finally, the timing of serial coagulation measurements (INR) was not standardized and was determined by physician choice. Nonetheless, our study is the first one to report the superiority of 4-PCC + FFP compared with FFP alone in the coagulopathy of trauma.

CONCLUSION

Prothrombin complex concentrate is an important therapeutic adjuvant for the reversal of coagulopathy of trauma. Results of our study demonstrated that the use of 4-PCC in conjunction with FFP is associated with the rapid reversal of INR and reduction in transfusion requirements as compared to FFP alone. Four-factor PCC along with FFP is an effective therapy for the reversal of COT.

AUTHORSHIP


DISCLOSURE

The authors declare no conflicts of interest. The authors have no financial or proprietary interest in the subject matter or materials discussed in the article.

REFERENCES


**EDITORIAL CRITIQUE**

The acute coagulopathy of trauma continues to be a highly researched and debated topic in the trauma literature. Identification and correction of this highly lethal condition improves survival. However, there continues to be debate regarding the methods of identification and correction. Dr. Aziz et al. have added to the body of literature with this investigation into the addition of 4-factor prothrombin complex concentrate to plasma during resuscitation. The authors focused on the reversal of INR as a major endpoint of the study, with multiple data points related to the INR, including the correction, time to correction, and rate of correct of the INR. The authors showed that the addition of 4-factor prothrombin complex plasma to plasma during resuscitation decreased the time to...
correction of INR and inferred from this that the time to the
correction of the coagulopathy of trauma was also decreased.
In the era of more readily available data with respect to the en-
tire clot and clot formation, such as thromboelastometry or
thromboelastography, is the conclusion that 4-factor PCC, in
addition to FFP, an effective therapy for the reversal of the co-
agulopathy of trauma by correction of INR? INR is a value
that is more readily available in most hospitals; however, does
the correction of INR correlate well with the correction of the
cogulopathy of trauma?

The authors showed an improvement in the time to correc-
tion of the INR in the 4-factor PCC group to just over 6 hours,
from around 16 hours in the plasma-only group. This is a re-
markable difference in correction; however, patients that die
from acute coagulopathy of trauma do so within the first 3 to 6
hours. Therefore, applying this paradigm to the “sickest of the
sick” trauma patients may not be of value as the expedient iden-
tification and correction of the acute coagulopathy of trauma is
paramount to the survival of this population. Based on the data
presented, how would the authors modify their massive transfu-
sion protocol to include 4-factor PCC?

Finally, the authors utilized abnormalities in INR to iden-
tify patients with acute coagulopathy of trauma. The 4-factor
PCC group was found to require less packed red blood cells
and plasma to be transfused overall. However, there were no
indications made as to the hemodynamic status of the patients
enrolled. The question then becomes, does an abnormal INR
matter if a patient is not hemorrhaging and does a normal
INR matter if a patient is?

I commend the authors on their contribution to this ever
evolving body of literature and look forward to their continued
efforts in this field.

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