**4-Factor Prothrombin Complex Concentrate is associated with Improved Survival in Trauma Related Hemorrhage: A Nationwide Propensity Matched Analysis**

**Short Title:** “Prothrombin Complex Concentrate in Trauma”

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**Introduction:** Post-traumatic hemorrhage is the most common preventable cause of death in trauma. Numerous small single-center studies have shown the superiority of 4-factor prothrombin complex concentrate(4-PCC) along with fresh frozen plasma (FFP) over FFP-alone in resuscitation of trauma patients. The aim of our study was to evaluate outcomes of severely injured trauma patients who received 4-PCC+FFP compared to FPP-alone.

**Methods:** 2-year(2015-2016) analysis of theAmerican College of Surgeons-Trauma Quality Improvement Program database. All adult (age≥18years) trauma patients who received 4-PCC+FFP or FFP-alone were included. We excluded patients who were on preinjury anticoagulants. Patients were stratified into two groups: 4-PCC+FFP *vs.* FFP-alone and were matched in a 1:1 ratio using propensity-score-matching for demographics, vitals, injury parameters, comorbidities and level of trauma centers. Outcome measures were packed red blood cells (pRBC), plasma & platelets transfused, complications, and mortality.

**Results:** A total of 468 patients (4-PCC+FFP:234 , FFP-alone:234) were matched. Mean age was 50±21years; 70% were males, median injury severity score was 27[20–36], and 86% had blunt injuries. 4-PCC+FFP was associated with a decreased requirement for pRBC (6 units *vs*. 10 units; *p*=0.02) and FFP (3 units *vs.* 6 units; *p*=0.01) transfusion compared to FFP-alone. Patients who received 4-PCC+FFP had a lower mortality (17.5% *vs* 27.7%, p=0.01) and lower rates of acute respiratory distress syndrome(1.3% *vs* 4.7%, p=0.04) & acute kidney injury(2.1% *vs* 7.3%, *p=*0.01). There was no difference in the rates of deep venous thrombosis(p=0.11) & pulmonary embolism(p=0.33), adverse discharge disposition(p=0.21) and platelets transfusion(p=0.72) between the two groups.

**Conclusions:** Our study demonstrates that the use of 4-factor PCC as an adjunct to FFP is associated with improved survival and reduction in transfusion requirements compared to FFP alone in resuscitation of severely injured trauma patients. Further studies are required to evaluate the role of addition of PCC to the massive transfusion protocol.

**Level of Evidence:**

Level III, Therapeutic studies

**Keywords:**

4-factor PCC; Prothrombin complex concentrate; Coagulopathy of trauma; TQIP; Factor based resuscitation;

**Introduction:**

Trauma is one of the leading causes of morbidity and mortality in the United States (U.S.), and post-traumatic hemorrhage is the second leading cause of death after trauma ([1](#_ENREF_1), [2](#_ENREF_2)). Mortality due to exsanguinating hemorrhage can reach as high as 40% in severely injured trauma patients ([3](#_ENREF_3)). ([2](#_ENREF_2)). Trauma induced coagulopathy (TIC) further raises the death toll in these patients. Every 1 out of 4 hemorrhagic trauma patients develops biochemically evident and clinically significant coagulopathy upon presentation and patients with TIC are four times more likely to die within the first 24 hours compared to those who do not have TIC at presentation ([4-6](#_ENREF_4)). TIC is a multifactorial process and involves acidemia, hypothermia, and a depletion of coagulation factors secondary to blood loss and/or hemodilution ([4](#_ENREF_4), [7](#_ENREF_7)). With an increased understanding of the pathophysiology of TIC, there is a paradigm shift towards a more goal-directed resuscitation strategies with early factor replacement. Fresh frozen plasma (FFP) has been used frequently for this purpose, it replaces the coagulation factors and provides volume support in the bleeding trauma patients who are often hemodynamically unstable([8](#_ENREF_8)). However, the use of concentrated factor products like the prothrombin complex concentrates (PCC), 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 evolved and they are now used for the rapid correction of elevated international normalized ratio (INR) ([9](#_ENREF_9)).

Since its approval from U.S. Food and Drug Administration in 2013, 4-factor PCC (4-PCC)is the standard of care for the reversal of INR in trauma patients with anticoagulants (warfarin) induced coagulopathy ([10-12](#_ENREF_10)). Additionally, PCC has emerged as an effective therapy for the reversal of trauma induced coagulopathy (patients with INR>1.5 and not on preinjury anticoagulants)([13](#_ENREF_13), [14](#_ENREF_14)). Numerous animal and small single-center studies have shown that 4-PCC+FFP is superior to FFP alone in resuscitation of trauma patients ([15](#_ENREF_15), [16](#_ENREF_16)). However, there is paucity of multi-institutional data regarding the safety and efficacy of 4-PCC as an adjunct to FFP for resuscitating patients with trauma induced coagulopathy. The aim of our study was to evaluate outcomes in severely injured trauma patients who received 4-PCC+FFP compared to FPP alone utilizing the national American College of Surgeons Trauma Quality Improvement Program dataset (ACS-TQIP). We hypothesized that the use of 4-factor PCC as an adjunct to FFP is associated with improved survival and reduction in transfusion requirements for resuscitating trauma patients.

**Methods:**

***Study design and population:***

We performed a two-year (2015-2016) retrospective analysis of the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) database, and identified all trauma patients who received either FFP or 4-PCC during their initial resuscitation. The TQIP is a well-known effort to elevate the standard of trauma care at participating centers. As of 2018, more than 775 trauma centers are participating in the TQIP. Trained data abstractors collect more than 100 patient and institutional related variables, including patient demographics (age, gender, race); comorbidities; injury parameters [type and mechanism of injury, injury severity score (ISS), and abbreviated injury scale (AIS)]; vitals on presentation in emergency department (ED); in-hospital procedures; complications, mortality and, discharge disposition. The TQIP collects data, provide feedback about centers’ performance and identify the possible characteristics that a trauma center can implement to improve outcomes. Although TQIP is administered by ACS, the authors of the study are solely responsible for the analyses and conclusions presented in this study. As the TQIP only contains de-identified data, Institutional Review Board (IRB) approval was exempted.

***Inclusion & Exclusion Criteria:***

We included all adult trauma patients (age ≥18years) who were presented to trauma center and received either FFP alone or 4-PCC+FFP for initial resuscitation in the ED. We excluded patients with documented bleeding disorders, chronic liver disease, history of pre-injury anticoagulants use and those who received PCC alone (without FFP). The ICD10 procedure codes were used to identify patients who received 4-PCC **(Supplementary Table 1)**, while “TQIP Processes of Care Measures file (TQIP\_RDS\_PM)” was used to abstract data regarding transfusion. Around 23% of the trauma centers reported data using ICD-10 codes in 2015 and 97% of centers were using ICD-10 codes in 2016. Only 117 trauma centers ever used ICD-10 codes for 4-PCC and we only included the patients who were managed at trauma centers using these ICD-10 codes.

***Data points***

Following data points were abstracted for each patient: patient demographics (age, gender, race, ethnicity); injury parameters (mechanism of injury, injury severity score [ISS], different body regions abbreviated injury scale score [h-AIS]); vitals on presentation in ED (systolic blood pressure [SBP], heart rate [HR], temperature, Glasgow coma scale [GCS]); data regarding the blood components transfused for resuscitation (including packed red blood cells [pRBC], platelets, fresh frozen plasma [FFP]); hospital length of stay (LOS); intensive care unit (ICU) LOS, in-hospital complications; mortality; and, discharge disposition.

***Patient stratification:***

Patients were stratified into two groups based on the modality of initial resuscitation: those who received 4-PCC along with FFP (4-PCC+FFP group) for initial resuscitation in the ED and those who received FFP alone (FFP group) for initial resuscitation in the ED.

***Outcomes:***

The primary outcome measures of our analysis were transfusion requirements at 4-hours & 24-hours from ED-presentation and in-hospital mortality. Our secondary outcome measures were in-hospital complications [acute kidney injury (AKI); acute respiratory distress syndrome (ARDS); venous thromboembolic complications i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE)], hospital LOS, ICU LOS, and adverse discharge disposition.

***Definitions:***

*Time to initiation of therapy:* Time from ED presentation to receipt of 4-PCC in 4-PCC+FFP group or time from ED presentation to transfusion of 1st unit of FFP in FFP alone group.

*Acute Kidney Injury:* A patient was determined to have AKI if met the following criteria: No history of chronic renal failure prior to injury and an abrupt reduction in kidney function during the hospital course (Increase in serum creatinine (SCr) ≥3x baseline or; increase in SCr to ≥4mg/dl(≥ 353.3μmol/l) or; a decrease in Estimated Glomerular Filtration Rate (eGFR) to <35 ml/min per 1.73 m² or; reduction in urine output of <0.3 ml/kg/hrs for ≥24 hours or; anuria for ≥12 hours or; requiring renal replacement therapy.

*Acute Respiratory Distress Syndrome (ARDS):* A patient was defined to have ARDS if met the following criteria: New or worsening respiratory symptoms within 1 week of known clinical insult and bilateral opacities on chest X-ray not fully explained by effusions, lobar/lung collage, or nodules and symptoms not explained by heart failure or volume overload and decreased PaO2/FiO2 ratio.

*Deep Venous Thrombosis (DVT)*: The diagnosis of DVT was confirmed by venogram, ultrasound, or CT scan.

*Pulmonary Embolism (PE):* A patient was defined to have a PE if the V-Q scan was interpreted as high probability of pulmonary embolism or pulmonary angiogram or CT angiogram was positive.

*Adverse discharge disposition*: It was defined as discharge or transfer to a skilled nursing facility, inpatient rehab, or long term care hospital.

***Statistical analysis***

**We performed propensity score matching (PSM) which is a well-established method to control for confounding variables and to get two comparable groups among which outcome of interest can be analyzed without any confounding bias. Patients** who received 4-PCC along with FFP for initial resuscitation in the ED were matched in a 1:1 ratio to a similar cohort of patients who received FFP alone for initial resuscitation in the ED. PSM was used to match both groups for **demographics (age, gender, race, body mass index), vitals (SBP, HR, GCS), time to initiation of therapy, mechanism of injury, ISS, head-AIS, chest-AIS, abdominal-AIS, spine-AIS, extremity-AIS, comorbidities, preinjury antiplatelet use and level of trauma center. In our PSM, dependent variable was the receipt of 4-PCC. Using a logistic regression model, a propensity score was generated for each patient based on confounding factors. The two groups were matched using the nearest neighbor method without replacement. Due to unavailability of hospital specific data, we could not account for intra-hospital cluster effects. However, to decrease the inter-hospital variation of management strategies both groups were matched for the level of trauma centers.**

**Multivariate regression was performed to compare outcomes in a sub-group of patients with isolated traumatic brain injury (head AIS≥3 and other body region AIS≤2). To assess the association between each potential dependent variable and the binary outcomes, we performed a univariate analysis. Variables with a *p*-value less than 0.2 on the univariate analysis were then used in a multivariate logistic regression model. On the multivariate logistic regression analysis, variables were considered significant at a *p*-value less than 0.05. We then performed the Hosmer-Lemeshow test to assess the fitness of model. In the logistic regression model, the Hosmer-Lemeshow test exceeded 0.05 and the tolerance was greater than 0.1 for all independent variables with a variance inflation factor of less than 10.0**

**We performed descriptive statistics to report the data. Continuous parametric variables are reported as a mean (with standard deviation), continuous non-parametric variables are presented as a median [with interquartile range] while the categorical variables are reported as a proportion. We used**Pearson’s chi square test *(X2*) to analyze the differences among **categorical variables. Mann-Whitney U test and Student’s t-test were performed to evaluate the differences between the two groups regarding continuous non-parametric and parametric variables, respectively. Kaplan Meier survival analysis was performed and Log-rank test was used to compare the difference of survival between the two groups. Alpha was set at 5% and a *p*-value of less than 0.05 (*p<* 0.05) was considered statistically significant in our analysis. All the statistical analyses were performed using the Statistical Package for Social Services (SPSS, version 24; SPSS, Inc., Armonk, NY).**

***Missing data analysis***

Missing data were treated as missing completely at random (MCAR). Variables with missing data included: [Variable (percentage of patients missing these data)] ED Systolic Blood Pressure (4.4%), ED heart rate (4.5%), ED GCS (3.3%). We performed multiple imputations to account for the missing values. The Little’s MCAR test and the Markov Chain Monte Carlo method were used to perform multiple imputations.

**Results:**

We analyzed 593,818 trauma patients, of which 118,970 patients met inclusion/exclusion criteria and were included in our study. 99.7% (118,585/118,970) patients received FFP alone for initial resuscitation while 0.3% (385/118,970) patients received 4-PCC along with FFP for initial resuscitation. The demographics, ED vitals, injury parameters, and comorbidities of the pre-match patient cohorts are summarized in **Table 1**. Patients who received 4-PCC+FFP were more likely to be younger (*p=*0.01) non-white (*p=0.04*) males (*p*=0.03) and were less likely to have a history of hypertension (*p=*0.02), diabetes (*p=*0.04) and preinjury antiplatelet use (*p=0.02*). They were more likely to be presented with a lower SBP (*p*=0.01), a higher HR (*p*=0.03), and a lower GCS (*p*=0.04). Furthermore, they were more likely to have sustained a blunt injury (*p*=0.02) with higher injury severity i.e. ISS (*p*=0.03). Patients in 4-PCC+FFP group had a higher head-AIS (*p*=0.01) and higher chest-AIS (*p=*0.04) compared to those in FFP-alone group. However, there was no difference between the two groups regarding abdominal, spine, and extremity injury severity score. The most common mechanism of injury was motor vehicle crash followed by pedestrian stuck and falls. Patients in 4-PCC+FFP group were more likely to present after a MVC (*p=*0.03) or pedestrian stuck by motor vehicle (*p=*0.03) compared to their counterparts.

On propensity score matching, 468 patients (4-PCC+FFP: 234; FFP-alone: 234) were matched. The mean age was 50±21 years, the median ISS was 27 [20-36], 70% were males, and 86% of patients had a blunt mechanism of injury. All the patients in our analysis received either 4-PCC or FFP in the ED during initial resuscitation (within 60 minutes of presentation to ED). The mean time to administration of 4-PCC was 30 ± 18 minutes (in 4-PCC+FFP group) while the mean time to transfusion of 1st unit of FFP (in FFP alone group) was 27 ± 16 minutes. The overall mortality was 22.6%. The demographics and injury parameters of the match cohort of trauma patients are demonstrated in **Table 2**. Between the two groups, there was no difference regarding age (*p*=0.28), gender (*p*=0.16), race (*p*=0.24), SBP (*p*=0.31), HR (*p*=0.27), GCS (*p*=0.18), mechanism of injury (*p*=0.39), ISS (*p*=0.28), head-AIS (*p*=0.35), chest-AIS (*p*=0.41), Abd-AIS (*p*=0.37), ext-AIS (*p*=0.24), spine-AIS (*p*=0.41), time to initiation of therapy (*p=0.84*), hemorrhage control interventions and time to hemorrhage control interventions (p=0.37).

The mean 4 hours requirements for pRBC were 4±2 units, platelets 2±2 units and plasma 3±2 units, while the 24 hours requirements for pRBC were 8±4, platelets 3±3, and plasma 5±3. The transfusion requirements of both groups are represented in in **Table 3**. Compared to the FFP-alone group, patients in the 4-PCC+FFP group had a lower requirement for pRBCs and plasma transfusion at 4-hours or 24 hours. However, there was no difference between the two groups regarding the platelet transfusion at 4-hours or 24-hours. Patients who received 4-PCC along with FFP had lower in-hospital mortality (17.5% *vs* 27.7%, *p=*0.01) compared to the patients who received FFP alone as shown in **Figure 1**. However, both groups had similar ED-mortality (*p=0.28*). To analyze the independent effect of 4-PCC on mortality, we performed a regression analysis controlling for volume and type of blood products transfused. Even after controlling for these factors, 4-PCC+FFP was independently associated with improved survival (OR: 3.25 [1.78 – 4.96]). The overall rate of complications was 13.6%. The median hospital LOS was 7[3-10], and the ICU stay was 1[1-3]. The secondary outcomes of our analysis are demonstrated in **Table 4**. Patients in 4-PCC+FFP group were less likely to develop AKI (2.1% vs 7.3%, *p=*0.01) or ARDS (1.3% vs 4.7%, *p=*0.04) during their hospital stay compared to patients in FFP-alone group. Additionally, they had shorter hospital length of stay (5-days *vs*. 8-days, *p=*0.03). However, there was no difference between the two groups regarding the rates of DVT (*p=*0.11), or PE (*p=*0.33). Additionally, both patient cohorts had similar ICU-LOS (*p=*0.19) and rates of adverse discharge disposition (*p=*0.21). Most of the patients in our analysis had poly-trauma. Only 21.2% (n=99) of the patients had an isolated TBI (head AIS≥3 and other body region AIS≤2). We performed a sub-analysis of these patients and on sub-analysis, transfusion of 4-PCC+FFP was independently associated with higher odds of survival (OR: 2.54[1.88 – 3.49]) compared to FFP alone.

**Discussion:**

The results of our study demonstrate that the use of 4-PCC as an adjunct to FFP in the resuscitation of trauma patients is associated with improved outcomes. Numerous small sample single-center studies have demonstrated the efficacy of the adjunctive use of 4-PCC in resuscitation of trauma patients. However, no single larger multicenter data has validated these outcomes. This is the first study from a large nationwide database in the US, to analyze the outcomes of 4-PCC as an adjunct to FFP for resuscitation in trauma patients. It shows an improved survival and decreased blood products transfusion with the use of 4-PCC+FFP compared to FFP alone. Furthermore, there was no difference in thromboembolic complications between the two groups.

Resuscitation of trauma patients has evolved in the past two decades. There has been a shift from the aggressive use of crystalloids to early utilization of blood products, minimal crystalloids and concomitant factor replacement. The PROPPR trial has recommended the early use of plasma, platelets and packed red cells in a 1:1:1 ratio ([17](#_ENREF_17)). A few problems persist in the use of fresh frozen plasma (FFP) alone for the reversal of severe coagulopathy of trauma. First, FFP requires cross-matching that hinders the readily availability to the early administration in trauma patients ([18](#_ENREF_18)). Second it has lower concentration of clotting factors and requires multiple units to be transfused in order to reverse coagulopathy ([19](#_ENREF_19)). This can potentially pose the risk of volume overload and related complications. These limitations of FFP led to the early adjunctive use of factor replacement in trauma resuscitation. Different factor replacements have been used including fibrinogen, Prothrombin Complex Concentrate (PCC), activated factor-VII, and Factor Eight Inhibitor Bypassing Activity (FEIBA). A recently published randomized clinical trial from UK analyzed the feasibility and outcomes of early fibrinogen transfusion in trauma patients and concluded that early administration of fibrinogen concentrate was not feasible ([20](#_ENREF_20)). Furthermore, the RETIC trial has investigated the use of coagulation factor concentrates primarily fibrinogen for reversal of trauma induced coagulopathy and demonstrated the superiority of factor concentrates over FFP ([21](#_ENREF_21)). The emerging literature is supporting the use of PCC as an adjunct to FFP for the correction of TIC. Some of the advantages of PCC over FFP are higher concentration of clotting factors in PCC; its rapid availability as it does not require thawing or cross matching and the smaller volumes of FFP needed to reverse anticoagulation ([22](#_ENREF_22)).

Several studies have evaluated the impact of PCC on outcomes. The results of our study are consistent with the previously published data ([13-15](#_ENREF_13), [23](#_ENREF_23), [24](#_ENREF_24)). We found that the 4-PCC along with FFP is associated with improved outcomes in terms of transfusion requirements and survival. On the contrary, Moe and colleagues analyzed the efficacy of PCC in a porcine hemorrhaging shock model, and have demonstrated opposite results. They concluded that PCC increased the rate of consumption coagulopathy, failed to correct the TIC, and PCC administration may not improve outcomes in hemorrhagic shock. The results are contrary to our study. This might be due to multiple reasons. First, they administered PCC alone without FFP while in our analysis, PCC was used as an adjunct to FFP for resuscitating trauma patients. Second, after a controlled hemorrhage, the animals were resuscitated with crystalloids only. In contrast, in our study, all patients received a balanced blood product resuscitation. Third, they infused the first dose of PCC at 4 hours after the hemorrhage while the mean time to PCC administration in our patient population was only 30 minutes. Fourth, the physiological derangements produced in their porcine model may not represent the actual TIC in humans ([25](#_ENREF_25)).

Another study was recently published by same study group, in which Kuckelman et al. looked at the efficacy of PCC in combination with FFP in swine model of hemorrhagic coagulopathy. They concluded that PCC as an adjunct to FFP is superior in improving outcomes in resuscitation of hemorrhagic shock by decreasing lactic acidosis, improving coagulopathy and clot formation ([16](#_ENREF_16)). Similarly, Jehan et al. in their study of severely injured trauma patients demonstrated that 4-factor PCC in conjunction with FFP was associated with improved & earlier correction of INR, and decreased PRBC & FFP requirements compared to FFP alone. The improved survival of patients who received 4-PCC+FFP in our analysis can be attributed to above mentioned effects of 4-PCC+FFP on the homeostatic balance of body. In our analysis the 4-PCC+FFP group had lower requirements of pRBCs and FFP, it can be argued that the improved survival might be due to differences in the blood product resuscitation and ratios. To overcome this bias we performed a regression analysis and controlled for the number and type of blood products transfused and even after accounting for the differences in blood product transfused, 4-PCC+FFP was independently associated with higher odds of survival.

One of the feared complications that may limit the use of factor concentrates is the risk of thromboembolism. Previous studies have reported a thromboembolic risk of up to 4% with the use of PCC ([26](#_ENREF_26), [27](#_ENREF_27)). However, the true risk of thromboembolic complications cannot be estimated due to the small sample size, different formulations with varying clotting factors concentration and heterogeneity of population. A study by Joseph et al. showed no difference in the DVT and VTE rates in patients receiving PCC+FFP compared to FFP alone in trauma. Similarly, Goldstein et al. in a randomized control trial demonstrated no difference in the thromboembolic complications between PCC compared to FFP when used for the reversal of warfarin in patients undergoing surgery/invasive intervention ([10](#_ENREF_10)). Another study by Jehan at al. demonstrated similar results between 4-factor PCC+FFP and FFP alone ([15](#_ENREF_15)). However, all these studies were limited by their small sizes to detect a difference. Our study has overcome this limitation by including 468 patients from a nationwide database and demonstrated no difference in the thromboembolic complications (both DVT and PE) between PCC+FFP and the FFP alone group. As the 4-factor PCC has higher concentrations of II, VII, IX, X compared to FFP, it should have a higher risk of thromboembolic complications, at least in theory. However, this was not seen in our study and all the previous reported studies. The presence of some of the anticoagulant proteins (Protein C, Proten S, Antithrombin III and heparin) might be in part the reason for this. Moreover, we found that the patients who received 4-PCC along with FFP had a lower rates of AKI and ARDS. Studies have shown that a high volume of FFP transfusion is independently associated with AKI, ARDS, and multiple organ failure in trauma patients ([28](#_ENREF_28), [29](#_ENREF_29)). Administration of 4-PCC as an adjunct for resuscitation decreases the requirement for FFP which might explain the lower rates of AKI and ARDS in patients who received 4-PCC+FFP compared to FFP alone group.

Our study has certain limitations and results of our study should be interpreted accordingly. First, it is a retrospective study and can only demonstrate an association and not necessary a causality. Second, the patients were not randomized into two groups and this may impart an inherent bias. We also could not capture the individual institutional protocols in deciding one treatment over the other. As the TQIP database does not capture the coagulation indices including the prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR), hence we could not control for these parameters. In addition, we could not determine if some institutions used thromboelastography (TEG) or Rotational thromboelastometry (ROTEM) based product products replacement. Moreover, due to limitations of database, we could not control for hospitals which might have caused a clustering effect in our analysis and we do not have data regarding the use of Vitamin K. Although we have excluded the patients who were on pre-injury anticoagulants using ICD-10 codes, there may be a possibility that TQIP did not code for the use of anticoagulants and some patients might have received PCC for anticoagulant reversal. We think this is an inherent limitation for all the studies published from TQIP. Only a randomized control trial can overcome these limitations. Despite these limitations, it is the first nationwide study to report that the use of 4-factor PCC in conjunction with FFP is associated with improved survival and decreased blood transfusion requirements compared to FFP alone without increasing the risk of thromboembolic complications.

**Conclusion:**

PCC is an important adjunct for resuscitation of severely injured trauma patients. Our study demonstrates that compared to FFP alone, the use of 4-factor PCC as an adjunct to FFP is associated with improved survival and reduction in transfusion requirements without increasing the risk of venous thromboembolic complications. Randomized clinical trials are warranted to further study the safety and efficacy of PCC for resuscitating trauma patients.

**Authors Contributions:**

B.J, M.Z, M.H, F.J, J.S, A.F, T.O, and A.N designed this study.

B.J, M.Z, M.H, F.J, J.S, A.F, N.K, and L.G searched the literature.

B.J, M.Z, M.H, F.J, T.O, A.N, N.K, and L.G collected the data.

B.J, M.Z, M.H, F.J, T.O, A.N, A.F, N.K, and L.G analyzed the data.

All authors participated in data interpretation and manuscript preparation.

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None

**Conflict of interest:**

There are no identifiable conflicts of interests to report.

**References:**

1. Rhee P, Joseph B, Pandit V, Aziz H, Vercruysse G, Kulvatunyou N, Friese RS. Increasing trauma deaths in the United States. *Ann Surg*. 2014;260(1):13-21.

2. Acosta JA, Yang JC, Winchell RJ, Simons RK, Fortlage DA, Hollingsworth-Fridlund P, Hoyt DB. Lethal Injuries and Time to Death in a Level I Trauma Center 1. *J Am Coll Surg*. 1998;186(5):528-33.

3. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma Acute Care Surg*. 2006;60(6):S3-S11.

4. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma Acute Care Surg*. 2003;54(6):1127-30.

5. Niles SE, McLaughlin DF, Perkins JG, Wade CE, Li Y, Spinella PC, Holcomb JB. Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma Acute Care Surg*. 2008;64(6):1459-65.

6. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. *J Trauma Acute Care Surg*. 2003;55(1):39-44.

7. Simmons JW, Pittet J-F, Pierce B. Trauma-Induced Coagulopathy. *Curr Anesthesiol Rep*. 2014;4(3):189-99.

8. Gonzalez EA, Moore FA, Holcomb JB, Miller CC, Kozar RA, Todd SR, Cocanour CS, Balldin BC, McKinley BA. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma Acute Care Surg*. 2007;62(1):112-9.

9. Hellstern P, Halbmayer W-M, Köhler M, Seitz R, Müller-Berghaus G. Prothrombin complex concentrates: indications, contraindications, and risks: a task force summary. *Thromb Res*. 1999;95(4):S3-S6.

10. Goldstein JN, Refaai MA, Milling TJ, Lewis B, Goldberg-Alberts R, Hug BA, Sarode R. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet*. 2015;385(9982):2077-87.

11. Kushimoto S, Fukuoka T, Kimura A, Toyoda K, Brainsky A, Harman A, Chung T, Yasaka M. Efficacy and safety of a 4-factor prothrombin complex concentrate for rapid vitamin K antagonist reversal in Japanese patients presenting with major bleeding or requiring urgent surgical or invasive procedures: a prospective, open-label, single-arm phase 3b study. *Int J Hematol*. 2017;106(6):777-86.

12. Martin MJ. Efficacy of Tranexamic Acid and Prothrombin Complex Concentrate for Traumatic Coagulopathy in Acidosis and Shock States, with Additional Evaluation of Resuscitative Endovascular Balloon Occlusion of the Aorta. USAFSAM/FHE Wright-Patterson AFB United States, 2018. Available at https://apps.dtic.mil/dtic/tr/fulltext/u2/1057854.pdf Accessed on December 7th, 2018.

13. Nienaber U, Innerhofer P, Westermann I, Schöchl H, Attal R, Breitkopf R, Maegele M. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. *Injury*. 2011;42(7):697-701.

14. Schöchl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, Kozek-Langenecker S, Solomon C. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM®)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Criti care*. 2010;14(2):R55.

15. Jehan F, Aziz H, O'Keeffe T, Khan M, Hamidi M, Zeeshan M, Kulvatunyou N, Joseph B. The role of four-factor prothrombin complex concentrate in coagulopathy of trauma: A propensity matched analysis. *J Trauma Acute Care Surg*. 2018;85(1):18-24.

16. Kuckelman J, Barron M, Moe D, Lallemand M, McClellan J, Marko S, Eckert M, Martin MJ. Plasma coadministration improves resuscitation with tranexamic acid or prothrombin complex in a porcine hemorrhagic shock model. *J Trauma Acute Care Surg.* 2018;85(1):91-100.

17. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, Del Junco DJ, Brasel KJ, Bulger EM, Callcut RA. Transfusion of plasma, platelets, and red blood cells in a 1: 1: 1 vs a 1: 1: 2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471-82.

18. Schulman S, Bijsterveld NR. Anticoagulants and their reversal. *Transfus Med Rev*. 2007;21(1):37-48.

19. Franchini M, Lippi G. Prothrombin complex concentrates: an update. *Blood Transfusion*. 2010;8(3):149.

20. Curry N, Foley C, Wong H, Mora A, Curnow E, Zarankaite A, Hodge R, Hopkins V, Deary A, Ray J. Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial. *Crit Care*. 2018;22(1):164.

21. Innerhofer P, Fries D, Mittermayr M, Innerhofer N, von Langen D, Hell T, Gruber G, Schmid S, Friesenecker B, Lorenz IH, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. *Lancet Haematol*. 2017;4(6):e258-e71.

22. Vigué B, Ract C, Tremey B, Engrand N, Leblanc PE, Decaux A, Martin L, Benhamou D. Ultra-rapid management of oral anticoagulant therapy-related surgical intracranial hemorrhage. *Intensive Care Med*. 2007;33(4):721-5.

23. Joseph B, Aziz H, Pandit V, Hays D, Kulvatunyou N, Yousuf Z, Tang A, O'keeffe T, Green D, Friese RS. Prothrombin complex concentrate versus fresh-frozen plasma for reversal of coagulopathy of trauma: is there a difference? *World J Surg*. 2014;38(8):1875.

24. Zeeshan M, Hamidi M, Kulvatunyou N, Jehan F, O'Keeffe T, Khan M, Rashdan L, Tang A, Zakaria E-R, Joseph B. 3-Factor Vs. 4-Factor PCC in Coagulopathy of Trauma: Four is Better Than Three. *Shock* (Augusta, Ga). 2018.

25. Moe DM, Lallemand MS, McClellan JM, Smith JP, Marko ST, Eckert MJ, Martin MJ. Three-versus four-factor prothrombin complex concentrates for “factor-based” resuscitation in a porcine hemorrhagic shock model. *J Trauma Acute Care Surg*. 2017;83(6):1114-23.

26. Bruce D, Nokes TJ. Prothrombin complex concentrate (Beriplex P/N) in severe bleeding: experience in a large tertiary hospital. *Crit Care*. 2008;12(4):R105.

27. Majeed A, Eelde A, Ågren A, Schulman S, Holmström M. Thromboembolic safety and efficacy of prothrombin complex concentrates in the emergency reversal of warfarin coagulopathy. *Thromb Res*. 2012;129(2):146-51.

28. Watson GA, Sperry JL, Rosengart MR, Minei JP, Harbrecht BG, Moore EE, Cuschieri J, Maier RV, Billiar TR, Peitzman AB. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma Acute Care Surg*. 2009;67(2):221-30.

29. Inaba K, Branco BC, Rhee P, Blackbourne LH, Holcomb JB, Teixeira PG, Shulman I, Nelson J, Demetriades D. Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg*. 2010;210(6):957-65.

**Figure legends:**

**Figure 1.** Survival curve analysis.