Journal of Rural Medicine

Original article

Changes in coagulation factor XIII activity during resuscitation for hemorrhagic shock

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Abstract

Objective: Little is known about the coagulation activity of factor XIII (FXIII) during resuscitation for hemorrhagic shock and the effects of plasma transfusions. We performed a single-center observational study to evaluate the changes in FXIII activity during resuscitation for hemorrhagic shock.

Patient and Methods: Twenty-three adult patients with hemorrhagic shock were enrolled in this study. Blood samples were drawn upon arrival (T1), at the time of hemostasis completion (T2), and on day 2 (T3). Baseline and changes in FXIII activity and the proportion of patients with adequate levels of FXIII activity (FXIII activity >70%) were evaluated. The effects of plasma transfusion on these parameters were also investigated.

Results: At T1, the median (interquartile range) FXIII activity was 53% (47–85%), which did not increase (T1 vs. T3: 53% [47–85%] vs. 63% [52–70%], *P*=0.8766). The proportion of patients with adequate FXIII activity decreased throughout the resuscitation period (T1, T2, and T3: 30, 34, and 21%, respectively). Plasma transfusion did not affect FXIII activity (T1 vs. T2, 66.4% [23.4] vs. 70.0% [16.2%], *P*=0.3956; T2 vs. T3, 72.0% [19.5] vs. 63.5% [8.6%], *P*=0.1161) or the proportion of adequate levels of FXIII activity at 44% at T2 and 27% at T3.

Conclusion: FXIII activity is low during the early phase of a hemorrhagic shock. Even with plasma transfusion, FXIII levels were not adequately maintained throughout resuscitation.

Key words: blood transfusion, Factor XIII, fibrinogen, hemorrhage, shock

(J Rural Med 2024; 19(2): 76–82)

Introduction

Hemorrhagic shock is a life-threatening condition frequently encountered in emergency departments. Hemorrhagic shock is a fatal condition that causes a decrease in oxygen supply to peripheral tissues, leading to metabolic acidosis and coagulopathy. The outcome of severe hemorrhage remains poor, with mortality rates approaching 50% in patients who require transfusion or develop significant coagulopathy[1]. In patients with trauma, 20% develop coagulopathy, with mortality rates reported to be three–four times higher in patients with coagulopathy[2, 3]. The main goals of treatment for hemorrhagic shock are to recover circulatory status with early hemostasis and restore circulating blood volume.

Transfusion is an essential treatment for hemorrhagic shock. Early transfusion results in an improved coagulation profile, reduced coagulation products, and improved transfusion outcomes[4]. In addition to the general benefit of intravascular volume supplementation, each blood product has a specific aim, such as packed red blood cells to increase hemoglobin, and platelet concentrate to maintain the platelet count. Plasma transfusion is a critical therapy that replenishes coagulation factors and controls coagulopathy progression. Indicators for plasma transfusion include coagulation tests such as prothrombin time (PT) and fibrinogen level test[5]. In particular, fibrinogen levels decrease from the onset of bleeding. Thus, fibrinogen levels are considered an important indicator of coagulation factor deficiencies and

Received: August 2, 2023
Accepted: November 28, 2023
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plasma transfusion[6–8].

Factor XIII (FXIII), or fibrin stabilizing factor, is a heterotetramer (FXIII-A_2B_2) protein in plasma consisting of two subunits. FXIII-A is synthesized in monocytes/macrophages, megakaryocytes/platelets, chondrocytes, and osteoblasts[9–11], whereas FXIII-B is expressed only in hepatocytes and is secreted in the plasma as a dimer (FXIII-B_2)[12]. FXIII is activated by thrombin, and in the presence of calcium ions, the B subunit dissociates, opening the FXIII-A structure to form active FXIII (FXIIIa). FXIIIa cross-links and insolubilizes fibrin polymers covalently at the end of the coagulation cascade[13–15]. FXIIIa also promotes wound healing by cross-linking and binding fibronectin to fibrin and collagen[16]. Several reports have established the relationship between FXIII deficiency and the risk of postoperative rebleeding[17, 18], although it can only be diagnosed by measuring FXIII activity[19–21].

Although decreased FXIII levels have been reported in obstetric hemorrhagic shock[22], little is known about changes in FXIII levels during a hemorrhagic shock and resuscitation. Furthermore, the effect of plasma transfusions on FXIII maintenance is unclear. Therefore, we conducted a single-center prospective observational study to examine the changes in FXIII levels during a hemorrhagic shock. Our study aimed to establish the FXIII activity levels during resuscitation for hemorrhagic shock and investigate whether plasma transfusion could maintain sufficient FXIII activity.

Methods

Study design and patient enrollment

This study was conducted at an academic hospital in Japan. The study participants were adult patients with hemorrhagic shock who were transported to the Critical Care Center at the University of Miyazaki Hospital between February 2018–March 2020. Hemorrhagic shock was diagnosed when systolic blood pressure was <90 mmHg and/or serum lactate level was ≥2 mmol/L due to hemorrhage at the time of arrival. The exclusion criteria were as follows: 1) incomplete FXIII and/or fibrinogen values, 2) inability to obtain written consent, 3) patients in a state of shock other than hemorrhage, and 4) patients with known bleeding disorders.

All patients received standard care, including hemostatic procedures, based on their circulatory status and bleeding site. Hemostasis completion was defined as admission to the critical/intensive care unit after initial hemostatic procedures such as transarterial embolization, surgical hemostasis and/or external fixation for bone fractures, and endoscopic hemostasis.

Transfusion of each blood product was triggered to maintain hemoglobin levels ≥7 g/dL for packed red blood cells, platelet count ≥ 100 × 10^3/μL for platelet concentration, and fibrinogen levels ≥150 mg/dL and/or within 1.5 times-elongation of the normal upper limit of prothrombin time and activated partial thromboplastin time for fresh frozen plasma/cryoprecipitate. Massive transfusion protocols were not used. Each volume of one unit of blood product was calculated according to the standard volumes used in Japan: packed red blood cells, 140 mL; platelet concentrate, 20 mL; and fresh frozen plasma, 120 mL. The institutional standard volume of cryoprecipitate was 50 mL/pack. The estimated amounts of FXIII administered by transfusion were calculated using 1.2 U/mL for fresh frozen plasma and 2.8 U/mL for cryoprecipitates[23].

Blood sampling, measurement, and data collection

Whole blood was collected in an ethylenediaminetetraacetic acid tube for hematological measurements, citrate plasma was collected for coagulation tests, and FXIII activity was measured. Blood samples were collected upon arrival (T1), at the time of hemostasis completion (T2), and on the day after admission (T3). Hematological and coagulation tests were performed using a commercially available system in the hospital laboratory (XN-3000, Sysmex Corp., Kobe, Japan; Coapresta3000, SEKISUI Chemical Corp., Tokyo, Japan). Samples were measured within 30 min of blood collection. FXIII activity was measured using the synthetic substrate method. Plasma was collected after centrifugation at 2,000 × g for 10 min within 30 min of blood collection and stored at −20 °C before measurement. Patient characteristics, etiologies of bleeding, treatments, complications, and prognoses were collected from the clinical records.

Outcome measures

The primary outcome was change in FXIII activity during resuscitation for hemorrhagic shock. Sufficient levels of FXIII activity were defined as >70%, and FXIII activity below 70% was considered as FXIII deficiency[24]. The changes in these outcomes were compared with those in fibrinogen levels at each time point. A sufficient fibrinogen level was >150 mg/dL. For secondary outcomes, subgroup analyses were also performed according to the presence or absence of plasma transfusion (fresh frozen plasma and/or cryoprecipitates).

Statistical analyses

Categorical data were presented as numbers and percentages. Continuous variables with a normal distribution were presented as means and standard deviations (SD), while the others were presented as medians and interquartile ranges (IQR, 25th–75th). The Shapiro–Wilk test was used to test the normality of the continuous variables, and Fisher's exact test was used to compare the categorical variables. Chronological changes were tested using a paired t-test for normally distributed variables and the Wilcoxon signed-rank test

for other variables. All statistical analyses were performed using the Prism 9 software (ver. 9.4.1, GraphPad Software, LLC, San Diego, CA, USA). All statistical tests were performed at a two-tailed significance level of 0.05 (two-sided).

Ethics approval and participant consent

Written informed consent was obtained from each patient or their close relatives before enrolment in the study. The Ethics Review Board of the hospital approved the study (protocol: O-0278).

Results

A total of 31 patients with hemorrhagic shock were enrolled in this study. Eight patients were excluded (four, for incomplete fibrinogen and/or FXIII values; three, due to inability to obtain consent; and one, experiencing shock other than hemorrhage), and the remaining 23 patients were eligible for the analysis.

The median (IQR) age was 70 years (50–79) years, and 16 (70%) were male. The hemorrhage in 19 patients (83%) was caused by trauma. Upon arrival, the mean (SD) systolic blood pressure was 97.9 (21.4) mmHg, the mean (SD) shock index was 1.03 (0.28), and the median (IQR) lactate level was 3.4 (2.7–4.7) mmol/L. Regarding the hemostatic procedure, 15 (65%) patients underwent transarterial embolization and 6 (28%) underwent surgical treatment. Until T3, 21 (91%) patients received a transfusion, including 20 (87%) receiving fresh frozen plasma and/or cryoprecipitate. Twenty-two (96%) patients received red blood cell transfusions; however, one patient did not because the hemoglobin level was maintained at >7 g/dL. Three (13%) patients experienced rebleeding and two (9%) eventually died (Table 1). Fibrinogen and FXIII concentrates were not administered.

At T1, the median FXIII activity was 53 (47–85) %, the number of patients with FXIII activity <70% was 16 (70%), the mean fibrinogen was 183.7 (89.0) mg/dL, and the number of patients with fibrinogen levels <150 mg/dL was 11 (48%).

FXIII activity did not increase throughout the observation period (T1 vs. T3: 53 [47–85] vs. 63 [52–70] %, P=0.8766), whereas fibrinogen levels increased (T1 vs. T3: 165 [120–242] vs. 231 [190–281] mg/dL, P<0.0001) (Figure 1A, 1D). Fibrinogen did not increase before hemostasis completion (T1 vs. T2: 165 [120–242] vs. 184 [128–242] mg/dL, P=0.3564), but it did so after hemostasis (T2 vs. T3: 184 [128–242] vs. 231 [190–281] mg/dL, P<0.0001) (Figure 1E, 1F). However, FXIII activity did not change before or after hemostasis (T1 vs. T2: 53 [47–85] vs. 63 [52–70] mg/dL, P<0.4142; T2 vs. T3: 62 [51–75] vs. 63 [52–70] %, P=0.1346) (Figure 1B, 1C). The proportion of patients with sufficient levels of FXIII decreased (T1, T2, and T3: 30, 34, and 21%, respectively), while that of fibrinogen increased (T1, T2, and T3: 52, 65, and 96%, respectively). Differences in the proportions of FXIII and fibrinogen tended to differ at T2 (P=0.0758) and T3 (P<0.0001) (Figure 2).

Table 1 Demographics of the patients

	Overall (N=23)
Age (years), median (IQR)	70 (50–79)
Male sex, n (%)	16 (70)
Cause of bleeding, n (%)	
Trauma	19 (83)
Non-trauma	4 (17)
Under antithrombotic therapy, n (%)	
Antiplatelets	2 (9)
Anticoagulants	0 (0)
Laboratory findings on arrival	
Lactate (mmol/L), median (IQR)	3.4 (2.7–4.7)
Base excess, median (IQR)	–3.4 (–7.5–0.2)
Hemoglobin (g/dL), mean (SD)	9.3 (2.6)
Prothrombin time (INR), median (IQR)	1.35 (1.21–1.55)
APTT (sec), mean (SD)	32.3 (5.8)
Transfusions (until T3)	
Packed red blood cells, n (%)	22 (96)
mL, median (IQR)	840 (560–1,330)
Platelet concentrates, n (%)	7 (30)
mL, median (IQR)	0 (0–200)
Fresh frozen plasma, n (%)	20 (87)
mL, median (IQR)	960 (480–1,440)
Cryoprecipitate, n (%)	10 (43)
mL, median (IQR)	0 (0–150)
Antifibrinolytic agent administration, n (%)	16 (70)
Hemostatic interventions (with duplicates), n (%)	
Surgery	
External fixation	5 (22)
Laparotomy	2 (9)
Transcatheter arterial embolization	15 (65)
Endoscopic hemostasis	4 (17)
Times	
T1–T2 (min), mean (SD)	224 (101.9)
T2–T3 (min), mean (SD)	891.5 (268.1)
Outcomes, n (%)	
Rebleeding	3 (13)
Death	2 (9)

Continuous values are expressed as mean (standard deviation) for normally distributed variables and median (interquartile range) for non-normally distributed variables. Categorical values are expressed as numbers (%).

T1: upon arrival: T2: at the time of hemostasis completion; T3: on the day after admission; IQR: interquartile range; SD: standard deviation.

For the secondary outcomes, we performed a subgroup analysis according to the presence or absence of plasma transfusion. Fresh frozen plasma and/or cryoprecipitate was transfused in 18 patients before the completion of hemostasis (from T1 to T2) (fresh frozen plasma and cryoprecipitate, nine patients and fresh frozen plasma only, nine patients), and fresh frozen plasma was transfused in 11 patients from T2 to T3. The plasma infusion details and estimated amounts of

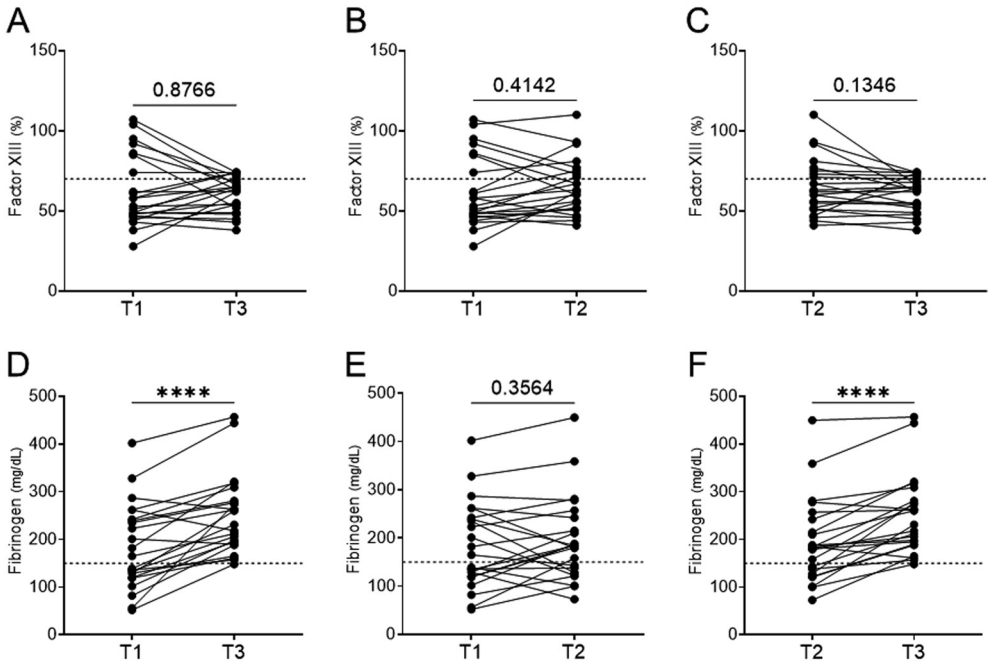

Figure 1 Changes in factor XIII (A–C) and fibrinogen (D–F) values at each timepoint (N=23).
Factor XIII activity did not change from T1 to T3 (A) and did not change before (B) or after hemostasis (C). Fibrinogen increased from T1 to T3 (D) and was mainly attributed to the change from T2 to T3 after hemostasis (C).
The dashed lines represent sufficient levels of fibrinogen at 150 mg/dL and factor XIII at 70%.
ns, not significant; ****P<0.0001 (Wilcoxon matched-pairs signed-rank test).
T1: upon arrival: T2: at the time of hemostasis completion; T3: on the day after admission.

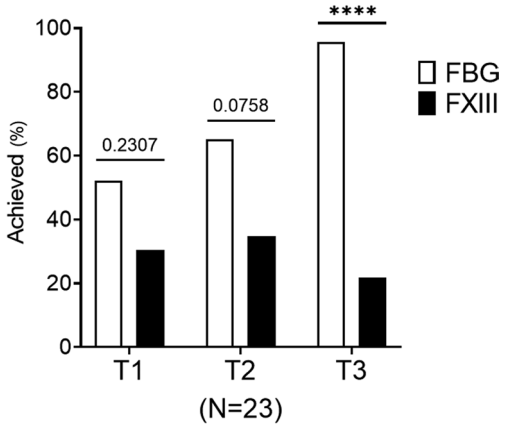

Figure 2 Proportion of maintained sufficient levels of factor XIII activity and fibrinogen.
White columns represent fibrinogen and black columns represent factor XIII.
****P<0.0001 (Fisher's exact test).
T1: upon arrival: T2: at the time of hemostasis completion; T3: on the day after admission.

FXIII are shown in Table 2. Before hemostasis completion, fibrinogen levels did not increase in patients without (T1 vs. T2: 254 [134.2] vs. 261.8 [150.7] mg/dL, P=0.7621) and with plasma transfusion (T1 vs. T2: 164.2 [64.5] vs. 175.9 [53.9] mg/dL, P=0.4305) (Figure 3E, 3G), while its levels increased after hemostasis completion in patients with (T2 vs. T3: 154.4 [50.3] vs. 213.2 [54.7] mg/dL, P=0.0049) and without plasma transfusion (T2 vs. T3: 231.5 [99.8] vs. 282.5 [90.9] mg/dL, P=0.0013) (Figure 3F and 3H). FXIII activity also did not change regardless of plasma transfusion before hemostasis completion (T1 vs. T2: without plasma transfusion, 46.4 [2.8] vs. 46.8 [4.7] %, P=0.8746; with plasma transfusion, 66.4 [23.4] vs. 70.0 [16.2] %, P=0.3956) and after hemostasis (T2 vs. T3: without plasma transfusion, 58.5 [12.8] vs. 57.8 [12.4] %, P=0.8035; with plasma transfusion, 72.0 [19.5] vs. 63.5 [8.6] %, P=0.1161) (Figure 3A–3D).

The proportion of patients with adequate levels of FXIII activity was only 27% of patients without plasma transfusion at T2 and 0% of those at T3. In contrast, fibrinogen levels were adequately maintained at 100% at T2 and 85.7% at T3 in patients even without plasma transfusion, which was significantly different for FXIII at T3 (P<0.0001) (Figure 4A). Plasma transfusion maintained sufficient levels of FXIII activity in only 44% and 27% of patients at T2 and T3, respectively, whereas sufficient fibrinogen levels were maintained in 67% and 91% of patients at T2 and T3, respectively (Figure 4B).

Table 2 The volume of plasma transfused and the estimated amount of FXIII administered

	T1–T2[†]	T2–T3
Any plasma transfusion	(N=19)	(N=11)
Volume (mL)	870 (480–1,035)	480 (480–960)
Estimated volume of infused FXIII (units)	1,152 (576–1,428)	576 (576–1,152)
FFP + cryoprecipitate	(N=9)	(N=0)
Volume (mL)	870 (870–1,110)	N.A.
Estimated volume of infused FXIII (units)	1,284 (1,284–1,572)	N.A.
FFP only	(N=9)	(N=11)
Volume (mL)	480 (480–960)	480 (480–960)
Estimated volume of infused FXIII (units)	576 (576–1,152)	576 (576–1,152)

All values are expressed in median (IQR)

[†]One patient received a cryoprecipitate infusion only.

T1: upon arrival: T2: at the time of hemostasis completion; T3: on the day after admission; FFP: fresh frozen plasma; FXIII: factor XIII; IQR: interquartile range; N.A.: not applicable.

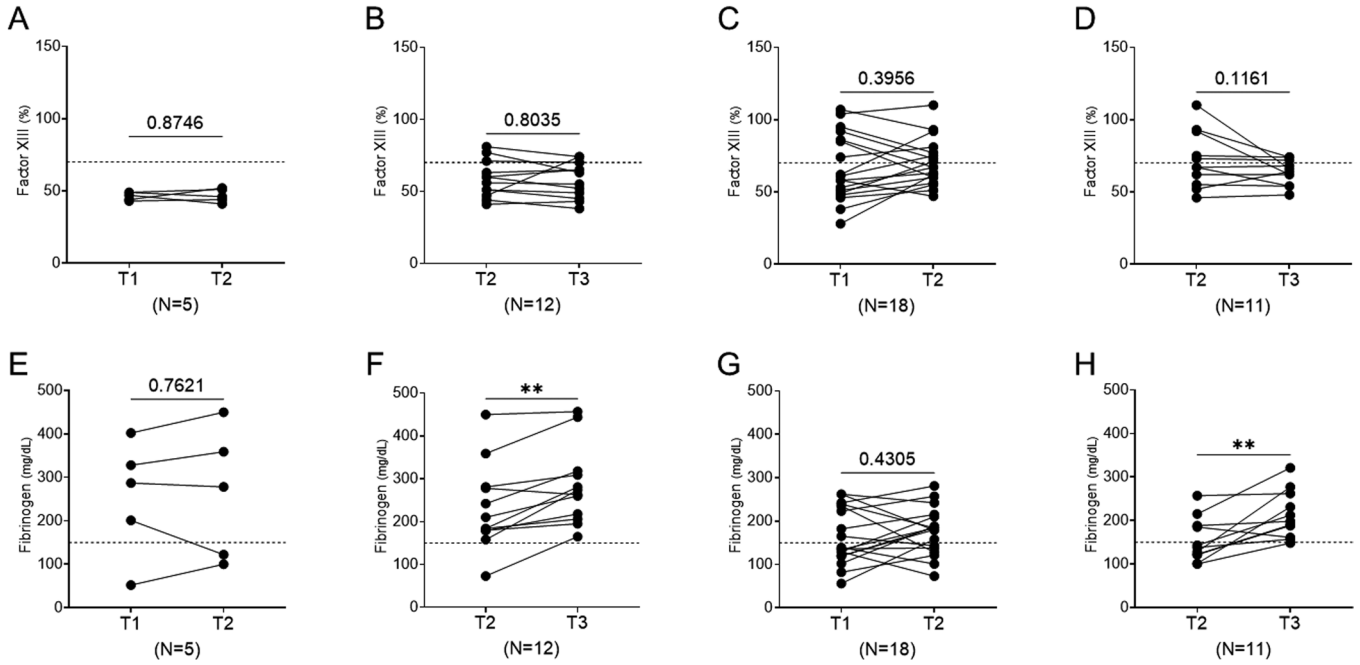

Figure 3 Subgroup analyses of changes in factor XIII levels (A–D) and fibrinogen (E–H) based on the presence or absence of plasma transfusion. Fresh frozen plasma and/or cryoprecipitate were transfused to 20 patients until T3 (18 patients until T2 and 11 patients from T2 to T3). Changes in factor XIII (A, B) and fibrinogen (E, F) levels in patients without plasma transfusion and factor XIII (C, D) and fibrinogen (G, H) levels in patients who received plasma transfusion.

**P<0.01 (Paired t-test).

T1: upon arrival: T2: at the time of hemostasis completion; T3: on the day after admission.

Discussion

This single-center prospective observational study showed the changes in FXIII activity during hemorrhagic shock and after resuscitation. On admission, FXIII activity was low in 70% of the patients, and the proportion of patients with low FXIII activity increased as the levels of acquired FXIII deficiency increased after resuscitation. Plasma transfusion triggered by low fibrinogen levels was insufficient to increase FXIII activity during and after hemostasis, whereas fibrinogen levels were sufficiently maintained.

In our study, FXIII activity was not maintained in 70% of patients upon admission, suggesting that FXIII activity is low during the very early phase of hemorrhagic shock. In patients with unexpected bleeding during elective surgeries,

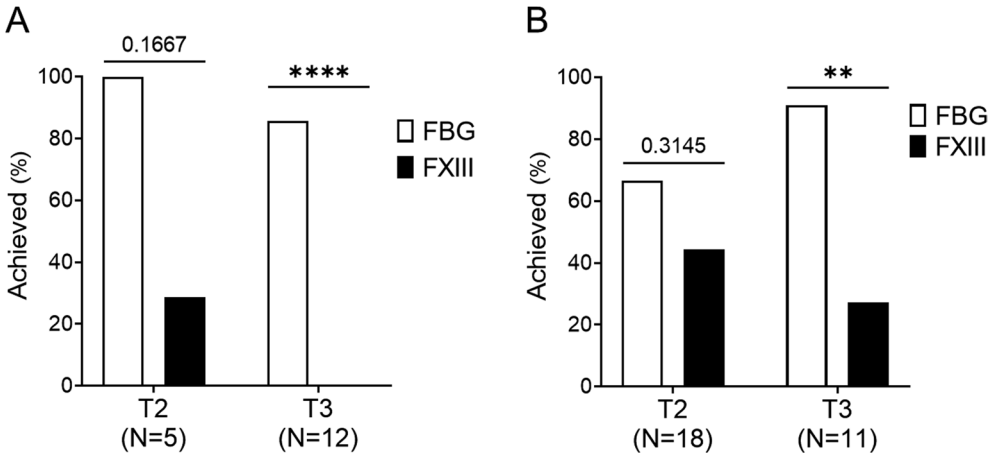

Figure 4 Subgroup analyses of the proportion of maintained sufficient levels of factor XIII activity and fibrinogen based on the presence or absence of plasma transfusion.
The proportion of patients with sufficient levels of factor XIII (black columns) and fibrinogen (white columns) is expressed in patients without (A) and with plasma transfusion (B).
****P<0.0001 (Fisher's exact test), **P<0.01 (Fisher's exact test).
T1: upon arrival: T2: at the time of hemostasis completion; T3: on the day after admission.

fibrinogen and FXIII were lower and the fibrin monomers were higher than those in the non-bleeding group despite surgery. Additionally, FXIII availability relative to the generated thrombin was lower in the bleeding group[18]. Together with these findings, our results suggest that FXIII is consumed rapidly by massive hemorrhage and is reduced to the levels of FXIII deficiency, even in the early stage of hemorrhagic shock.

In this study, plasma transfusions did not increase FXIII activity during resuscitation, before, or after hemostasis. Because fresh-frozen plasma and cryoprecipitate contain 1.2 and 2.8 units/mL of FXIII activity, respectively[23], these plasma products are used for the treatment of FXIII deficiency in some countries. In our study participants, the estimated amounts of FXIII administered were approximately 1,284 U and 576 U in patients with and without cryoprecipitate infusion until T2, respectively, and 576 U during T2–T3. Because these amounts of FXIII are theoretically sufficient for the treatment of FXIII deficiency, the downward change would overwhelm the replenishment by plasma transfusion in hemorrhagic shock. In other words, cryoprecipitate before hemostasis completion and fresh-frozen plasma transfusion before and after hemostasis completion may not be considered adequate replacements for FXIII and may miss the acquired FXIII deficiency.

The limitations of our study include the small number of cases, which may be characterized by potential selection bias and lead to beta errors. We did not examine the FXIII antigen; thus, we could not determine whether the low FXIII activity was caused by a lower concentration of FXIII or by underactivation. Furthermore, we cannot ascertain the relationship between FXIII activity and prognosis, such as rebleeding or death, because our study design excluded three patients from whom we could not complete the blood collections. In addition, we cannot comprehensively determine the efficacy of FXIII treatment for hemorrhagic shock, for which further research is required..

Conclusion

In patients with hemorrhagic shock, FXIII activity is insufficient during resuscitation, whereas fibrinogen levels are sufficiently maintained. Plasma transfusions cannot sufficiently maintain FXIII levels. Further studies are needed to clarify the relationship between FXIII activity and patient outcomes.

Approval of research protocol with approval no. and committee name: The study protocol was approved by the Ethics Review Board of the University of Miyazaki Hospital (O-0278).

Informed consent: Written consent was obtained from each patient or their close relatives before enrolment in the study.

Registry and registration no. of the study/trial: Not applicable.

Animal studies: Not applicable.

Conflict of interest: The authors declare no Conflict of

Interests for this article.

Funding: This study was supported by a Grant-in-Aid for Clinical Research from Miyazaki University Hospital.

Acknowledgments

The authors thank the staff of the Department of Emergency and Critical Care Medicine and the Clinical Research Support Center at the University of Miyazaki.

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