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ORIGINAL ARTICLE - BRAIN TRAUMA

A retrospective study of the effect of fibrinogen levels during fresh frozen plasma transfusion in patients with traumatic brain injury

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Abstract

Background The association between traumatic brain injury (TBI) and coagulopathy is well established. While coagulopathy prophylaxis in TBI involves replenishing coagulation factors with fresh frozen plasma (FFP), its effectiveness is controversial. We investigated the relationship between plasma fibrinogen concentration 3 h after initiating FFP transfusion and outcomes and evaluated the correlation with D-dimer levels at admission.

Methods We retrospectively examined data from 380 patients with severe isolated TBI with blood samples collected a maximum of 1 h following injury. Plasma fibrinogen and D-dimer concentrations were obtained at admission, and plasma fibrinogen concentration was again assessed 3–4 h following injury. The patients were divided into two groups based on whether or not they received FFP transfusion. Patients were also divided into subgroups according their fibrinogen level: ≥ 150 mg/dL (high-fibrinogen subgroup) or < 150 mg/dL (low-fibrinogen subgroup) 3 h after injury. Demographic, clinical, radiological and laboratory data were compared between these subgroups.

Results Glasgow Outcome Scale (GOS) scores at discharge and 3 months after injury were significantly lower in the FFP transfusion group than in the FFP non-transfusion group. Among patients who received FFP, GOS scores at discharge and 3 months after injury were significantly higher in the high-fibrinogen subgroup than in the low-fibrinogen subgroup. Elevated admission D-dimer predicted subsequent fibrinogen decrease.

Conclusions In FFP transfusion, fibrinogen level ≥ 150 mg/dL 3 h after injury was associated with better outcomes in TBI patients. Assessing the admission D-dimer and tracking the fibrinogen are crucial for optimal coagulopathy prophylaxis in TBI patients.

Keywords Blood coagulation disorders · Brain injuries, traumatic · Fibrinogen · Fibrinolysis · Prognosis

Introduction

Coagulation abnormalities are often observed in patients with traumatic brain injury (TBI) [6, 15, 40]. According to a meta-analysis, the overall incidence of TBI-associated coagulopathy is 32.7–35.2%, and there is a strong association between abnormal haemostasis and unfavourable outcomes [6, 15]. Likewise, in a large trauma registry study in Germany, 22.7% of patients with isolated TBI exhibited acute coagulopathy in the emergency department, the occurrence of which was correlated with increased morbidity and mortality [40].

Hyperfibrinolysis is implicated in causing coagulopathy following TBI [26]. One treatment option for hyperfibrinolysis in TBI uses fresh frozen plasma (FFP) to replenish coagulation factors. However, a number of studies [2, 7, 42, 43] have found that this method results in no improvement in outcomes. For example, Zhang et al. [43] showed that increased perioperative FFP infusion was independently associated with mortality or worse outcomes for a number of surgical risk profiles. Although FFP contains fibrinogen, no studies have analysed fibrinogen levels during FFP transfusion.

We hypothesised that tracking fibrinogen levels during FFP transfusion may improve outcomes for those with severe TBI. The fibrinolytic factor D-dimer is increased in patients with

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elevated fibrinogen consumption in the acute phase of TBI [31]. We aimed to investigate the relationship between the plasma fibrinogen concentration 3 h after initiating FFP transfusion and patient outcomes and evaluated the correlation with D-dimer levels at admission.

Materials and methods

Setting

The Emergency and Critical Care Center of Kawaguchi Municipal Medical Center (Saitama, Japan) is a top-level critical care centre in Saitama Prefecture, Japan. The centre treats around 1000–1200 patients per year, of which 300–350 are severe trauma cases.

Patients

This study is a retrospective review of data from patients with TBI who were admitted to the Emergency and Critical Care Center of Kawaguchi Municipal Medical Center from April 2007 to December 2017. Cases were included if the admitting diagnosis was severe isolated TBI, identified by an intracranial Abbreviated Injury Score (AIS) ≥ 3 and an extracranial AIS < 3, according to previous studies [6, 14, 24, 31, 38, 40]. TBI was diagnosed according to findings on CT scans and MR images. Intracranial and extracranial AIS, CT scans and MR images were separately examined by intensivists and neurointensivists (R.N., Y.T., Y.F., G.S. and Y.N.). Exclusion criteria were an initial fibrinogen sample obtained > 1 h after injury; absent plasma fibrinogen level measurements at admission and/or 3 h after injury and/or 12 h after injury; absent plasma D-dimer level measurement at admission; insufficient data on the injury time; age < 16 years; use of anticoagulants or antiplatelet drugs; hypotension (systolic blood pressure < 90 mmHg) or hypoxaemia (PaO_2 < 60 mmHg) at admission; cardiopulmonary arrest prior to or at admission to hospital; liver failure, haematological disease, sepsis, malignancy, or pregnancy, which may affect coagulation and fibrinolytic parameters; and insufficient data on the outcome 3 months after injury (some patients had more than one of the above exclusion criteria).

Data on factors considered relevant to the outcome such as age [1, 12, 19, 30, 31, 39, 40], sex, Glasgow Coma Scale (GCS) score at admission [24, 31, 33, 38, 40] and AIS-head were collated [1, 3, 24, 31, 40]. CT scans and MR images at admission and follow-up were separately examined, and the type of head injury according to radiologic data was categorized as acute subdural haematoma (ASDH), acute epidural haematoma (AEDH), intracerebral haematoma/contusion (ICH) or traumatic subarachnoid haemorrhage (TSAH). Blood samples for determining initial (within 1 h following injury) plasma fibrinogen and D-dimer concentrations were obtained on arrival at the emergency department. The plasma fibrinogen concentration was additionally determined 3–4 h and 12–13 h following injury. The volumes of red cell concentrate (RCC) and FFP transfused within 3 h of injury and the occurrence of transfusion-associated complications including multiple organ failure (MOF) and acute respiratory distress syndrome (ARDS) were noted. MOF was diagnosed when the maximum Marshall multiple organ dysfunction score was > 5 [27], and ARDS was diagnosed when PaO_2/FiO_2 was ≤ 300 mmHg within 1 week of an identified medical insult or new or worsening respiratory symptoms, bilateral opacities on a chest X-ray and respiratory failure unable to be completely accounted for by cardiac failure or fluid overload [8]. Whether or not operation for TBI was performed and the surgical method(s) used in cases requiring surgery, such as burr hole surgery for placement of an intracranial pressure sensor and/or ventricular drainage and/or evacuation of the haematoma, craniotomy/craniectomy or craniotomy/craniectomy plus burr hole surgery, as well as duration of mechanical ventilation, were noted.

Management of TBI

Treatment was immediately administered upon patient arrival at the emergency department based on guidelines for the management of TBI by the Japan Society of Neurotraumatology [13, 34]. Brain CT was performed for all patients following a detailed neurological examination and initial resuscitation. A second routine CT scan was performed within 3 h after admission and subsequently if patients showed signs of clinical deterioration or increased intracranial pressure. In cases where CT scans revealed no significant abnormality but TBI was suspected, MR imaging was promptly performed.

Assay of coagulation/fibrinolytic parameters

Blood samples were collected into vacuum tubes containing ethylenediaminetetraacetic acid and sodium citrate. Fibrinogen concentrations were measured using the coagulation method (Thrombocheck Fib [L]®, Sysmex Corp., Kobe, Japan), while D-dimer concentrations were measured using the latex immunoassay method (LIAS Auto D-dimer Neo®, Sysmex Corp., Kobe, Japan).

Statistical analysis

Data were analysed using commercial software (SPSS Version 25.0®; IBM Corp., Armonk, NY, USA). The patients were divided into two groups based on whether or not they received FFP transfusion: FFP transfusion group and FFP non-transfusion group. Both groups were also divided into subgroups according to the patients' plasma fibrinogen concentration 3 h following injury: the high-fibrinogen subgroup (≥ 150 mg/dL) and low-fibrinogen subgroup (< 150 mg/dL) (Fig. 1). This fibrinogen

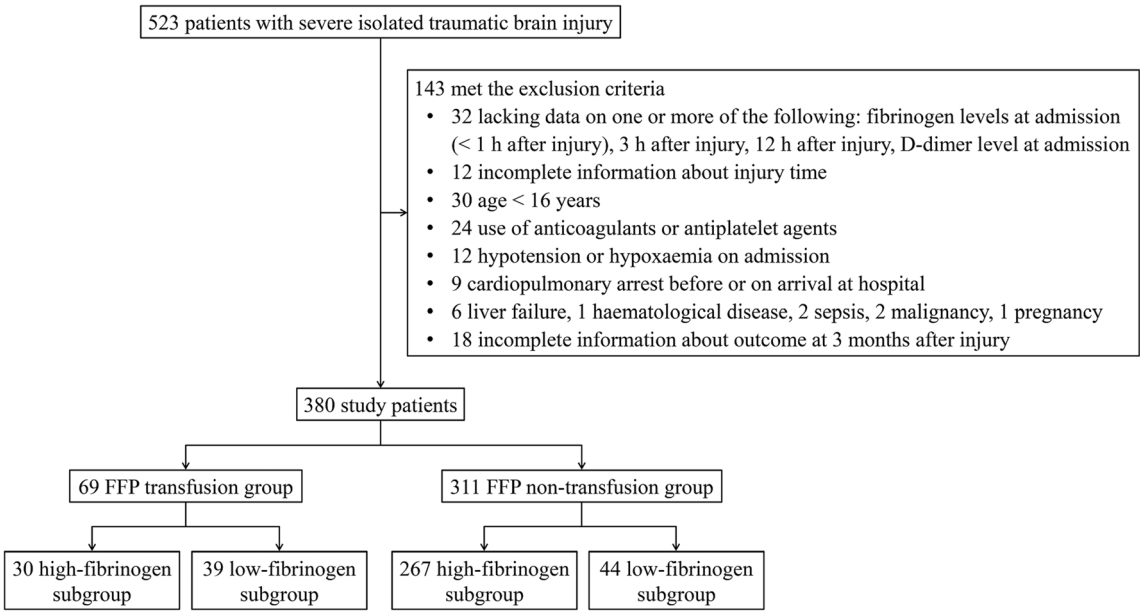

Fig. 1 Study flowchart

threshold value is the suggested minimum fibrinogen concentration required to prevent haemorrhage expansion [9, 23, 36]. Patient outcomes were assessed using the Glasgow Outcome Scale (GOS) [20] at discharge and 3 months after injury. A good outcome (GR or MD) is defined as good recovery or no more than moderate disability. A poor outcome (SD, VS or D) includes severe disability, vegetative state or death. The GOS scores were separately determined by neurointensivists (R.N., Y.T. and Y.F.) through in-person contact or communication via the telephone and postal mail with the hospital where patients were transferred following discharge from our centre. Demographic, clinical, radiological and laboratory data were analysed using Student's *t* test, the Mann-Whitney *U* test or chi-squared test for continuous normally distributed, continuous non-normally distributed and dichotomous data, respectively. Multivariate logistic regression analysis was used to analyse independent risk factors for poor prognosis in the FFP transfusion group and FFP non-transfusion group, with the odds ratio (OR) and 95% confidence interval (CI) being calculated for each variable. Variables included age; GCS score at admission; AIS-head; the presence of ASDH, AEDH, ICH, or TSAH; fibrinogen level 3 h after injury; whether or not operation for TBI was performed; and duration of mechanical ventilation. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

Data from 380 patients were analysed (Fig. 1). Demographic, clinical, radiological and laboratory findings are summarized in Table 1. ASDH, AEDH, ICH and TSAH were identified in 256 (67.4%), 71 (18.7%), 281 (73.9%) and 318 (83.7%) patients, respectively, with some patients having more than one diagnosis. There were 69 and 311 patients in the FFP transfusion group and FFP non-transfusion group, respectively. Patients in the FFP transfusion group were significantly older and had lower GCS scores, higher AIS-head scores, a higher incidence of ASDH, higher surgery rates and longer duration of mechanical ventilation, indicating more severe injury (Table 1). There were no differences in gender or incidence of MOF or ARDS between the two groups. The FFP transfusion group also had significantly lower GOS scores, indicating a poorer outcome, at discharge and 3 months. The plasma fibrinogen concentration (normal range 200–400 mg/dL) was significantly lower in the FFP transfusion group than in the FFP non-transfusion group at admission and 3 h and 12 h following injury (Table 1).

Patients' characteristics in the FFP transfusion subgroups

There were 30 and 39 patients in the high and low fibrinogen subgroups, respectively. Demographic, clinical, radiological and laboratory findings are summarized in Table 2. Age; gender; GCS score; AIS-head; diagnosis of ASDH, AEDH, ICH and TSAH; incidence of MOF or ARDS; surgery rate and distribution of the surgical methods; and duration of mechanical ventilation were similar between the two subgroups. There were no significant differences in the plasma fibrinogen concentration at admission or the transfusion volumes of RCC and FFP between the subgroups. GOS scores at discharge and 3 months following injury were significantly higher in the high-fibrinogen subgroup than in the low-fibrinogen subgroup. In the low-fibrinogen

Table 1 Demographic, clinical, radiologic and laboratory characteristics of the study population

	Total ($n = 380$)	FFP transfusion group ($n = 69$)	FFP non-transfusion group ($n = 311$)	P
Demographics				
Age (years) (median; first to third quartile)	62 (40–73)	68 (54–77)	61 (38–72)	0.009*
Male, *n* (%)	266 (70.0)	44 (63.8)	222 (71.4)	0.21
Clinical score at admission				
GCS score (median; first to third quartile)	10 (6–14)	7 (4–12)	12 (7–14)	< 0.0001*
AIS-head (median; first to third quartile)	4 (4–5)	5 (4–5)	4 (4–5)	< 0.0001*
Radiologic findings				
ASDH, *n* (%)	256 (67.4)	59 (85.5)	197 (63.3)	0.0004*
AEDH, *n* (%)	71 (18.7)	16 (23.2)	55 (17.7)	0.29
ICH, *n* (%)	281 (73.9)	57 (82.6)	224 (72.0)	0.07
TSAH, *n* (%)	318 (83.7)	62 (89.9)	256 (82.3)	0.13
Laboratory parameters				
Fibrinogen concentration at admission (mg/dL) (mean ± SD)	239.0 ± 82.8	198.6 ± 81.3	248.0 ± 80.6	< 0.0001*
Fibrinogen concentration 3 h after injury (mg/dL) (mean ± SD)	204.9 ± 93.8	137.9 ± 72.5	227.8 ± 89.2	< 0.0001*
Fibrinogen concentration 12 h after injury (mg/dL) (mean ± SD)	249.9 ± 113.4	189.1 ± 70.9	269.6 ± 117.7	< 0.0001*
D-dimer concentration at admission (μg/mL) (mean ± SD)	46.4 ± 60.3	78.6 ± 73.5	39.2 ± 54.5	< 0.0001*
Volume of transfusion				
RCC (mL) (median; first to third quartile)	0 (0–0)	560 (0–1400)	0 (0–0)	< 0.0001*
FFP (mL) (median; first to third quartile)	0 (0–0)	960 (720–1320)	0 (0–0)	< 0.0001*
Complications				
MOF, *n* (%)	30 (7.9)	6 (8.7)	24 (7.7)	0.79
ARDS, *n* (%)	13 (3.4)	3 (4.3)	10 (3.2)	0.64
Operation, *n* (%)	177 (46.6)	59 (85.5)	118 (37.9)	< 0.0001*
Burr hole surgery, *n* (%)	101 (26.6)	21 (30.4)	80 (25.7)	
Craniotomy/craniectomy, *n* (%)	29 (7.6)	11 (15.9)	18 (5.8)	
Burr hole surgery and craniotomy/craniectomy, *n* (%)	47 (12.4)	27 (39.1)	20 (6.4)	
Duration of mechanical ventilation (days) (median; first to third quartile)	4 (0–13)	11 (4–14)	3 (0–12)	< 0.0001*
GOS score at discharge, *n* (%)				0.0006*
4–5	224 (58.9)	28 (40.6)	196 (63.0)	
1–3	156 (41.1)	41 (59.4)	115 (37.0)	
GOS score at 3 months, *n* (%)				< 0.0001*
4–5	244 (64.2)	30 (43.5)	214 (68.8)	
1–3	136 (35.8)	39 (56.5)	97 (31.2)	

All values are expressed as median (first to third quartile), mean ± standard deviation or number (%). GOS score of 1 indicates death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; and 5, good recovery

FFP fresh frozen plasma, *GCS* Glasgow Coma Scale, *AIS* Abbreviated Injury Score, *ASDH* acute subdural haematoma, *AEDH* acute epidural haematoma, *ICH* intracerebral haematoma/contusion, *TSAH* traumatic subarachnoid haemorrhage *RCC* red cell concentrate, *MOF* multiple organ failure, *ARDS* acute respiratory distress syndrome, *GOS* Glasgow Outcome Scale

*Statistical significance was assumed for P values < 0.05

subgroup, the plasma fibrinogen levels showed an increase from 3 to 12 h following injury but remained below normal.

Patients' characteristics in the FFP non-transfusion subgroups

There were 267 and 44 patients in the high and low fibrinogen subgroups, respectively. Demographic, clinical, radiological and laboratory findings are summarized in Table 3. The low fibrinogen subgroup had significantly lower GCS scores, higher AIS-head scores, higher incidence of ASDH, higher surgery rates, higher duration of mechanical ventilation, lower GOS scores at discharge and 3 months after injury, indicating more severe injury. In the low-fibrinogen nontransfusion subgroup, the plasma fibrinogen levels showed an increase from 3 to 12 h following injury but remained below normal as with the low-fibrinogen subgroup in the FFP transfusion group.

Table 2 Univariate analysis of patients in the high-fibrinogen subgroup (concentration 3 h after injury ≥ 150 mg/dL) and low-fibrinogen subgroup (< 150 mg/dL) who received FFP transfusion

	High-fibrinogen subgroup ($n = 30$)	Low-fibrinogen subgroup ($n = 39$)	P
Demographics			
Age (years) (median; first to third quartile)	66 (43–77)	70 (56–77)	0.50
Male, *n* (%)	20 (66.7)	24 (61.5)	0.66
Clinical score at admission			
GCS score (median; first to third quartile)	7 (3–12)	7 (5–13)	0.45
AIS-head (median; first to third quartile)	5 (4–5)	5 (4–5)	0.60
Radiologic findings			
ASDH, *n* (%)	27 (90.0)	32 (82.1)	0.35
AEDH, *n* (%)	7 (23.3)	9 (23.1)	0.98
ICH, *n* (%)	22 (73.3)	35 (89.7)	0.07
TSAH, *n* (%)	25 (83.3)	37 (94.9)	0.12
Laboratory parameters			
Fibrinogen concentration at admission (mg/dL) (mean ± SD)	202.6 ± 74.7	195.6 ± 86.8	0.94
Fibrinogen concentration 3 h after injury (mg/dL) (mean ± SD)	206.3 ± 46.8	85.3 ± 34.8	< 0.0001*
Fibrinogen concentration 12 h after injury (mg/dL) (mean ± SD)	234.5 ± 60.5	158.8 ± 61.0	< 0.0001*
Volume of transfusion			
RCC (mL) (median; first to third quartile)	560 (0–1120)	840 (280–1400)	0.10
FFP (mL) (median; first to third quartile)	720 (480–1200)	1200 (720–1440)	0.13
Complications			
MOF, *n* (%)	3 (10.0)	3 (7.7)	0.74
ARDS, *n* (%)	2 (6.7)	1 (2.6)	0.41
Operation, *n* (%)	27 (90.0)	32 (82.1)	0.65
Burr hole surgery, *n* (%)	11 (36.7)	10 (25.6)	
Craniotomy/craniectomy, *n* (%)	4 (13.3)	7 (17.9)	
Burr hole surgery and craniotomy/craniectomy, *n* (%)	12 (40.0)	15 (38.5)	
Duration of mechanical ventilation (days) (median; first to third quartile)	13 (3–14)	10 (4–13)	0.63
GOS score at discharge, *n* (%)			
4–5	17 (56.7)	11 (28.2)	0.02*
1–3	13 (43.3)	28 (71.8)	
GOS score at 3 months, *n* (%)			0.004*
4–5	19 (63.3)	11 (28.2)	
1–3	11 (36.7)	28 (71.8)	

All values are expressed as median (first to third quartile), mean ± standard deviation or number (%). GOS score of 1 indicates death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; and 5, good recovery. High fibrinogen subgroup, patients with plasma fibrinogen concentration ≥ 150 mg/dL 3 h after injury; low fibrinogen subgroup, patients with plasma fibrinogen concentration < 150 mg/dL 3 h after injury

FFP fresh frozen plasma, *GCS* Glasgow Coma Scale, *AIS* Abbreviated Injury Score, *ASDH* acute subdural haematoma, *AEDH* acute epidural haematoma, *ICH* intracerebral haematoma/contusion, *TSAH* traumatic subarachnoid haemorrhage, *RCC* red cell concentrate, *MOF* multiple organ failure, *ARDS* acute respiratory distress syndrome, *GOS* Glasgow Outcome Scale

*Statistical significance was assumed for P values < 0.05

Independent risk factors for poor prognosis in the FFP transfusion group and FFP non-transfusion group

To identify independent risk factors for poor prognosis in the FFP transfusion group and FFP non-transfusion group, multivariate logistic regression analysis was performed using age; GCS score at admission; AIS-head; the presence of ASDH, AEDH, ICH or TSAH; fibrinogen level 3 h after injury; whether or not operation for TBI was performed; and duration of mechanical ventilation (Tables 4 and 5). In the FFP transfusion group, old age ($P = 0.008$), decreased fibrinogen level

Table 3 Univariate analysis of patients in the high-fibrinogen subgroup (concentration 3 h after injury ≥ 150 mg/dL) and low-fibrinogen subgroup (< 150 mg/dL) who did not receive FFP transfusion

	High-fibrinogen subgroup ($n = 267$)	Low-fibrinogen subgroup ($n = 44$)	P
Demographics			
Age (years) (median; first to third quartile)	61 (38–72)	65 (45–73)	0.51
Male, *n* (%)	194 (72.7)	28 (63.6)	0.22
Clinical score at admission			
GCS score (median; first to third quartile)	13 (7–14)	7 (3–12)	< 0.0001*
AIS-head (median; first to third quartile)	4 (3–5)	5 (4–5)	0.0003*
Radiologic findings			
ASDH, *n* (%)	158 (59.2)	39 (88.6)	0.0002*
AEDH, *n* (%)	47 (17.6)	8 (18.2)	0.93
ICH, *n* (%)	188 (70.4)	36 (81.8)	0.12
TSAH, *n* (%)	207 (77.5)	39 (88.6)	0.09
Laboratory parameters			
Fibrinogen concentration at admission (mg/dL) (mean ± SD)	252.4 ± 78.4	217.3 ± 90.6	0.06
Fibrinogen concentration 3 h after injury (mg/dL) (mean ± SD)	247.3 ± 81.7	116.1 ± 25.4	< 0.0001*
Fibrinogen concentration 12 h after injury (mg/dL) (mean ± SD)	276.2 ± 88.6	140.0 ± 124.3	< 0.0001*
Volume of transfusion			
RCC (mL) (median; first to third quartile)	0 (0–0)	0 (0–0)	0.10
Complications			
MOF, *n* (%)	20 (7.5)	4 (9.1)	0.71
ARDS, *n* (%)	8 (3.0)	2 (4.6)	0.59
Operation, *n* (%)	87 (32.6)	31 (70.5)	< 0.0001*
Burr hole surgery, *n* (%)	58 (21.7)	22 (50.0)	
Craniotomy/craniectomy, *n* (%)	17 (6.4)	1 (2.3)	
Burr hole surgery and craniotomy/craniectomy, *n* (%)	12 (4.5)	8 (18.2)	
Duration of mechanical ventilation (days) (median; first to third quartile)	2 (0–10)	12 (3–15)	< 0.0001*
GOS score at discharge, *n* (%)			< 0.0001*
4–5	188 (70.4)	8 (18.2)	
1–3	79 (29.6)	36 (81.8)	
GOS score at 3 months, *n* (%)			< 0.0001*
4–5	204 (76.4)	10 (22.7)	
1–3	63 (23.6)	34 (77.3)	

All values are expressed as median (first to third quartile), mean ± standard deviation or number (%). GOS score of 1 indicates death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; and 5, good recovery. High fibrinogen subgroup, patients with plasma fibrinogen concentration ≥ 150 mg/dL 3 h after injury; low fibrinogen subgroup, patients with plasma fibrinogen concentration < 150 mg/dL 3 h after injury

FFP fresh frozen plasma, *GCS* Glasgow Coma Scale, *AIS* Abbreviated Injury Score, *ASDH* acute subdural haematoma, *AEDH* acute epidural haematoma, *ICH* intracerebral haematoma/contusion, *TSAH* traumatic subarachnoid haemorrhage, *RCC* red cell concentrate, *MOF* multiple organ failure, *ARDS* acute respiratory distress syndrome, *GOS* Glasgow Outcome Scale

*Statistical significance was assumed for P values < 0.05

3 h after injury ($P = 0.0005$) and the need for operation ($P = 0.02$) were significant risk factors for poor prognosis, whereas older age ($P < 0.0001$), low GCS score ($P < 0.0001$), high AIS-head score ($P = 0.04$) and decreased fibrinogen level 3 h after injury ($P = 0.03$) were significant risk factors for poor prognosis in the FFP non-transfusion group.

Correlation between D-dimer and reduction in fibrinogen in the FFP non-transfusion group

To examine the correlation between plasma D-dimer concentrations at admission and reduction in fibrinogen concentration between admission and 3 h following injury in the absence of FFP effects, we compared these parameters in the

Table 4 Multivariate logistic regression analysis for independent risk factors of poor prognosis in FFP transfusion group ($R^2 = 0.30$)

Factor	Odds ratio (95% CI)	*P*
Age (10-year increments)	1.83 (1.23–3.03)	0.008*
GCS score (1-point decrements)	1.16 (1.00–1.37)	0.051
AIS-head (1-point increments)	1.36 (0.28–7.26)	0.71
ASDH	3.89 (0.43–44.69)	0.24
AEDH	1.30 (0.26–6.28)	0.74
ICH	3.27 (0.34–41.28)	0.32
TSAH	1.93 (0.09–43.75)	0.67
Fibrinogen level 3 h after injury (10 mg/dL decrements)	1.16 (1.07–1.28)	0.0005*
Operation	28.15 (1.96–619.4)	0.02*
Duration of mechanical ventilation (1-day increments)	1.02 (0.79–1.33)	0.85

FFP fresh frozen plasma, *CI* confidence interval, *GCS* Glasgow Coma Scale, *AIS* Abbreviated Injury Score, *ASDH* acute subdural haematoma, *AEDH* acute epidural haematoma, *ICH* intracerebral haematoma/contusion, *TSAH* traumatic subarachnoid haemorrhage

*Statistical significance was assumed for *P* values < 0.05

FFP non-transfusion group. The plasma D-dimer concentration (normal range 0.0–1.0 μg/mL) at admission was significantly associated with decreases in fibrinogen between admission and 3 h following injury in the FFP non-transfusion group ($R^2 = 0.29$, $P < 0.0001$) (Fig. 2).

Discussion

The key finding in this study was that GOS scores at discharge and 3 months following injury were significantly greater in patients after FFP transfusion with high fibrinogen concentrations 3 h following injury than in those with low fibrinogen concentrations, and a decreased fibrinogen level 3 h after injury was an independent risk factor for poor prognosis. Rapid increases in fibrinogen levels to ≥ 150 mg/dL may contribute to improved outcomes in patients with TBI.

An imbalance in coagulation factors due to TBI can result in hypercoagulation with microthrombogenesis and ischaemia or hypocoagulation with potential development of haemorrhagic lesions [22, 25, 37]. Although a large proportion of patients develop haemocoagulative disorders following severe TBI, coagulopathy is rare following mild TBI [11]. Severe TBI is linked to marked decreases in fibrinogen (hypofibrinogenaemia), which leads to uncontrollable bleeding and massive haemorrhage. This pathology occurs as a result of dilutional coagulopathy caused by fluid resuscitation to maintain blood pressure and hyperfibrinolysis and hyperfibrinogenolysis induced by the secretion of tissue-type plasminogen activator and urokinase-type plasminogen activator from damaged endothelial cells [10, 17]. Fibrinogen has been reported to be the first coagulation factor to drop below optimal levels during the early phase of bleeding and dilutional coagulopathy [16].

Table 5 Multivariate logistic regression analysis for independent risk factors of poor prognosis in FFP non-transfusion group ($R^2 = 0.53$)

Factor	Odds ratio (95% CI)	*P*
Age (10-year increments)	2.10 (1.56–2.98)	< 0.0001*
GCS score (1-point decrements)	1.30 (1.15–1.49)	< 0.0001*
AIS-head (1-point increments)	1.36 (1.03–5.73)	0.04*
ASDH	1.57 (0.39–6.38)	0.52
AEDH	0.39 (0.10–1.40)	0.15
ICH	1.07 (0.24–5.24)	0.93
TSAH	2.05 (0.48–14.14)	0.24
Fibrinogen level 3 h after injury (10 mg/dL decrements)	1.10 (1.03–1.17)	0.03*
Operation	1.33 (0.96–4.00)	0.06
Duration of mechanical ventilation (1-day increments)	1.04 (0.62–1.12)	0.26

FFP fresh frozen plasma, *CI* confidence interval, *GCS* Glasgow Coma Scale, *AIS* Abbreviated Injury Score, *ASDH* acute subdural haematoma, *AEDH* acute epidural haematoma, *ICH* intracerebral haematoma/contusion, *TSAH* traumatic subarachnoid haemorrhage

*Statistical significance was assumed for *P* values < 0.05

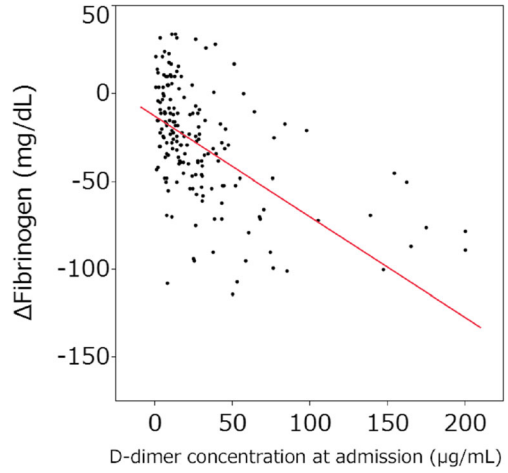

Fig. 2 Correlation between D-dimer concentration at admission and decreases in fibrinogen levels between admission and 3 h following injury in the FFP non-transfusion group. ΔFibrinogen = fibrinogen at 3 h − fibrinogen at admission

Treatments for hyperfibrinolysis and hyperfibrinogenolysis in TBI should target coagulation with the aim of reversing hyperfibrinolysis and hyperfibrinogenolysis and restoring coagulation factors using FFP. Some studies recommend FFP infusion for patients with deranged coagulation profiles on admission [4, 28]. May et al. [28] advocate FFP transfusion as an empiric treatment for coagulopathy in TBI patients with a GCS score ≤ 6. However, a number of studies [2, 7, 42, 43] have reported a lack of improvement in outcomes in TBI patients using FFP. In a double-blind controlled trial, Etemadrezaie et al. [7] randomized 90 patients with severe TBI to receive FFP or normal saline for the prevention of delayed traumatic intracerebral haematoma. They found that in addition to delayed traumatic intracerebral haematoma being more common in patients who received FFP, a significantly larger proportion of these patients died compared to those who received normal saline. Zhang et al. [43] showed that perioperative FFP infusion was independently associated with mortality or worse outcomes for a number of surgical risk profiles. Moreover, patients who received FFP transfusions had significantly greater rates of overall complications, ARDS and pneumonia. However, these studies did not examine the change in plasma fibrinogen concentration during FFP transfusion. We propose that it is important for clinicians to calculate the timing, thresholds and volume of FFP transfusion when treating patients with TBI.

Fibrinogen is a key molecule in FFP transfusion therapy. We previously reported the time course of changes in coagulation/fibrinolytic parameters after TBI [31]. We showed that the plasma fibrinogen concentration significantly decreased between admission (within 1 h following injury) and 3 h following injury. The concentration subsequently showed a non-significant increase by 6 h following injury, before significantly increasing from 6 to 12 h following injury, consistent with the present study (Tables 1, 2 and 3). The rapid decrease in fibrinogen in the first hour after TBI may be due to consumption for generating fibrin clots or due to direct destruction [21]. We propose that early treatment of TBI patients with low fibrinogen levels with FFP may be effective for controlling intracranial bleeding. Chang et al. [4] showed that early plasma infusion was associated with improved in-hospital survival in patients with multifocal intracranial haemorrhage. As shown in Table 2, the prognosis only improved using FFP if patients' plasma fibrinogen concentration was ≥ 150 mg/dL 3 h following injury. In addition, a decreased fibrinogen level 3 h after injury was an independent risk factor for poor prognosis, and in the low-fibrinogen subgroup, plasma fibrinogen levels remained below normal levels 12 h after injury. FFP transfusion is an important way to maintain or increase fibrinogen. Therefore, we propose that FFP transfusion should be considered for TBI patients and patients' plasma fibrinogen concentrations must be maintained at ≥ 150 mg/dL 3 h following injury. The increasing trend in the fibrinogen concentration from 3 h suggests a haemostatic shift, as indicated by inhibition of fibrinolysis and fibrinogenolysis; that is, FFP transfusion > 3 h following injury may lead to the provision of coagulation factors for thrombus formation and increase the frequency of microvascular thrombosis. This can cause subtle cerebral ischemia and vascular injuries that do not appear on CT scans [7]. Similarly, early transfusion of FFP to TBI patients with high fibrinogen levels may cause hypercoagulation and cerebral ischemia.

We found that a decreased fibrinogen level 3 h after injury was an independent risk factor for poor prognosis in both the FFP transfusion group and FFP non-transfusion group. In addition, old age and the need for operation were significant risk factors for poor prognosis in the FFP transfusion group, while older age, low GCS score and high AIS-head score were significant risk factors for poor prognosis in the FFP non-transfusion group. The plasma fibrinogen levels 3 h after injury may be able to be improved with FFP transfusion in the acute phase of TBI, whereas other prognostic parameters such as age, GCS score and AIS-head score are uncontrollable. We believe that early treatment of TBI patients with FFP transfusion will be useful in improving the prognosis of TBI patients.

The standard preparation of FFP contains approximately 2.0 g/L fibrinogen and other pro- and anti-coagulant factors [32]. The minimum activity required to maintain physiological haemostasis in blood is about 20 to 30% of the normal activity of most coagulation factors. If the volume of circulating plasma is 40 mL/kg and the transfused coagulation factors enter 100% of the blood volume, the volume of FFP needed to increase the coagulation factor activity by 20–30% is

theoretically 8–12 mL/kg. As consumption of fibrinogen is more rapid in the acute phase of TBI, a larger volume of FFP is recommended to maintain plasma fibrinogen levels at ≥ 150 mg/dL [9, 23, 36].

In general, FFP transfusion for TBI patients is indicated for those with acute traumatic coagulopathy, defined as prothrombin time-international normalized ratio (INR) > 1.2, activated partial thromboplastin time > 35 s and/or fibrinogen < 150 mg/dL [26], and for patients undergoing massive RCC transfusion [5, 18]. In the present study, 22 out of 69 (31.9%) patients in the FFP transfusion group had low fibrinogen concentrations (< 150 mg/dL) 3 h following injury, despite their plasma fibrinogen concentration at admission being within the normal range and having received FFP transfusion. To maintain plasma fibrinogen levels at ≥ 150 mg/dL 3 h following injury, it is important to predict the reduction of fibrinogen concentration between admission and 3 h following injury. We previously reported that the plasma D-dimer concentration becomes abnormal in the acute phase of TBI earlier than the plasma fibrinogen concentration [31]. Therefore, we examined the correlation between the reduction in fibrinogen concentration between admission and 3 h following injury and initial plasma concentrations of D-dimer. Figure 2 shows that, in the FFP non-transfusion group, the plasma D-dimer concentration at admission was significantly negatively correlated with the change in fibrinogen levels between admission and 3 h following injury. This suggests that, to maintain plasma fibrinogen levels at ≥ 150 mg/dL, FFP transfusions should be considered when the plasma D-dimer concentration at admission is elevated even if the plasma fibrinogen concentration at admission is within the normal range.

The findings of a number of studies have suggested that the transfusion of large volumes of FFP during early acute resuscitation following trauma is associated with the occurrence of MOF and ARDS [29, 35, 41]. For example, Watson et al. showed that, among the plasma-rich transfusion components, FFP was the greatest independent predictor of morbid complications, with each unit transfused correlating with a > 2% increased risk for MOF and ARDS developments [41]. However, a causal link between TBI and FFP-induced MOF and ARDS has not been described. We found no significant differences in the incidence of MOF or ARDS between the FFP transfusion group and the FFP non-transfusion group. A larger study is required to determine the incidence of transfusion-associated complications including MOF and ARDS.

Limitations

Several limitations warrant mention. First, the sample size was relatively small and may have provided insufficient power for comprehensive statistical analysis. Further large prospective studies are needed to validate our results. Second, we did not follow a strict protocol for FFP transfusion for TBI patients. Third, we could not accurately evaluate the relationship between the plasma fibrinogen concentration and haematoma progression because we performed burr hole surgery and/or craniotomy in some of the patients, in particular those in the FFP transfusion group. Finally, long-term outcomes of the patients were not available.

Conclusions

The outcomes of isolated TBI patients were significantly better in the high-fibrinogen subgroup than in the low-fibrinogen subgroup. Maintaining plasma fibrinogen concentrations at ≥ 150 mg/dL 3 h following injury by closely tracking fibrinogen concentration values and assessing the admission D-dimer level may contribute to improved outcomes in TBI patients who receive FFP transfusion.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

IRB approval This study was approved by the hospital's Institutional Review Board (approval #2018-27).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study design Retrospective cohort study.

References

1. Allard CB, Scarpelini S, Rhind SG, Baker AJ, Shek PN, Tien H, Fernando M, Tremblay L, Morrison LJ, Pinto R, Rizoli SB (2009) Abnormal coagulation tests are associated with progression of traumatic intracranial hemorrhage. J Trauma 67:959–967
2. Anglin CO, Spence JS, Warner MA, Paliotta C, Harper C, Moore C, Sarode R, Madden C, Diaz-Arrastia R (2013) Effects of platelet and plasma transfusion on outcome in traumatic brain injury patients with moderate bleeding diatheses. J Neurosurg 118:676–686
3. Association for the Advancement of Automotive Medicine (1998) The Abbreviated Injury Scale (AIS) 1998 revision. Des Plaines, Illinois

4. Chang R, Folkerson LE, Sloan D, Tomasek JS, Kitagawa RS, Choi HA, Wade CE, Holcomb JB (2017) Early plasma transfusion is associated with improved survival after isolated traumatic brain injury in patients with multifocal intracranial hemorrhage. Surgery 161:538–545
5. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP (2009) Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma 66:41–48 discussion 48–49
6. Epstein DS, Mitra B, O'Reilly G, Rosenfeld JV, Cameron PA (2014) Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: a systematic review and meta-analysis. Injury 45:819–824
7. Etemadrezaie H, Baharvahdat H, Shariati Z, Lari SM, Shakeri MT, Ganjeifar B (2007) The effect of fresh frozen plasma in severe closed head injury. Clin Neurol Neurosurg 109:166–171
8. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS (2012) Acute respiratory distress syndrome: the Berlin definition. JAMA 307: 2526–2533
9. Fries D, Innerhofer P, Perger P, Gutl M, Heil S, Hofmann N, Kneifel W, Neuner L, Pernerstorfer T, Pfanner G, Schochl H, Ziegler B, Kolblinger C, Kozek-Langenecker S (2010) Coagulation management in trauma-related massive bleeding. Recommendations of the Task Force for Coagulation (AGPG) of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (OGARI). Anasthesiol Intensivmed Notfallmed Schmerzther 45: 552–561
10. Gando S (2015) Hemostasis and thrombosis in trauma patients. Semin Thromb Hemost 41:26–34
11. Gomez PA, Lobato RD, Ortega JM, De La Cruz J (1996) Mild head injury: differences in prognosis among patients with a Glasgow Coma Scale score of 13 to 15 and analysis of factors associated with abnormal CT findings. Br J Neurosurg 10:453–460
12. Greuters S, van den Berg A, Franschman G, Viersen VA, Beishuizen A, Peerdeman SM, Boer C (2011) Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury. Crit Care 15:R2
13. Guidelines committee on the management of severe head injury, Japan society of neurotraumatology (2013) Guidelines for the management of severe head injury, 3rd edn. Igaku-Shoin Ltd., Tokyo (Japanese)
14. Halpern CH, Reilly PM, Turtz AR, Stein SC (2008) Traumatic coagulopathy: the effect of brain injury. J Neurotrauma 25:997–1001
15. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI (2008) Coagulation disorders after traumatic brain injury. Acta Neurochir 150:165–175 discussion 175
16. Hiippala ST, Myllyla GJ, Vahtera EM (1995) Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 81:360–365
17. Hijazi N, Abu Fanne R, Abramovitch R, Yarovoi S, Higazi M, Abdeen S, Basheer M, Maraga E, Cines DB, Higazi AA (2015) Endogenous plasminogen activators mediate progressive intracerebral hemorrhage after traumatic brain injury in mice. Blood 125: 2558–2567
18. Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, Cox ED, Gehrke MJ, Beilman GJ, Schreiber M, Flaherty SF, Grathwohl KW, Spinella PC, Perkins JG, Beekley AC, McMullin NR, Park MS, Gonzalez EA, Wade CE, Dubick MA, Schwab CW, Moore FA, Champion HR, Hoyt DB, Hess JR (2007) Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma 62:307–310
19. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, Murray GD, Maas AI (2003) Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg 99:666–673
20. Jennett B, Snoek J, Bond MR, Brooks N (1981) Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry 44:285–293
21. Kushimoto S, Shibata Y, Yamamoto Y (2003) Implications of fibrinogenolysis in patients with closed head injury. J Neurotrauma 20:357–363
22. Laroche M, Kutcher ME, Huang MC, Cohen MJ, Manley GT (2012) Coagulopathy after traumatic brain injury. Neurosurgery 70:1334–1345
23. Levy JH, Welsby I, Goodnough LT (2014) Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion (Paris) 54:1389–1405
24. Lustenberger T, Talving P, Kobayashi L, Inaba K, Lam L, Plurad D, Demetriades D (2010) Time course of coagulopathy in isolated severe traumatic brain injury. Injury 41:924–928
25. Maegele M (2013) Coagulopathy after traumatic brain injury: incidence, pathogenesis, and treatment options. Transfusion (Paris) 53(Suppl 1):28S–37S
26. Maegele M, Schochl H, Menovsky T, Marechal H, Marklund N, Buki A, Stanworth S (2017) Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. Lancet Neurol 16:630–647
27. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ (1995) Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 23: 1638–1652
28. May AK, Young JS, Butler K, Bassam D, Brady W (1997) Coagulopathy in severe closed head injury: is empiric therapy warranted? Am Surg 63:233–236 discussion 236–237
29. Moore FA, Moore EE, Sauaia A (1997) Blood transfusion. An independent risk factor for postinjury multiple organ failure. Arch Surg 132:620–624 discussion 624–625
30. Murray GD, Butcher I, McHugh GS, Lu J, Mushkudiani NA, Maas AI, Marmarou A, Steyerberg EW (2007) Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. J Neurotrauma 24:329–337
31. Nakae R, Takayama Y, Kuwamoto K, Naoe Y, Sato H, Yokota H (2016) Time course of coagulation and fibrinolytic parameters in patients with traumatic brain injury. J Neurotrauma 33:688–695
32. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM, British Committee for Standards in Haematology BTTF (2004) Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br J Haematol 126:11–28
33. Olson JD, Kaufman HH, Moake J, O'Gorman TW, Hoots K, Wagner K, Brown CK, Gildenberg PL (1989) The incidence and significance of hemostatic abnormalities in patients with head injuries. Neurosurgery 24:825–832
34. Shigemori M, Abe T, Aruga T, Ogawa T, Okudera H, Ono J, Onuma T, Katayama Y, Kawai N, Kawamata T, Kohmura E, Sakaki T, Sakamoto T, Sasaki T, Sato A, Shiogai T, Shima K, Sugiura K, Takasato Y, Tokutomi T, Tomita H, Toyoda I, Nagao S, Nakamura H, Park YS, Matsumae M, Miki T, Miyake Y, Murai H, Murakami S, Yamaura A, Yamaki T, Yamada K, Yoshimine T, Guidelines committee on the management of severe head injury, Japan society of neurotraumatology (2012) Guidelines for the management of severe head injury, 2nd edition guidelines from the guidelines committee on the management of severe head injury, the Japan society of neurotraumatology. Neurol Med Chir (Tokyo) 52:1–30
35. Silverboard H, Aisiku I, Martin GS, Adams M, Rozycki G, Moss M (2005) The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. J Trauma 59:717–723

36. Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL, Rossaint R (2013) Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care 17:R76
37. Stein SC, Smith DH (2004) Coagulopathy in traumatic brain injury. Neurocrit Care 1:479–488
38. Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D (2009) Coagulopathy in severe traumatic brain injury: a prospective study. J Trauma 66:55–61
39. Vollmer DG, Torner JC, Jane JA, Sadovnic B, Charlebois D, Eisenberg HM, Foulkes MA, Marmarou A, Marshall LF (1991) Age and outcome following traumatic coma: why do older patients fare worse? J Neurosurg 75:S37–S49
40. Wafaisade A, Lefering R, Tjardes T, Wutzler S, Simanski C, Paffrath T, Fischer P, Bouillon B, Maegele M (2010) Acute coagulopathy in isolated blunt traumatic brain injury. Neurocrit Care 12:211–219
41. Watson GA, Sperry JL, Rosengart MR, Minei JP, Harbrecht BG, Moore EE, Cuschieri J, Maier RV, Billiar TR, Peitzman AB, Inflammation, Host Response to Injury I (2009) Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma 67:221–227 discussion 228–230
42. Winter JP, Plummer D, Bottini A, Rockswold GR, Ray D (1989) Early fresh frozen plasma prophylaxis of abnormal coagulation parameters in the severely head-injured patient is not effective. Ann Emerg Med 18:553–555
43. Zhang LM, Li R, Zhao XC, Zhang Q, Luo XL (2017) Increased transfusion of fresh frozen plasma is associated with mortality or worse functional outcomes after severe traumatic brain injury: a retrospective study. World Neurosurg 104:381–389