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Hemostatic effect of fibrinogen concentrate on traumatic massive hemorrhage: a propensity score matching study

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ABSTRACT

Background Fibrinogen concentrate (FC) can be administered during massive transfusions to manage trauma-induced coagulopathy. However, its effectiveness in survival remains inconclusive due to scarce high-level evidence. This study aimed to investigate the hemostatic effects of FC regarding mortality in massive hemorrhage caused by trauma.

Methods This retrospective study analyzed 839 patients who received massive transfusions (red blood cells (RBCs) ≥5 units in 4 hours or ≥10 units in 24 hours) at a level I trauma center between 2015 and 2022. Patients who were transferred to other hospitals or were deceased upon arrival, suffered or died from severe brain injury, and were aged 15 years or less were excluded (n=334). 1:2 propensity score matching was performed to compare the 'FC (+)' group who had received FC in 24 hours (n=68) with those who had not ('FC (–)', n=437). The primary outcome was mortality, and the secondary outcomes included transfusion volume.

Results The variables for matching included vital signs, injury characteristics, prehospital time, implementation of resuscitative endovascular balloon occlusion of the aorta, and blood gas analysis results. The administration of FC did not significantly reduce or predict mortality (in-hospital, 24 hours, 48 hours, or 7 days). The FC (–) group received more units of RBC (25.69 units vs. 16.71 units, p<0.001, standardized mean difference [SMD] 0.595), fresh frozen plasma (16.79 units vs. 12.91 units, p=0.023, SMD 0.321), and platelets (8.76 units vs. 5.46 units, p=0.002, SMD 0.446) than the FC (+) group.

Conclusion The use of FC did not show survival benefits but reduced transfusion requirements in traumatic massive hemorrhages, highlighting a need for future investigations. In the future, individualized goal-directed transfusion with FC may play a significant role in treating massive bleeding.

Level of evidence IV, retrospective study having more than one negative criterion.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hypofibrinogenemia increases mortality in trauma patients. Fibrinogen concentrate (FC) is used to manage this, but its effect on survival is inconclusive.

WHAT THIS STUDY ADDS

⇒ This study found that although FC reduces the need for blood transfusions, it does not significantly impact mortality rates in massively hemorrhaging trauma patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings underscore the need for further studies and suggest a potential usage of FC in trauma care to achieve individualized goal-directed transfusion. These findings are worth considering for institutions that are not yet using FC in traumatic bleeding or are under-resourced.

INTRODUCTION

Initial hypofibrinogenemia is an independent predictor of in-hospital mortality in trauma.[1] Early consumption and lysis of fibrinogen are linked to worsened trauma-induced coagulopathy (TIC) and adverse outcomes, including increased transfusion requirements and higher mortality rates.[2 3] A recent open-label randomized controlled trial demonstrated that early fibrinogen supplementation is crucial in severe multiple trauma to prevent prolonged bleeding and multiple organ failure.[4] Hence, there is consensus that fibrinogen concentrate (FC) needs to be administered to hemorrhaging patients once hypofibrinogenemia is documented by standard laboratory test (SLT) or viscoelastic hemostatic assay (VHA), although the triggering serum level varies by guideline.[5] Therefore, administering FC can also be a rational therapeutic option for managing TIC.[6]

Several guidelines have advocated fibrinogen replacement with either FC or cryoprecipitate during massive transfusion protocol (MTP) implementation in trauma.[7–13] However, others have yet to since clinical evidence regarding the survival gain of FC supplements remains inconclusive.[14 15] Informed by prior observations and literature, this study hypothesized that using FC with massive transfusion may correlate with rapid control of hemorrhage or coagulopathy. This hypothesis was based on the potential of FC to enhance blood product utilization efficiency, thereby minimizing the risks associated with high-volume transfusions. Thus, this study aimed to evaluate the impact of FC administration on survival in massively bleeding trauma patients, with a propensity score matching (PSM) analysis to minimize the effect of patient group heterogeneity.

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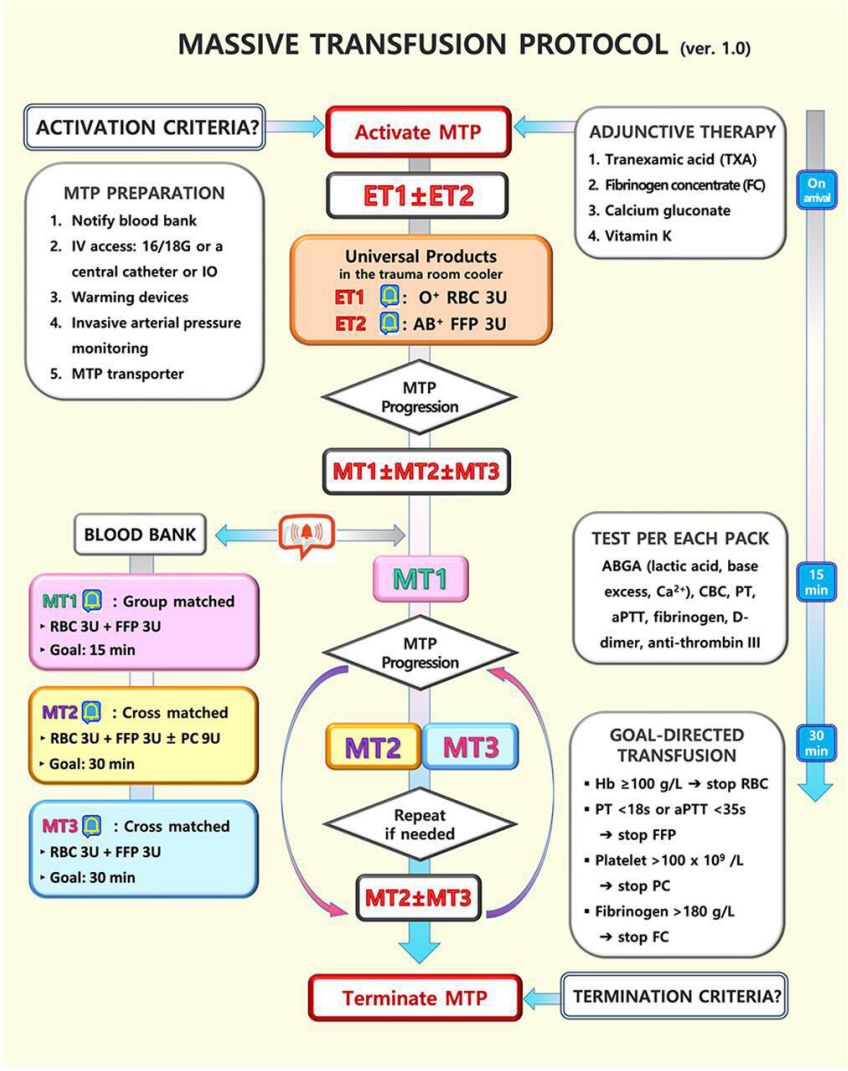
A



B

ACTIVATION CRITERIA

<Emergency department>

1. Hemodynamically unstable and actively bleeding
2. Significant chest, abdominal, pelvic, or multiple extremity injuries with hemodynamic instability
3. (+) e-FAST with hemodynamic instability
4. Hemodynamically unstable pelvic fracture with (-) e-FAST
5. Hemodynamically unstable extremity injury with (-) e-FAST
6. Hemodynamic stabilization is not achieved with fluid resuscitation
7. Arrangement of surgery or embolization requiring blood product preparation
8. ABC score ≥ 2 or Shock Index > 1.0
9. Necessity for massive transfusion based on trauma team's judgment

<Operating room & angiography suite>

1. Persistent hemodynamic instability post-trauma resuscitation area activation
2. Identification of an uncontrolled bleeding source
3. Necessity for massive transfusion based on anesthesia or trauma teams' judgment

<Intensive care unit>

1. Development of hemodynamic instability in a patient with prior trauma activation
2. Occurrence of hemodynamic instability due to hypovolemia
3. Suspected rebleeding after surgery or embolization

GOAL-DIRECTED TRANSFUSION

1. If serum Hb ≥100 g/L, stop RBC transfusion
2. If PT <18 s or aPTT <35 s, stop FFP transfusion
3. If serum platelet >100 x 10^9 /L, stop platelet transfusion
4. If serum fibrinogen >180 g/L, stop cryoprecipitate or FC

ADJUNCT THERAPY (detailed)

① Tranexamic Acid
- Administration within 3h of trauma
- 1st TXA 1000mg + N/S 100mL, 10mL/min IV
- 2nd TXA 1000mg + N/S 500mL, 60ml/hr (over 8hrs) IV

② Fibrinogen concentrate
- Consider administration when transfusing ≥ 2U of RBCs
- FC 3g + water for injection 150mL (20mg/ml), ≤5ml/min (over 30min) IV
- Target: serum fibrinogen ≥100mg/dL

③ Calcium gluconate
- Consider administration when transfusing ≥ 3U of RBCs
- 20mL of 10% calcium gluconate, over 10min IV
- Target: serum ionized calcium (total calcium) ≥1.0mmol/L (4.0mg/dL)

④ Vitamin K
- Warfarin history, if present
- Vitamin K 10mg + 5% D/W 50mL, over 20min IV

TERMINATION CRITERIA

1. Completion of hemostasis and hemodynamic stabilization based on trauma team's judgment
2. Infeasibility of resuscitation, based on trauma team or emergency medical teams' judgment
3. Death on arrival or prehospital cardiac arrest meeting criteria to discontinue resuscitation
4. Achievement of the goal-directed transfusion criteria

Figure 1 A flow chart (A) and the details (B) of the massive transfusion protocol (MTP) at the level I trauma center involved in this study. The trauma team leader initiates each step sequentially, as required: emergency transfusion (ET) 1, then ET2, followed by massive transfusion (MT) 1 and MT2. If further transfusions are necessary, either MT2 or MT3 is repeated. This MTP reflects the reality of the platelet shortage, with platelets being supplied from the MT2. ABC, assessment of blood consumption; ABGA, arterial blood gas analysis; aPTT, activated partial thromboplastin; CBC, complete blood count; D/W, dextrose in water; e-FAST, extended focused assessment with sonography for trauma; FFP, fresh frozen plasma; Hb, hemoglobin; IO, intraosseous; IV, intravenous; N/S, normal saline; PC, platelet concentrate; PT, prothrombin time; RBCs, red blood cells.

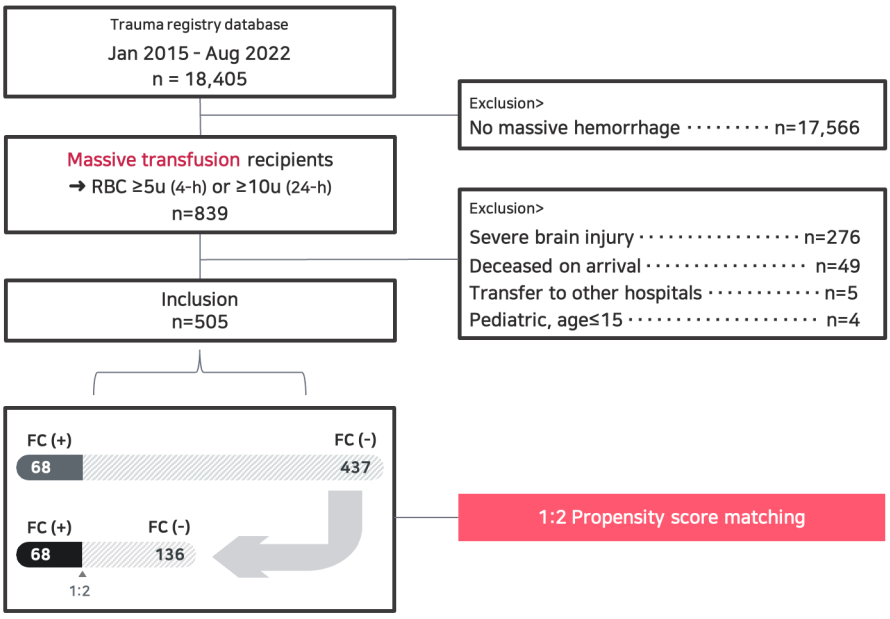


Figure 2 A flow chart of the patient enrollment process. FC fibrinogen concentrate; RBC red blood cell.

METHODS

This study was a retrospective review of patients who received a massive transfusion after trauma. The level I trauma center involved in this study is a 1060-bed tertiary teaching hospital covering an area with approximately 2 million people. More than 2500 trauma patients are treated annually, and about 30% are severely injured (Injury Severity Score (ISS) >15). It established MTP according to the standards required for trauma center verification and has adhered to the protocol since 2020.[16] We applied the protocol to the trauma patients with suspected or proven massive hemorrhage showing a low systolic blood pressure (SBP) lower than 90 mm Hg (figure 1).

Patient selection

We analyzed the electronic medical records of 18 405 patients registered to the trauma database of the institute from January 2015 to August 2022. We identified patients who received a massive transfusion, defined as receiving 5 or more units of red blood cells (RBCs) within 4 hours or 10 or more units within 24 hours.[17] Then, we screened patients who received a massive transfusion subsequently. The following patients were excluded: (1) patients who were transferred from the trauma center to other hospitals or deceased upon arrival; (2) those who suffered or died from severe brain injury (Abbreviated Injury Scale (AIS) head score of 5); and (3) those who were 15 years old or younger.

Intervention

FC was administered to the massive transfusion recipients, which involves the transfusion of two or more units of RBCs, independent of initial serum fibrinogen level. Three grams of FC was dissolved in 150 mL of injection water (20 mg/mL) to be infused intravenously at a ≤5 mL/min rate over 30 minutes. The goal was to reach a serum fibrinogen level of ≥100 mg/dL. Additional administration of the FC was decided at the discretion of the trauma team leader. A more detailed protocol of the adjunct therapy, including other therapeutic agents, can be found in figure 1B.

Outcome measures

The primary outcome measure was mortality (in-hospital, 24 hours, 48 hours, and 7 days). Secondary outcomes included transfusion volume (the number of units of RBC, fresh frozen plasma (FFP), and platelets transfused). Other outcomes measured included hemostatic interventions, reason for death, length of hospital and intensive care unit stay, and thromboembolic events. For patients who died, their length of stay would be the duration from their admission to the hospital until their time of death. The prehospital time was defined as the time between injury and presentation to the trauma center. The outcomes were only analyzed during the patients' hospitalization, and no post-discharge follow-up period was necessary for the purpose of the study. None of the variables we analyzed had missing data.

Statistical analysis

To minimize the impact of confounding factors, such as different injury panoramas and the progression of physiologic derangement between the groups, a 1:2 PSM analysis was used. Considering the total number of patients included in the study, propensity scores were estimated using multivariable logistic regression to avoid overfitting in the matching. The covariates used in the model were initial parameters regarding vital signs and consciousness (SBP, mean arterial pressure, Revised Trauma Score (RTS) and Glasgow Coma Scale (GCS) score); injury characteristics (ISS and AIS chest/abdomen); prehospital time; implementation of resuscitative endovascular balloon occlusion of the aorta; and results of initial blood gas analysis (pH, arterial oxygen pressure, base excess, and lactate). These variables were chosen as they were identified as potentially influential in determining whether FC was administered and affecting study outcomes. Covariate balance was evaluated by standardized mean differences (SMDs).

We compared baseline characteristics and clinical outcomes between the two groups before and after PSM using X^2 tests for categorical variables and independent t-tests for continuous variables. To describe continuous variables, a mean with an SD and a

Table 1 (A) The pre-match patient characteristics and (B) the pre-match clinical outcomes

Variable	FC (+) n=68	FC (–) n=437	P value	SMD
A. The pre-match patient characteristics				
Age, year	53.84±19.56	54.45±17.05	0.807	0.034
Male gender, n (%)	17 (25.0)	83 (19.0)	0.321	0.145
Injury mechanism, n (%)			NA	0.506
Traffic accident, in car	20 (29.4)	147 (33.6)		
Traffic accident, pedestrian	19 (27.9)	76 (17.4)		
Traffic accident, cycles	10 (14.7)	66 (15.1)		
Ground-level fall	10 (14.7)	56 (12.8)		
Stab or cutting wound	2 (2.9)	36 (8.2)		
Press by machine	7 (10.3)	30 (6.9)		
Others	0 (0.0)	26 (6.0)		
Blunt trauma, n (%)	66 (97.1)	398 (91.2)	0.154	0.253
Trauma score, median (IQR)				
Injury Severity Score	32.50 (22.00–41.00)	25.00 (17.00–33.00)	<0.001	0.575
Revised Trauma Score (RTS)	9.00 (5.00–10.00)	10.00 (8.00–11.00)	<0.001	0.46
RTS weighted	5.64 (2.53–6.38)	6.38 (4.71–7.11)	<0.001	0.431
Abbreviated Injury Scale (AIS)				
AIS head & neck	0.91±1.39	0.86±1.34	0.757	0.041
AIS face	0.34±0.75	0.25±0.66	0.344	0.129
AIS chest	2.72±1.63	2.17±1.70	0.012	0.33
AIS abdomen	2.79±1.67	2.27±1.72	0.018	0.312
AIS extremity & pelvis	2.44±1.85	2.00±1.63	0.066	0.254
AIS external	0.65±0.62	0.63±0.66	0.871	0.021
Prehospital time, min	93.69±61.17	139.65±269.00	0.002	0.234
Cardiac arrest in ED, n (%)	8 (11.8)	21 (4.8)	0.043	0.254
REBOA implementation, n (%)	28 (41.2)	65 (14.9)	<0.001	0.612
Initial vital signs, median (IQR)				
Systolic blood pressure, mm Hg	78.00 (54.75–103.00)	97.00 (74.00–121.00)	<0.001	0.49
Mean arterial pressure, mm Hg	47.15 (37.45–57.78)	53.30 (41.70–66.70)	0.013	0.326
Heart rate, per min	99.50 (78.00–122.25)	98.00 (0.00–116.00)	0.965	0.112
Respiratory rate, per min	21.00 (11.25–29.25)	20.00 (16.00–24.00)	0.515	0.014
Body temperature, °C	36.10 (36.00–36.30)	36.00 (36.00–36.50)	0.924	0.074
Glasgow Coma Scale	13.00 (3.00–14.00)	14.00 (8.00–15.00)	0.001	0.339
Initial laboratory tests, median (IQR)				
pH	7.27 (7.17–7.35)	7.33 (7.24–7.39)	0.001	0.411
PaO_2, mm Hg	105.50 (73.95–142.50)	88.00 (66.00–121.00)	0.019	0.255
Base excess, mmol/L	−8.25 (−13.50 to −4.80)	−6.80 (−11.00 to −2.90)	0.016	0.253
Lactate, mmol/L	6.90 (4.07–9.70)	4.60 (2.70–7.50)	0.001	0.448
Hemoglobin, g/L	112.5 (89.0–127.0)	111.0 (90.0–130.0)	0.595	0.125
Platelet, 10^9/L	192.50 (136.00–233.25)	182.00 (140.00–233.00)	0.915	0.056
PT-INR	1.18 (1.10–1.36)	1.15 (1.05–1.29)	0.019	0.006
Creatinine, mg/dL	1.17 (0.92–1.39)	1.05 (0.85–1.28)	0.025	0.233
Underlying disease, n (%)				
Hypertension	17 (25.0)	126 (28.8)	0.611	0.087
Diabetes mellitus	12 (17.6)	66 (15.1)	0.719	0.069
Cardiac disease	1 (1.5)	28 (6.4)	0.157	0.256
Cerebrovascular disease	2 (2.9)	17 (3.9)	1	0.05
B. The pre-match clinical outcomes				
Transfusion in 24 hours				
Red blood cells, unit	16.71±10.37	18.68±14.86	0.174	0.154
Fresh frozen plasma, unit	12.91±9.96	11.73±11.19	0.374	0.111
Platelets, unit	5.46±6.09	7.10±7.74	0.049	0.236
Hemostatic interventions, n (%)				
Any emergency operations	53 (77.9)	323 (73.9)	0.576	0.094
Laparotomy	36 (52.9)	201 (46.0)	0.349	0.139
Temporary abdominal closure	20 (29.4)	65 (14.9)	0.005	0.356

Continued

Table 1 Continued

Variable	FC (+) n=68	FC (−) n=437	P value	SMD
Orthopedic damage control	11 (16.2)	81 (18.5)	0.764	0.062
Thoracotomy	5 (7.4)	47 (10.8)	0.519	0.119
Preperitoneal pelvic packing	12 (17.6)	19 (4.3)	<0.001	0.435
Angioembolization	31 (45.6)	120 (27.5)	0.004	0.383
Mortality, n (%)				
In-hospital mortality	28 (41.2)	124 (28.4)	0.046	0.271
24-hour mortality	17 (25.0)	61 (14.0)	0.031	0.282
48-hour mortality	3 (4.4)	20 (4.6)	1	0.008
7-day mortality	26 (38.2)	100 (22.9)	0.01	0.338
Reason for death, n (%)				
Hemorrhagic shock	22 (32.4)	83 (19.0)	0.018	0.309
MODS, septic shock	6 (8.8)	35 (8.0)	1	0.029
Respiratory failure	0 (0.0)	4 (0.9)	1	0.136
Cardiovascular failure	0 (0.0)	2 (0.5)	1	0.096
Length of days				
Hospital stay	37.63±49.57	33.89±39.66	0.555	0.083
Intensive care unit stay	7.65±9.59	9.24±12.53	0.225	0.143
Ventilator maintenance	5.10±6.42	5.18±8.87	0.93	0.01
Thromboembolic events, n (%)	0 (0.0)	3 (0.7)	1	0.118

ED, emergency department; FC, fibrinogen concentrate; MODS, multiorgan dysfunction syndrome; NA, not applicable; PaO_2, arterial oxygen pressure; PT-INR, prothrombin time-international normalized ratio; REBOA, resuscitative endovascular balloon occlusion of the aorta; SMD, standardized mean difference.

median with an IQR were used for normal and non-normal distribution, respectively. We performed additional logistic regression analysis on the post-match data for the primary outcomes. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the R package (V.5.1-1; The R Project for Statistical Computing).

RESULTS

Patient enrollment

A flow chart of the patient enrollment process is detailed below (figure 2). Among the 18 405 patients registered in the database, 505 were eligible for analysis and finally enrolled. These patients were divided into two groups based on whether or not they had received FC within the first 24 hours of care: the FC (+) group (n=68) and the FC (−) group (n=437).

Pre-match patient characteristics

The pre-match patient characteristics for the two groups exhibited specific differences (table 1A). Both groups had a similar average age, gender distribution, and prevalence of underlying diseases such as hypertension, diabetes mellitus, cardiac disease, and cerebrovascular disease. However, the FC (+) group showed a higher incidence of blunt and more severe trauma, as indicated by higher ISS, lower RTS, and increased scores on the AIS for the chest, abdomen, and extremities. This group also exhibited longer prehospital times and a higher incidence of cardiac arrest in the emergency department. Initial vital signs and laboratory tests showed more significant physiological derangement in the FC (+) group, including lower blood pressure, GCS score, higher lactate levels, and acidosis.

Pre-match clinical outcomes

In examining the pre-match clinical outcomes between the FC (+) group and the FC (−) group, several key differences were found (table 1B). The FC (+) group demonstrated a lower requirement for platelet transfusion within the initial 24 hours (5.46 units vs. 7.1 units; p=0.049, SMD=0.236). They also underwent significantly more temporary abdominal closures and preperitoneal pelvic packing procedures, indicative of more complex injuries. Moreover, higher in-hospital and 24-hour mortality rates were noted in the FC (+) group (p=0.046, SMD=0.271; p=0.031, SMD=0.282, respectively), suggesting that the severity of trauma in this group might be more intense, despite their lower transfusion needs. Hemorrhagic shock was also a more common cause of death in the FC (+) group (p=0.018, SMD=0.309).

Post-match patients' characteristics

For the post-match patient characteristics, no significant differences were found between the FC (+) and FC (−) groups in all variables (table 2A). Overall, both groups were well matched and comparable across the evaluated parameters.

Post-match clinical outcomes

There were significant differences in transfusion volume within the first 24 hours of post-match clinical outcomes (table 2B). The FC (−) group received more units of RBC (25.69 units vs. 16.71 units, p<0.001, SMD 0.595), FFP (16.79 units vs. 12.91 units, p=0.023, SMD 0.321), and platelets (8.76 units vs. 5.46 units, p=0.002, SMD 0.446) compared with the FC (+) group. Mortality rates, whether in-hospital, 24 hours, 48 hours, or 7 days, also did not differ significantly between the groups. Although transfusion requirements were significantly higher in the FC (−) group, other clinical outcomes, including emergency operations, mortality rates, causes of death, hospital stay duration, and thromboembolic events, did not show significant differences between the two groups.

Figure 3 outlines the pre-match and post-match SMD for the patient characteristics and clinical outcomes. Most SMD values were low post-match, addressing the efficacy of the PSM conducted in this study.

Table 2 (A) The post-match patient characteristics and (B) the post-match clinical outcomes

Variable	FC (+) n=68	FC (–) n=136	P value	SMD
A. The post-match patient characteristics				
Age, year	53.84±19.56	54.87±17.63	0.715	0.055
Male gender, n (%)	17 (25.0)	24 (17.6)	0.294	0.18
Injury mechanism, n (%)			0.724	0.38
Traffic accident, in car	20 (29.4)	47 (34.6)		
Traffic accident, pedestrian	19 (27.9)	29 (21.3)		
Traffic accident, cycles	10 (14.7)	16 (11.8)		
Ground-level fall	10 (14.7)	20 (14.7)		
Stab or cutting wound	7 (10.3)	12 (8.8)		
Press by machine	2 (2.9)	5 (3.7)		
Others	0 (0.0)	7 (5.2)		
Blunt trauma, n (%)	66 (97.1)	130 (95.6)	0.721	0.078
Trauma score, median (IQR)				
Injury Severity Score	32.50 (22.00–41.00)	31.00 (22.00–41.00)	0.94	0.026
Revised Trauma Score (RTS)	9.00 (5.00–10.00)	9.00 (6.00–10.00)	0.514	0.077
RTS weighted	5.64 (2.53–6.38)	5.64 (3.73–6.38)	0.631	0.058
Abbreviated Injury Scale (AIS)				
AIS head & neck	0.91±1.39	1.01±1.50	0.653	0.066
AIS face	0.34±0.75	0.21±0.65	0.241	0.179
AIS chest	2.72±1.63	2.68±1.67	0.88	0.022
AIS abdomen	2.79±1.67	2.74±1.77	0.839	0.03
AIS extremity & pelvis	2.44±1.85	2.12±1.77	0.234	0.179
AIS external	0.65±0.62	0.64±0.62	0.936	0.012
Prehospital time, min	93.69±61.17	96.91±73.83	0.742	0.048
Cardiac arrest in ED, n (%)	8 (11.8)	8 (5.9)	0.231	0.209
REBOA implementation, n (%)	28 (41.2)	52 (38.2)	0.8	0.06
Initial vital signs, median (IQR)				
Systolic blood pressure, mm Hg	78.00 (54.75–103.00)	84.00 (59.50–108.00)	0.633	0.085
Mean arterial pressure, mm Hg	47.15 (37.45–57.78)	46.70 (34.22–56.17)	0.37	0.078
Heart rate, per min	99.50 (78.00–122.25)	98.50 (73.75–120.50)	0.961	0.038
Respiratory rate, per min	21.00 (11.25–29.25)	18.00 (12.00–24.00)	0.164	0.148
Body temperature, °C	36.10 (36.00–36.30)	36.00 (36.00–36.30)	0.228	0.16
Glasgow Coma Scale	13.00 (3.00–14.00)	13.00 (6.00–15.00)	0.265	0.079
Initial laboratory tests, median (IQR)				
pH	7.27 (7.17–7.35)	7.29 (7.12–7.37)	0.379	0.136
PaO_2, mm Hg	105.50 (73.95–142.50)	94.00 (69.50–146.25)	0.332	0.085
Base excess, mmol/L	−8.25 (−13.50 to −4.80)	−8.95 (−15.40 to −4.68)	0.845	0.049
Lactate, mmol/L	6.90 (4.07–9.70)	6.55 (3.90–10.07)	0.875	0.089
Hemoglobin, g/dL	11.25 (8.90–12.70)	11.25 (8.80–12.83)	0.702	0.069
Platelet, 10^3/μL	192.50 (136.00–233.25)	177.00 (137.00–224.75)	0.569	0.058
PT-INR	1.18 (1.10–1.36)	1.18 (1.08–1.41)	0.707	0.145
Creatinine, mg/dL	1.17 (0.92–1.39)	1.13 (0.95–1.33)	0.679	0.14
Underlying disease, n (%)				
Hypertension	17 (25.0)	40 (29.4)	0.62	0.099
Diabetes mellitus	12 (17.6)	26 (19.1)	0.949	0.038
Cardiac disease	1 (1.5)	12 (8.8)	0.064	0.337
Cerebrovascular disease	2 (2.9)	6 (4.4)	0.721	0.078
B. The post-match clinical outcomes				
Transfusion in 24 hours				
Red blood cells, unit	16.71±10.37	25.69±18.68	<0.001	0.595
Fresh frozen plasma, unit	12.91±9.96	16.79±13.87	0.023	0.321
Platelets, unit	5.46±6.09	8.76±8.54	0.002	0.446
Hemostatic interventions, n (%)				
Any emergency operations	53 (77.9)	110 (80.9)	0.757	0.073
Laparotomy	36 (52.9)	76 (55.9)	0.804	0.059
Temporary abdominal closure	20 (29.4)	39 (28.7)	1	0.016
Orthopedic damage control	11 (16.2)	16 (11.8)	0.511	0.128
Thoracotomy	5 (7.4)	20 (14.7)	0.199	0.236
Preperitoneal pelvic packing	12 (17.6)	16 (11.8)	0.35	0.167
Angioembolization	31 (45.6)	47 (34.6)	0.169	0.227
Mortality, n (%)				
In-hospital mortality	28 (41.2)	65 (47.8)	0.456	0.133
24-hour mortality	17 (25.0)	31 (22.8)	0.861	0.052
48-hour mortality	3 (4.4)	12 (8.8)	0.393	0.178
7-day mortality	26 (38.2)	54 (39.7)	0.96	0.03
Reason for death, n (%)				
Hemorrhagic shock	22 (32.4)	44 (32.4)	1	<0.001
MODS, septic shock	6 (8.8)	17 (12.5)	0.584	0.119
Respiratory failure	0 (0.0)	3 (2.2)	0.552	0.212
Cardiovascular failure	0 (0.0)	1 (0.7)	1	0.122
Length of days, days				
Hospital stay	37.63±49.57	27.97±37.42	0.159	0.22
Intensive care unit stay	7.65±9.59	7.99±10.74	0.82	0.033
Ventilator maintenance	5.10±6.42	5.35±8.05	0.811	0.034
Thromboembolic events, n (%)	0 (0.0)	1 (0.7)	1	0.122

ED, emergency department; FC, fibrinogen concentrate; MODS, multiorgan dysfunction syndrome; PaO_2, arterial oxygen pressure; PT-INR, prothrombin time-international normalized ratio; REBOA, resuscitative endovascular balloon occlusion of the aorta; SMD, standardized mean difference.

Post-match logistic regression analysis predicting mortality

Table 3 elaborates on the post-match logistic regression analysis outcomes, predicting four types of mortality rates: in-hospital, 24-hour, 48-hour, and 7-day mortality. Each mortality rate was assessed for its relationship with four variables: FC (+) versus FC (−), RBC, FFP, and platelets. The use of RBC showed a

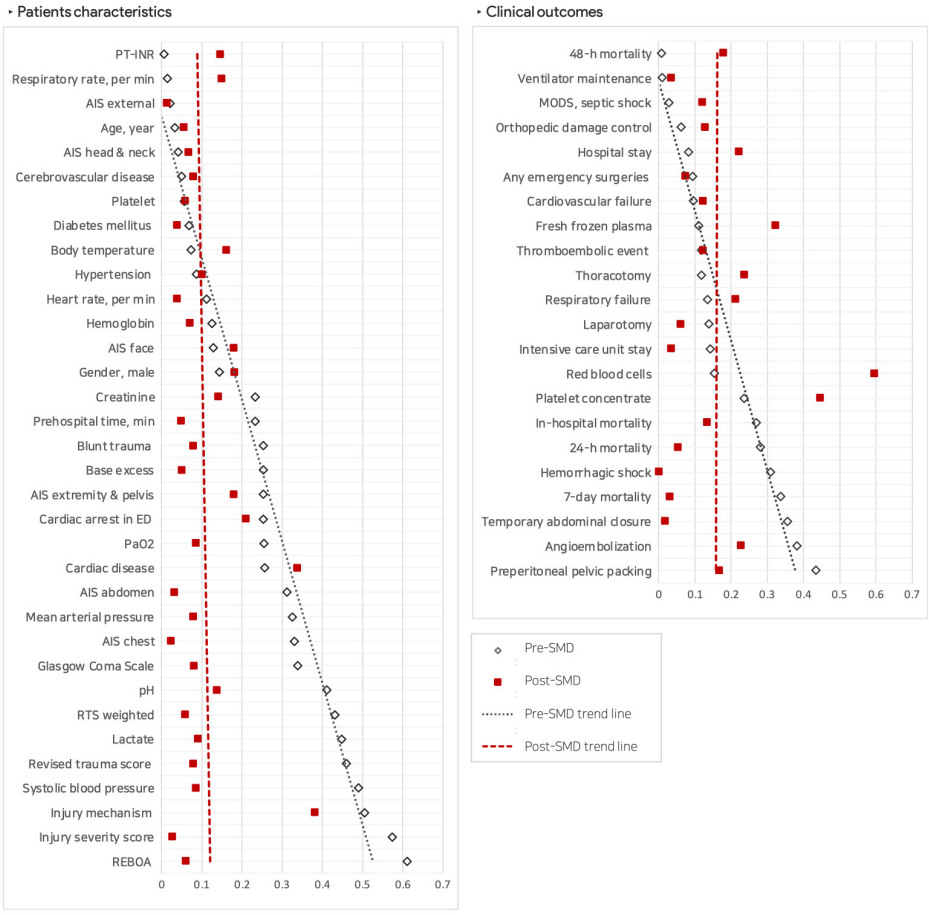


Figure 3 The pre-match and post-match standardized mean differences (SMDs) for the patient characteristics and clinical outcomes. AIS, Abbreviated Injury Scale; ED, emergency department; MODS, multiorgan dysfunction syndrome; PaO_2, arterial oxygen pressure; PT-INR, prothrombin time-international normalized ratio; REBOA, resuscitative endovascular balloon occlusion of the aorta; RTS, Revised Trauma Score.

statistically significant association with in-hospital (adjusted OR (adj. OR) 1.07, 95% CI 1.02 to 1.12; adj. p=0.008), 24-hour (adj. OR 1.07, 95% CI 1.02 to 1.12; adj. p=0.007) and 7-day mortality (adj. OR 1.08, 95% CI 1.03 to 1.14; adj. p=0.001). Similarly, platelets exhibited a significant association in reducing in-hospital (adj. OR 0.94, 95% CI 0.89 to 0.98; adj. p=0.01), 24-hour (adj. OR 0.84, 95% CI 0.78 to 0.91; adj. p<0.001) and 7-day mortality (adj. OR 0.92, 95% CI 0.87 to 0.97; adj. p=0.001). However, FC (+) versus FC (−) did not show any statistically significant impact on any of the mortality rates in the adjusted models.

DISCUSSION

MTP has been globally used in trauma practice since the American College of Surgeons provided high-quality evidence for the benefits of MTP.[7] However, a lack of consistent practices and regular updates on MTP can hinder the best treatment outcome of trauma-related bleeding. The question of when and how to transition from a traditional fixed-ratio strategy to goal-directed resuscitation introduces another layer of complexity to this issue. The wide variability in hemostatic defects in different individuals highlights a need for individualized resuscitation guided by VHA.[6 18]

VHA, such as thromboelastography and rotational thromboelastometry, provides a real-time assessment of hypofibrinogenemia and allows targeted FC administration.[19 20] VHA-guided blood transfusions were associated with fewer blood product transfusions and reduced mortality after trauma.[21] However, limited access to the VHA is a barrier to goal-directed resuscitation at some institutions, and ours is one of them. Therefore, organizations with limited equipment and resources may find our findings instructive. Moreover, caution is needed when using VHA as it has limitations. It has potential bias from the properties of each device, and there is no robust evidence that the VHA is superior to SLT in the treatment of coagulopathy.[20]

Our study showed an association between FC administration and the reduced transfusion volume of RBC, FFP, and platelets. This finding aligns with several previous studies that proposed the role of FC in decreasing the need for transfusion of blood products.[4 19 22–25] In the post-match logistic regression analysis of the factors predicting mortality, the use of RBC appeared to have a significant positive correlation with all four assessed mortality types in the adjusted models. Conversely, platelets showed an association with reducing in-hospital and 24-hour mortality. Although this might be due to the protective effect of platelet transfusions, it is more likely that the patients who died prematurely did not receive platelet transfusions due to inadequate platelet supply. Although higher transfusion volumes were observed in the FC (−) group, this might be attributed to several factors, such as more severe injuries or implementing different hemostatic interventions. Furthermore, the nature of our study design—a retrospective analysis—inherently limits

Table 3 Post-match logistic regression predicting four mortality rates

Variable	Crude OR (95% CI)	Crude p value	Adj. OR (95% CI)	Adj. p value
A. In-hospital mortality				
FC (+) vs. FC (–)	0.76 (0.42, 1.38)	0.371	1.12 (0.56, 2.26)	0.742
Red blood cells	1.08 (1.05, 1.11)	<0.001	1.07 (1.02, 1.12)	0.008
Fresh frozen plasma	1.08 (1.05, 1.12)	<0.001	1.04 (0.98, 1.11)	0.167
Platelets	1 (0.97, 1.04)	0.909	0.94 (0.89, 0.98)	0.01
No of observations	204			
AIC value	238.36			
B. 24-hour mortality				
FC (+) vs. FC (–)	1.13 (0.57, 2.23)	0.726	1.35 (0.6, 3.07)	0.467
Red blood cells	1.03 (1.01, 1.05)	0.003	1.07 (1.02, 1.12)	0.007
Fresh frozen plasma	1.02 (0.99, 1.04)	0.139	0.98 (0.92, 1.04)	0.502
Platelets	0.87 (0.82, 0.93)	<0.001	0.84 (0.78, 0.91)	<0.001
No of observations	204			
AIC value	184.61			
C. 48-hour mortality				
FC (+) vs. FC (–)	0.48 (0.13, 1.75)	0.264	0.71 (0.17, 2.9)	0.632
Red blood cells	1.03 (1.01, 1.06)	0.01	1.03 (0.97, 1.08)	0.326
Fresh frozen plasma	1.04 (1.01, 1.07)	0.018	1 (0.93, 1.08)	0.98
Platelets	1.04 (0.98, 1.11)	0.191	1.02 (0.95, 1.09)	0.602
No of observations	204			
AIC value	110.46			
D. 7-day mortality				
FC (+) vs. FC (–)	0.94 (0.52, 1.71)	0.839	1.43 (0.7, 2.93)	0.324
Red blood cells	1.06 (1.04, 1.09)	<0.001	1.08 (1.03, 1.14)	0.001
Fresh frozen plasma	1.06 (1.03, 1.09)	<0.001	1.01 (0.95, 1.07)	0.773
Platelets	0.98 (0.94, 1.01)	0.178	0.92 (0.87, 0.97)	0.001
No of observations	204			
AIC value	233.21			

Adj, adjusted; AIC, Akaike Information Criterion; FC, fibrinogen concentrate.

causal inference. Therefore, this result should be interpreted as indicative of a correlation for future research rather than definitive evidence of causation.

In contrast, our study did not demonstrate a significant impact on mortality rates with FC usage despite lower transfusion needs. A previous multicenter study with a similar design has reported the same results.[26 27] This can be attributed to the complex nature of trauma and its management regarding TIC, or the varied nature of the study cohorts, such as injury patterns, severity, comorbidities, and the timeliness and effectiveness of trauma care. Another aspect of this finding is that although FC helps control bleeding and reduces the need for transfusions, its effect may not correlate directly with mortality benefits due to the multifaceted nature of mortality in trauma patients. This assumption underscores the necessity for large-scale, randomized controlled trials to definitively determine the impact of FC on trauma-related mortality. Another study using PSM analysis reported increased survival in the group receiving FC within 1 hour of arrival but was limited by the small number of patients and matching variables and should be interpreted with caution.[28] Our study is significant in that it is the only one to exclude the severe brain injury group, which may affect the progression of coagulopathy, among studies using the PSM assay on the same subject.

The single-center retrospective design is the most critical limitation of the present study. Other limitations include the FC group's relatively small sample size and the potential selection bias from individual surgeon discretion. These may have also introduced survival bias, underscoring the need for further studies with larger, more diverse cohorts. Other major limitations include survival and selection bias from transfusion strategies based on the clinician's judgment. Not all control patients were treated during the same period as the FC group because FC was introduced to our institution in the fifth year of the 8-year study period. The evolution of medical care and institutional protocols during this period could have influenced the utilization of FC and clinical outcomes. Moreover, we could not control for potential confounders, such as variations in initial resuscitation strategies or the timing and dose of FC administration. When a patient received more than two units of RBC, the FC was administered based on a subjective decision by the trauma team leader, not based on results obtained from VHA or an existing scoring system. Unfortunately, data on general complications during trauma care, serum fibrinogen levels, and the effect of other hemostatic supplements, such as cryoprecipitate or tranexamic acids, were absent and not studied. In addition, the inclusion of an early mortality (eg, within 24 or 48 hours of admission) group may have reduced the average length of hospital stay despite adverse outcomes. Separation of early deaths from the overall analysis or subgroup analyses would minimize the limitations in the future study. Lastly, the impact of COVID-19 was not controlled in this study during the pandemic.

In the field of trauma care, ongoing research continually improves our understanding of the most effective strategies for managing hemorrhagic patients. A recent study investigating the efficacy and safety of four-factor prothrombin complex concentrate (4F-PCC), which includes human coagulation factors II, VII, IX, X, and proteins S and C, shows how our knowledge about this area is growing.[29] Although our study mainly focused on the role of FC, it is also essential to understand how various hemostatic agents like 4F-PCC work in different clinical situations. As trauma care continues to advance, in-depth studies are key to figuring out the best ways to resuscitate patients, thereby guiding the development of more refined and targeted therapeutic interventions.

CONCLUSION

Although our study suggests an association between FC and reduced transfusion requirements, the definitive impact of FC on mortality still needs to be defined. Future investigations are warranted to further establish this relationship. Simultaneously, integrating novel point-of-care coagulation tests into trauma care protocols would refine our understanding of FC

usage and facilitate more effective, patient-specific resuscitation strategies. Pairing these tools with novel biomarkers of fibrinogen function could significantly improve our knowledge of TIC and refine therapeutic interventions, including FC administration.

Contributors DHK developed the study concept and design as guarantor, revised the article, and had responsibility for the overall content. YH performed statistical analyses and wrote the article. SWC contributed to developing the study design and interpretation of data. SWL and DSM contributed to data acquisition.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and the institutional review board (IRB) and the ethics committee of Dankook University Hospital approved the study (no. DKUH 2023-03-029). The IRB waived the written informed consent for publication from the patient, because we conducted a retrospective review of the chart.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

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