

Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion

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BACKGROUND: Platelet (PLT) and plasma transfusion remain the mainstay hemostatic therapy for perioperative bleeding. Several studies have indicated that acquired fibrinogen (FIB) deficiency can be the primary cause of bleeding after cardiac surgery. The aim of this study was to compare hematologic and transfusion profiles between the first-line FIB replacement and PLT transfusion in post-cardiac surgical bleeding.

STUDY DESIGN AND METHODS: In this prospective, randomized, open-label study, 20 adult patients who underwent valve replacement or repair and fulfilled preset visual bleeding scale were randomized to 4 g of FIB or 1 unit of apheresis PLTs. Primary endpoints included hemostatic condition in the surgical field and 24-hour hemostatic product usage. Hematologic data, clinical outcome, and safety data were collected up to the 28th day postoperative visit.

RESULTS: In patients who received the first-line FIB concentrate ($n = 10$), the visual bleeding scale improved after intervention, and the incidence of PLT transfusion and total plasma donor exposure were lower compared to the PLT group ($n = 10$). Postintervention FIB level was statistically higher (209 mg/dL vs. 165 mg/dL) in the FIB group than in the PLT group, but PLT count and prothrombin were lower. There were no statistical differences in the postoperative blood loss and red blood cell transfusion between two groups.

CONCLUSIONS: Our preliminary data indicate that the primary FIB replacement may potentially reduce the incidence of PLT transfusion and the number of donor exposures. Plasma FIB level of 200 mg/dL is attainable with a single dose of 4 g, and this level seems to mitigate bleeding despite moderately decreased thrombin generation.

Postoperative hemorrhage remains a serious complication of cardiac surgery affecting 3% to 10% of the patients undergoing cardiopulmonary bypass (CPB).¹⁻⁴ Further, major bleeding and subsequent allogeneic blood transfusion can be associated with increased morbidity and mortality after cardiac surgery.⁴⁻⁶ Therefore, a rapid diagnosis of coagulopathy and targeted replacement of deficient cellular and/or soluble coagulation elements are pivotal in achieving hemostasis and decreasing complications associated with hemorrhage. Platelet (PLT) transfusion has been considered to be the mainstay approach to microvascular bleeding (i.e., oozing from the incision and cannulation sites).⁷⁻⁹ PLT dysfunction after CPB is common due to biochemical and mechanical damages during CPB as well as preoperative anti-PLT therapy.¹ However, there is a paucity of clinical data to validate the hemostatic efficacy of PLT transfusion after CPB.^{7,10} On the other hand, several retrospective and prospective studies in cardiac surgery

ABBREVIATIONS: aPTT = activated partial thromboplastin time; AT = antithrombin; CPB = cardiopulmonary bypass; CT = clotting time; FIB = fibrinogen; IQR = interquartile range; MCF = maximum clot firmness; POC = point of care; PT = prothrombin time; TG = thrombin generation.

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indicated the potential efficacy of fibrinogen (FIB) concentrate as a first-line hemostatic intervention.^{4,11-13}

Purified lyophilized human FIB concentrate (RiaStap, CSL Behring, Marburg, Germany) has been approved by the Food and Drug Administration (FDA) for the treatment of acute bleeding in patients with congenital afibrinogenemia and hypofibrinogenemia.¹⁴ However, it has not been clinically studied head to head with conventional transfusion therapies in acquired bleeding conditions in the United States. The RiaCT trial (RiaStap vs. Conventional Transfusion; NCT01283321) was designed to compare the fixed dose (4 g) of FIB and a single unit of apheresis PLTs in a prospective randomized manner in patients undergoing valve replacement surgery with CPB.

MATERIALS AND METHODS

Study design and subjects

The study was designed as a single-center, prospective, randomized, open-label, active drug controlled study in patients undergoing valve replacement or repair surgery. The protocol was approved by the institutional review board of the Emory University (Atlanta, GA), and informed written consent was obtained from each patient enrolled in the study. The inclusion criteria were elective CPB procedures via median sternotomy for a single-valve replacement or repair, combined mitral and aortic valve replacements, or combined valve replacement and coronary artery bypass grafting. Exclusion criteria were emergency surgery, redo valve procedure, age (<18 or >85 years), any known congenital or acquired bleeding disorders, dialysis-dependent renal failure, liver dysfunction (more than twofold increase in liver enzymes), pregnancy or nursing, and intake of clopidogrel or coumadin within 5 days of surgery.

Clinical management

Anesthetic induction consisted of intravenous (IV) etomidate and fentanyl. For maintenance, inhaled sevoflurane, continuous IV fentanyl, and rocuronium bromide were used. In all patients, 400 U/kg porcine heparin was given before instituting CPB. The circuit of CPB was primed with crystalloid solution (1000-1400 mL), 10,000 U of heparin, and 37.5 g of mannitol. During CPB, activated clotting time (CT) was maintained above 450 seconds (Hemochron Signature Elite, ITC, Edison, NJ). Heparin anticoagulation was reversed after CPB with 200 to 250 mg of protamine sulfate. After heparin neutralization (ACT < 155 sec) and corrections of physiologic variables (pH > 7.3, body temperature > 35°C), the visual assessment of surgical field was performed by the senior surgical staff as follows: 0 = excellent hemostasis (dry field), 1 = mild bleeding (oozing), 2 = moderate bleeding (controllable with applied pressure), and 3 = severe bleeding (multiple diffuse bleeding sites). If the visual bleeding scale was 2 to

3, the subjects were randomly assigned to a study intervention using a closed envelope method. Within 30 minutes of the decision of intervention, the patients in the FIB group were infused with 4 g of FIB (RiaStap, 20 mg/mL), and patients in the PLT group were transfused with 1 unit of apheresis PLTs. After the initial randomized intervention, additional transfusions were given in the presence of bleeding (>200 mL/hr) according to the institutional practice as follows: one apheresis unit if the PLT count was less than $100 \times 10^9/L$, 2 units of plasma if the international normalized ratio was greater than 1.6, or 10 units of cryoprecipitate if the FIB level was less than 200 mg/dL.

Study outcomes

Primary endpoints included hemostatic condition in the surgical field (0-3 scale as above) after the study intervention and 24-hour usage of hemostatic blood products including plasma, PLTs, and cryoprecipitate. Secondary endpoints were 12-hour volumes of chest tube drainage and reexploration within 24 hours of surgery. Primary safety endpoints included thromboembolic events and mortality percentage of subjects with thromboembolic events (acute myocardial infarction, cerebrovascular thromboembolic event, peripheral artery occlusion, deep vein thrombosis, pulmonary embolism, death through Day 28 visit [up to 6-8 weeks postoperatively]). Troponin levels (normal range, 0-0.05 ng/mL) at 24 hours after surgery, total intensive care unit stay (hr), and hospital stay (days) were also compared.

Laboratory analyses

Hematologic tests including hemoglobin (Hb), PLT count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and FIB were performed in the clinical laboratory at four time points: 1) baseline (preanesthetic induction); 2) after the trial intervention; 3) after the second intervention, if any; and 4) 24 hours after surgery. Hb and PLT count were measured using a hematology analyzer (LH 750, Beckman-Coulter, Miami, FL). FIB levels were determined using a modified Clauss method (BCS, Dade Behring, Deerfield, IL). Normal ranges were as follows: PT (10.8-13.1 sec), aPTT (25-39 sec), and FIB (160-442 mg/dL). In addition, Factor (F)II (prothrombin), FVIII, FXIII, and antithrombin (AT) levels were measured at the above time points using a coagulation analyzer (STA Compact, Diagnostica Stago, Parsippany, NJ). Normal ranges were as follows: FII (50%-150%), FVIII (50%-150%), FXIII (50%-130%), and AT (80%-125%).

Thrombin generation assay and thromboelastometry

The calibrated automated thrombin generation (TG) assay (Thrombinoscope, Diagnostica Stago) was used post hoc to evaluate the capability of plasma to generate

thrombin in each study subject at four time points: 1) baseline (preanesthetic induction), 2) before the trial intervention, 3) after the trial intervention, and 4) 24 hours after surgery. According to the published method,¹⁵ TG was measured using 5 pmol/L tissue factor–based reagent (Diagnostica Stago) in the mixture of PLT-poor plasma and the buffer containing CaCl₂-fluorogenic substrate (Z-Gly-Gly-Arg-AMC) buffer. The progress of TG was continuously monitored for 90 minutes at 37°C using a fluorescence reader (Fluoroscan Ascent, Thermo Lab-systems, Franklin, MA).

Rotational thromboelastometry was performed with whole blood samples using a ROTEM Delta device (TEM Innovations, Munich, Germany) at the same time points as TG assay. EXTEM and FIBTEM measurements were performed at 37°C using 300 µL of whole blood with 20 µL of 0.2 mol/L CaCl₂ and tissue factor–based reagent.¹⁶ CT (sec), alpha angle (°), and maximum clot firmness (MCF, mm) were analyzed at four time points as with TG assay. TG and ROTEM assessments were utilized (before clinical approval of ROTEM by the FDA) to follow the clinical decision for initiating the trial intervention. Neither TG nor ROTEM result was made available to the care team, but they were used post hoc to monitor the impact of trial interventions on the whole blood clotting.

Statistical analysis

This interim analysis (n = 20) was conducted for the comparative analyses of our data with previously published prospective FIB trials (n = 20) in terms of safety and efficacy.^{11,17}

Statistical analysis was performed using computer software (Prism, Version 5, GraphPad Software, La Jolla, CA). Perioperative changes of hematologic tests and the effect of hemostatic interventions were evaluated by repeated-measures analysis of variance within groups. Between-group variables were evaluated by means of the unpaired t test. Nonnormally distributed data (by Kolmogorov-Smirnov test) were analyzed by the Mann-Whitney test. Categorical variables are reported as numbers in the group, and between-group comparisons were performed by Fisher’s exact test. A p value below 0.05 was considered significant.

RESULTS

Fifty-one patients were approached after initial screening for eligibility, and 26 patients were consented over an

18-month period (Fig. 1). Four patients were disqualified before surgery: two due to the change in surgical plans, one due to elevated liver enzymes, and one due to dabigatran therapy. During surgery, two patients did not meet the inclusion criteria for bleeding, and therefore 20 (16 males and 4 females) were randomly assigned to receive FIB concentrate (Group FIB; n = 10) or PLTs (Group PLT; n = 10) as an initial transfusion therapy. There were no significant differences between the two groups in terms of demographic and surgical variables (Table 1).

Transfusion requirements and postoperative blood loss

The weight-averaged dose of FIB concentrate was 46.2 ± 5.0 mg/kg. The volume of infusion for 4 g of FIB concentrate was 200 mL, whereas one apheresis PLT unit had the median volume of 230 mL (interquartile range [IQR], 213-295). Bleeding scores before the trial intervention were similar between the FIB and PLT groups (2.0 ± 0.0 and 2.1 ± 0.3, respectively). However, there was a trend for the lower score in the FIB group than in the PLT group after the initial treatment (1.0 ± 0.7 vs. 1.7 ± 0.8; p = 0.052).

Three patients received PLTs in the FIB group, and seven patients in the PLT group required second intervention within 2 hours of the study intervention. The median interval between the first and second interventions was 69.3 minutes in the FIB group and 62.1 minutes in the PLT group. Thereafter, fresh-frozen plasma (FFP) and cryoprecipitate were transfused in two patients who required the

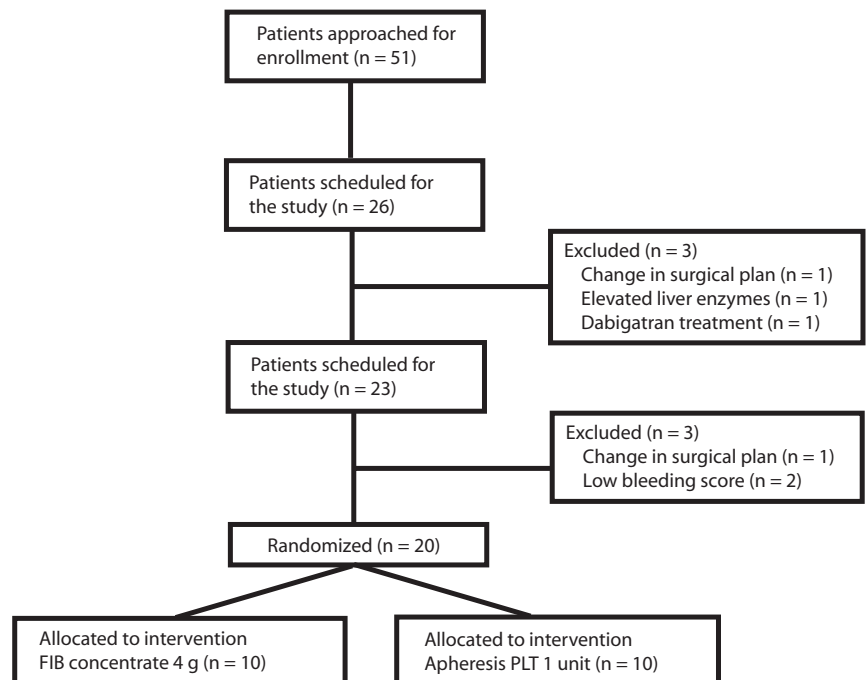


Fig. 1. Flow diagram of the patient recruitment and randomization process.

second intervention in the FIB group. One FIB-treated patient, who did not require any products during surgery, developed late bleeding (4 hr after surgery) and received PLTs, FFP, and cryoprecipitate. Among the PLT group, five patients received FFP, and four patients received cryoprecipitate as the second intervention. Total usage of components, and the volume of transfusion over 24 hours after surgery are summarized (Table 2). The incidence of PLT transfusion was decreased in the FIB group ($p = 0.015$). No other differences between two groups were found in the incidence of red blood cells (RBCs), FFP, or cryoprecipitate transfusion. The median volumes of transfused RBCs and FFP were not different (Figs. 2A and 2B), but there was a trend for decreased transfused volumes of PLTs and cryoprecipitate in the FIB group (Figs. 2C and 2D). Total donor exposures (median [IQR]) to hemostatic products (PLTs, FFP, and cryoprecipitate) were 0 (0-13.3) units in the FIB group and 16.5 (1.0-39.8) units in the PLT group ($p = 0.035$; Fig. 2E).

Median (IQR) blood losses at 12 hours after surgery were 925 (500-1693) and 1315 (653-2965) mL, respectively, in the FIB and PLT groups ($p = 0.21$; Fig. 2F).

Hematologic data

Preoperative Hb, PT, aPTT, and PLT count were comparable between the two groups (Table 3). The baseline values for FIB, FII, FVIII, FXIII, and AT were within normal range and comparable between the two groups.

After the initial treatment (posttreatment) with FIB (FIB group), both PT and aPTT were prolonged, and PLT

count was below the normal range. Plasma FIB and FVIII levels were maintained, but FII, FXIII, and AT levels were significantly decreased from preoperative values. After PLT transfusion (PLT group), PT was less prolonged, and PLT count was higher compared to those in the FIB group ($p = 0.028$). Posttreatment plasma FIB levels were 165 ± 48.6 mg/dL in the PLT group and 209 ± 49.6 mg/dL in the FIB ($p = 0.062$). Other plasma factor levels were also decreased at posttreatment compared to the baseline in both groups, but FII and AT levels were higher in the PLT group than in the FIB group ($p = 0.024$ and $p = 0.008$, respectively). Plasma FXIII levels were approximately half the baseline values at posttreatment, but no significances were observed between the two groups.

After the second intervention, three patients in the FIB group and seven patients in the PLT group had similar PLT counts higher than $90 \times 10^9/L$ and FIB levels of approximately 200 mg/dL (Table 3). In these patients, plasma factor levels remained lower in the FIB group as indicated by prolonged PT and lower FII and AT levels. FVIII and FXIII levels were not statistically different after the second intervention between the two groups. At 24 hours after surgery, all hematologic values between the two groups were statistically comparable. There were notable increases in plasma FIB and FVIII levels in both groups.

TG assay and thromboelastometry

Preoperative lag time and peak values of TG were comparable between the two groups. There were significant prolongations of lag time and decreases in peak thrombin levels in both groups at pretreatment (Figs. 3A and 3B). In the FIB group, lag time was increased by 80.8% and peak TG was decreased by 29.4% from the baseline, and these data are in agreement with the lower prothrombin level in this group (Table 3). The lag time and peak values were similar between the two groups after the study intervention. At 24 hours after surgery, both TG variables were recovered to normal ranges.

In both groups, CT was prolonged, alpha angle and MCF variables were decreased on EXTEM at pretreatment relative to the baseline, and these values were not statistically different between the two groups (Figs. 3C-3E). The pretreatment FIBTEM MCF values were decreased from the baseline by 54.3 and 49.5% in the FIB and PLT groups, respectively (Fig. 3F). These changes were more extensive than decreases in EXTEM MCF values of 20.1 and 16.9% in the respective group. After the initial intervention, FIBTEM MCF was higher in the FIB group than in the PLT group ($p = 0.024$). At 24 hours after surgery, thromboelastometric variables were normalized and statistically similar between the two groups.

TABLE 1. Demographic and surgical data

	Group		p value
	FIB	PLT	
Age	71.3 ± 5.3	66.1 ± 8.9	0.13
Male/female	8/2	8/2	1.0
Height (cm)	174 ± 9.1	177 ± 9.9	0.44
Weight (kg)	87.5 ± 8.9	85.6 ± 19.7	0.78
CPB time (min)	143 ± 28.1	119 ± 29.8	0.63
X-clamp time (min)	136 ± 37.5	107 ± 28.0	0.40
Minimal temp (°C)	31.9 ± 1.6	32.5 ± 2.3	0.53
Total heparin (kU)	482 ± 125	394 ± 84.0	0.08
Total protamine (mg)	249 ± 28.6	242 ± 55.5	0.73

X-clamp = aortic cross clamp.

TABLE 2. Incidence of blood transfusion

	Intraoperative			Postoperative			Total		
	FIB	PLT	p value	FIB	PLT	p value	FIB	PLT	p value
RBCs	8/10	7/10	1.0	8/10	9/10	1.0	9/10	9/10	1.0
PLTs	0/10	10/10	<0.001	4/10	5/10	1.0	4/10	10/10	0.011
FFP	0/10	2/10	0.47	3/10	4/10	1.0	3/10	5/10	0.65
CRYO	0/10	2/10	0.47	3/10	4/10	1.0	3/10	4/10	1.0

CRYO = cryoprecipitate.

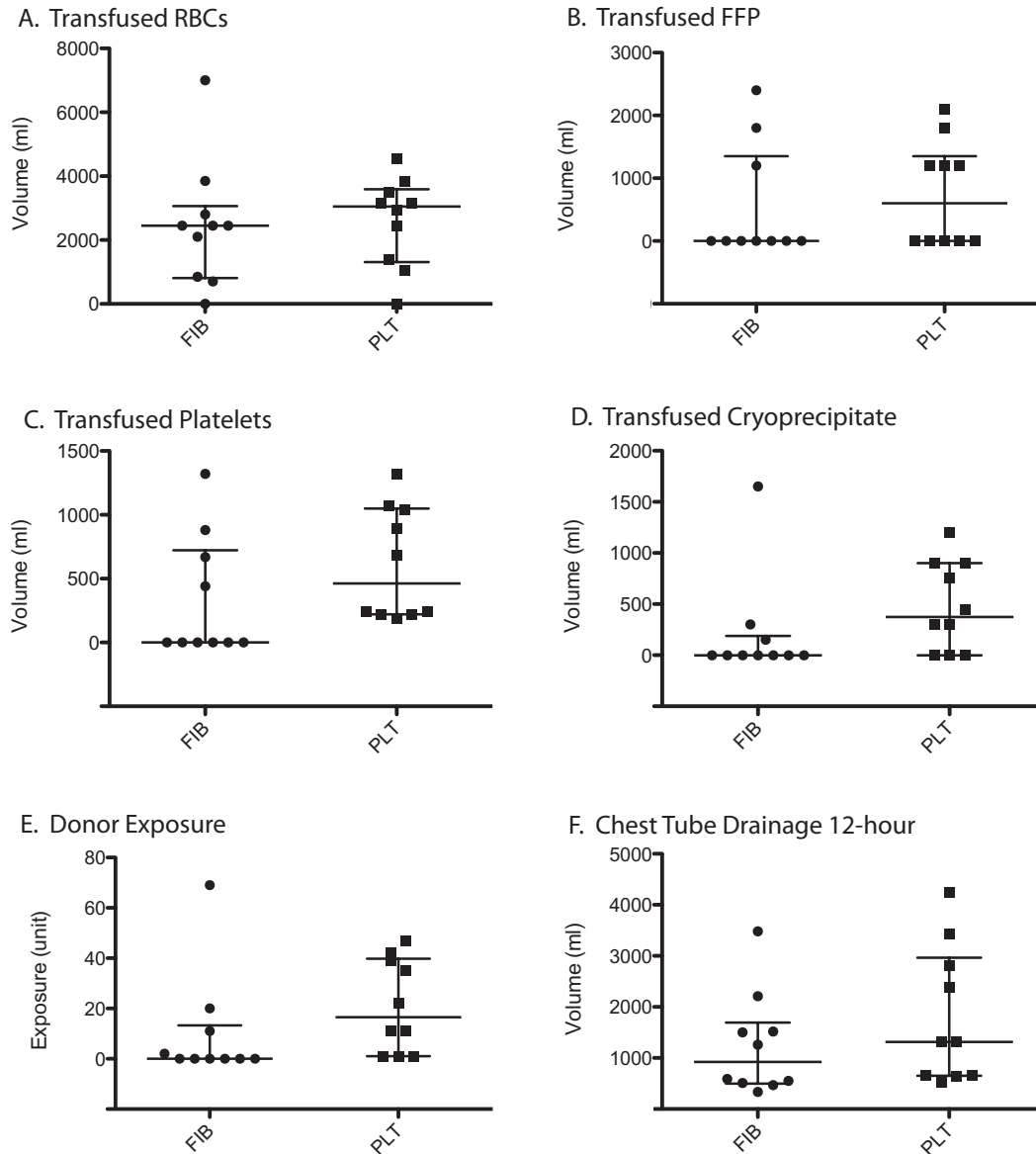


Fig. 2. Transfusion and postoperative chest tube drainage. Data are shown as median with the IQR. (A) Transfused RBCs ($p = 0.40$); (B) transfused FFP ($p = 0.55$); (C) transfused apheresis PLTs ($p = 0.066$); (D) transfused cryoprecipitates ($p = 0.075$); (E) donor exposure (total units) to hemostatic components ($p = 0.16$); (F) chest tube drainage (mL) 12 hours after surgery ($p = 0.21$).

Safety endpoints

The safety endpoints were summarized in Table 4. One patient in the FIB group and two patients in the PLT group underwent a reexploration for bleeding; one patient in the PLT group was found to have a small arterial bleeding site, but no apparent surgical causes were found in two others. Troponin levels at 24 hours after surgery were not statistically different. One patient in the PLT group was ruled in for acute myocardial infarction, but this patient recovered without complications. Pulmonary edema was diagnosed in three patients in the FIB group and five patients in the PLT group based on their chest X-ray findings. These patients had bled postoperatively and received transfu-

sion of plasma products and large amounts of fluid after surgery. Total lengths of intensive care unit stay and hospital stay after surgery were not statistically different between the two groups. Two patients in the PLT group required a rehospitalization within 28 days of surgery. One was treated for atrial fibrillation and pleural effusion, and the other was diagnosed with atrial fibrillation, dehydration, and thrombus on the prosthetic mitral valve.

DISCUSSION

The key findings from the preliminary analysis of the RiaCT trial were the lower incidence of PLT transfusion

TABLE 3. Hematologic data

	Baseline		Posttreatment		Post-2nd treatment		24-hr Post-op	
	FIB	PLTs	FIB	PLTs	FIB (n = 3)	PLTs (n = 7)	FIB	PLTs
Hb (g/dL)	12.3 ± 1.6	13.5 ± 1.0	9.2 ± 0.9†	9.1 ± 1.2‡	8.1 ± 2.3	8.6 ± 1.2	9.8 ± 0.9†	10.0 ± 1.1‡
PT (sec)	11.9 ± 0.8	11.5 ± 0.5	19.2 ± 2.0†*	16.8 ± 1.6‡	22.0 ± 3.5	17.5 ± 2.0	15.0 ± 1.7†	14.2 ± 1.2‡
aPTT (sec)	33.8 ± 5.1	34.8 ± 3.7	57.2 ± 14.8†	53.2 ± 10.8‡	71.1 ± 32.8	71.7 ± 27.9	43.6 ± 5.1†	44.7 ± 7.8‡
PLT count (×10 ⁹ /L)	218 ± 69.3	189 ± 38.7	101 ± 33.3†*	133 ± 25.5‡	96.3 ± 26.7	92.3 ± 48.3	86.3 ± 21.8†	90.0 ± 17.5‡
FIB (mg/dL)	378 ± 117	358 ± 117	209 ± 49.6†	165 ± 48.6‡	204 ± 38.7	201 ± 55.7	409 ± 95.1	363 ± 63.0
FII (%)	104 ± 16.4	97.0 ± 10.6	40.1 ± 9.6†*	53.6 ± 13.1‡	28.0 ± 5.6	47.7 ± 8.2	69.9 ± 12.1†	63.9 ± 11.1‡
FVIII (%)	157 ± 49.5	120 ± 36.5	125 ± 39.7†	114 ± 23.3‡	104 ± 14.7	108 ± 25.7	165 ± 50.4	135 ± 34.8
FXIII (%)	101 ± 16.2	109 ± 33.5	54.4 ± 13.0†	54.5 ± 18.9‡	55.0 ± 9.5	64.7 ± 22.3	69.9 ± 24.8†	77.2 ± 21.3
AT (%)	86.6 ± 6.2	92.2 ± 15.1	36.0 ± 9.0†*	46.6 ± 6.9‡	31.7 ± 9.7	42.2 ± 10.0	54.2 ± 9.4†	56.9 ± 13.0‡

* p < 0.05 versus PLT group.
† p < 0.05 versus baseline level (FIB group).
‡ p < 0.05 versus baseline level (PLT group).

and the reduced overall plasma donor exposure in the FIB group. The fixed dose (4 g) of FIB corresponded to the weight-based dose of 46.2 ± 5.0 mg/kg, and it was sufficient to restore plasma FIB to 200 mg/dL (Table 3). The visual bleeding scale was improved from Grade 2 to 1 in the FIB group, while it was only marginally improved from Grade 2 to Grade 1.7 in the PLT group in which FIB level remained at 165 ± 48.6 mg/dL. There were no statistical differences in the postoperative blood losses and RBC usages between the two groups in this pilot study. The lack of significant changes could be due to a small sample size (Type II error), but it might be also related to the type of surgical procedures or the dose of FIB. Our study patients underwent longer CPB runs (119-143 min) for valve replacement procedures. Karlsson and colleagues¹¹ reported a 32% reduction in the blood loss by preoperatively administering FIB (2 g) versus placebo in a small prospective randomized study (n = 20). However, their patients underwent shorter CPB runs (70-73 min) for coronary bypass grafting surgery, and their international normalized ratio and aPTT remained normal after CPB. Rahe-Meyer and coworkers¹⁸ recently reported a placebo-controlled randomized study of high-dose FIB (median, 8 g) in the patients undergoing a thoracic aortic replacement. They achieved higher plasma FIB levels, 260 ± 48 mg/dL (n = 29), after FIB replacement, while those after the placebo remained at 189 ± 34 mg/dL (n = 32). They were able to demonstrate fewer transfusions of apheresis PLTs (median, 0 units vs. 4 units, p < 0.001) and FFP (median, 0 units vs. 8 units, p < 0.001) as well as decreased 24-hour blood loss in the FIB group. The twofold higher dose of FIB than ours can in part explain their positive finding, but it is noteworthy that their mean CPB time was approximately 50 minutes. Although the incidence of reexploration for bleeding was not different between FIB and placebo treatments (14 and 13%, respectively), shorter CPB duration might have prevented extensive hemodilution and enzymatic defects of coagulation,¹⁹ leading to the avoidance of transfusion

except for FIB in 13 of 29 patients.¹⁸ Conversely, our present data suggested that persistent bleeding after FIB replacement could be due to enzymatic deficiency, for example, low prothrombin level below 40% (Table 3).

There is a potential need to correct enzymatic function of coagulation in addition to its primary substrate (FIB) in moderately complex cardiac surgical patients (CPB time, 148-166 min).⁴ In their study, Weber and coworkers⁴ randomized 100 patients to point-of-care (POC) versus central laboratory testing for hemostatic management. The median dose of FIB was 2 g for both groups, and posttreatment FIB levels were 200 to 230 mg/dL, a range between those in our study (Table 3) and those of Rahe-Meyer and colleagues.¹⁸ There were no statistical differences in the overall frequencies of FIB infusion (64% of POC and 60% of laboratory group; p = 0.837), prothrombin complex concentrate infusion (44% of POC and 52% of laboratory group; p = 0.433), and PLT transfusion (28% of POC and 33% of laboratory group; p = 0.412). However, FFP transfusion was less frequent in the POC than in the laboratory group (40% vs. 80%; p < 0.001).

In our study, data of TG assay and thromboelastometry were used post hoc to evaluate hematologic changes before and after FIB replacement or PLT transfusion. Before the study intervention, there were trends for prolonged lag time and lower peak TG in the FIB group compared to the PLT group (Figs. 3A and 3B). These data are consistent with the lower prothrombin level in the FIB group after FIB replacement (Table 3). At posttreatment, prolonged lag time and lower peaks of TG were comparable between the two groups, but they remained significantly different from the baseline values (Figs. 3A and 3B). On thromboelastometry, EXTEM variables (CT, MCF, and alpha angle) were statistically comparable between the two groups at baseline and before the trial intervention (Figs. 3C-3E). FIBTEM-MCF became statistically higher after 4 g of FIB was given (12.9 ± 4.1 mm vs. 9.0 ± 2.9 mm in the PLT group; Fig. 3F), but EXTEM angle and MCF were similar (Figs. 3D and 3F). FIBTEM has been increasingly

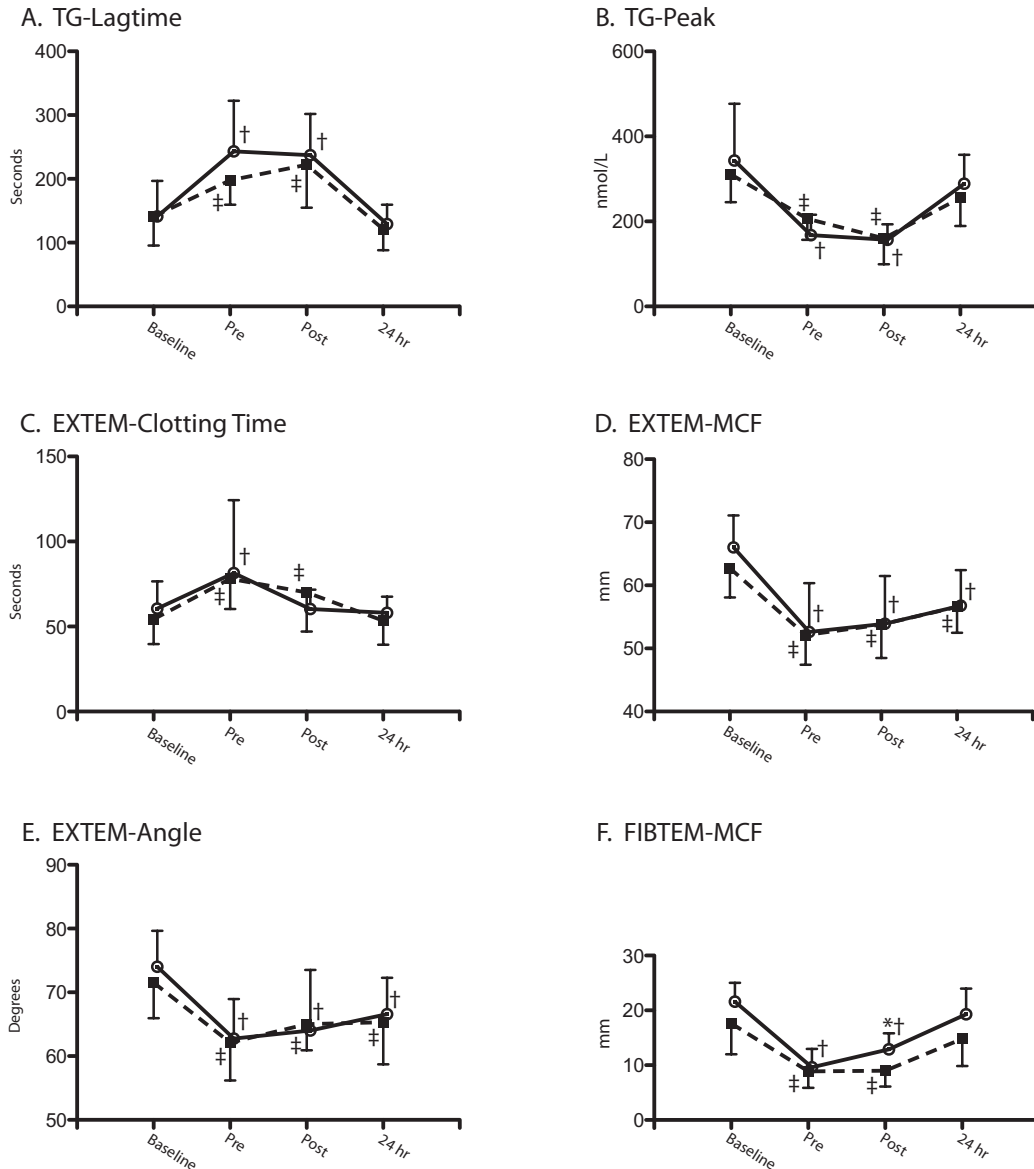


Fig. 3. TG assay and thromboelastometry data. Data are shown as mean ± SD. *p < 0.05 versus PLT group, †p < 0.05 vs. baseline level (FIB group, ○), ‡p < 0.05 versus baseline level (PLT group, ■). Pre = before the study intervention; Post = after the study intervention; 24 hr = 24 hours after surgery.

utilized to assess plasma FIB levels and the need for FIB replacement in a timely manner (<10-15 min).^{4,13,16} Although the Clauss method and its modifications are conventionally used, these FIB assays take time (30-60 min)^{20,21} and have significant variability depending on a method, calibration range, and other clinical variables (e.g., hydroxyethyl starch).^{22,23} Rapid availability of POC results possibly facilitate early diagnosis of coagulopathy and prompt hemostatic interventions, if necessary. According to our study protocol, additional hemostatic intervention(s) followed central laboratory testing, and the interval between first and second intervention was more than 1 hour. We speculate that an efficacy of hemo-

static intervention can be influenced by the delayed therapy as coagulopathy is progressively exacerbated.²⁴ Aforementioned data by Weber and coworkers⁴ support this speculation because 6- to 24-hour postoperative blood losses were consistently decreased, the overall cost of hemostatic products was reduced by the POC testing compared to the laboratory testing.

The cost of hemostatic products is an important consideration because most studies of perioperative FIB replacements had been carried out in Europe where cryoprecipitate is unavailable.^{4,11-13,17,18,25,26} One gram of FIB costs €233 (approx. \$300), and 1 unit of pooled PLTs and FFP cost €233 and €40, respectively, at one European

TABLE 4. Safety endpoints

	Group		p value
	FIB	PLT	
Reexploration	1/10	2/10	1.0
Acute MI	0/10	1/10	1.0
Thromboembolism	0/10	0/10	1.0
Pulmonary edema	3/10	5/10	0.65
30-day readmission	0/10	2/10	0.47
Death in 30 days	0/10	0/10	1.0
24-hours troponin	12.7 ± 23.8	10.2 ± 13.2	0.77
ICU hours	76.6 ± 44.7	105 ± 57.1	0.13
Hospital days*	8.0 ± 2.4	7.8 ± 3.9	0.13

* Hospital stay after surgery.
ICU = intensive care unit; MI = myocardial infarction.

hospital.⁴ Based on the following costs at this institution, FIB \$0.70/mg, cryoprecipitate \$136/U, apheresis PLT \$1040/U, and FFP \$128/U, the median costs of hemostatic components per case were similar between the two groups: \$2800 (\$2800-\$6826) in the FIB group and \$4036 (\$1040-\$9252) in the PLT group ($p = 0.51$).

PLT transfusion was chosen to be the comparator to FIB in our study because CPB associated with PLT dysfunction is considered to be the primary cause of microvascular bleeding.¹⁹ However, there is a paucity of clinical efficacy data on PLT transfusion. Simon and colleagues¹⁰ reported a randomized, controlled trial of prophylactic PLT transfusion (4 pooled units) in 28 patients who underwent coronary bypass grafting and/or valve replacement surgery. Prolonged Ivy bleeding time was prevented as the mean PLT count was increased to $132 \times 10^9 \pm 40 \times 10^9/L$ from $97 \times 10^9 \pm 40 \times 10^9/L$ in the PLT transfusion group (no FIB levels reported). However, postoperative chest drainage volumes overnight were not decreased by PLT transfusion (1375 ± 696 mL vs. 936 ± 36.5 mL in the control) in agreement with our present data (Fig. 2D). A number of studies on intraoperative autologous PLT-rich plasmapheresis conducted in 1990s showed that the treatment effects on postoperative bleeding and RBC exposure were small and inconsistent.²⁷ Although PLT transfusion is indicated for the patients on chronic dual anti-PLT therapy,^{4,13} additional studies are warranted to conduct a larger clinical trial to compare PLT transfusion and FIB replacement.

The recent transfusion guidelines in Europe suggest target FIB levels of 150 to 200 mg/dL for FIB replacement,²⁸ and several trial data in cardiac surgery support even higher FIB levels (200-250 mg/dL) to support hemostasis after CPB.^{4,11,18} As shown in our study, plasma FIB levels fell below 200 mg/dL after 2 hours of CPB without FIB replacement, and prothrombin levels fell to 28% in those who developed profuse bleeding despite the FIB replacement (Table 3). On the other hand, FVIII and FXIII levels were maintained at above 100 and 50%, respectively (Table 3). The latter data may in part explain inconsistent

data reported on desmopressin (to increase von Willibrand Factor or FVIII) and FXIII replacement after cardiac surgery.^{29,30}

There are some limitations in our present study. First, our study was designed to test a single, fixed dose of FIB (4 g) rather than the weight-based or escalating doses of FIB in managing post-CPB bleeding. However, our dose is similar to the reported dose of 4 g (median) administered to bleeding patients with acquired hypofibrinogenemia,³¹ and our weight-averaged dose (46.2 ± 5.0 mg/kg) was within the range of transfusion algorithm (initial FIB, 25-50 mg/kg).^{4,13} Secondly, the initial hemostatic intervention was given after the correction of physiologic variables (pH > 7.3, body temperature > 35°C) and visual assessment of microvascular bleeding.³² There is a concern for interobserver variability due to multilevel assessments (four grades) in our study. However, unnecessary transfusion was minimized by the presence of assessors who had sufficient surgical skills in the management of complex cardiac surgical cases. Although hemostatic interventions based on an initial visual field assessment reflect the most common practice in the United States,³² the use of thromboelastometry or thromboelastography in the transfusion algorithm could have facilitated the timing and choice of intervention(s).^{4,13,20,33,34} Finally, our data are preliminary, and a larger sample size is required to conclude on the efficacy of the FIB concentrate over PLT transfusion. This study is also underpowered to make any conclusion about safety outcomes of FIB therapy. Potential advantages of FIB concentrate including rapid availability, and manufacturing steps (e.g., pathogen inactivation, and antibody removal)²⁶ should be evaluated against conventional hemostatic components (PLTs, FFP, and cryoprecipitate) with a sufficient sample size.

In summary, our preliminary data indicate that the primary FIB replacement may potentially reduce the incidence of PLT transfusion and the number of donor exposures. The target FIB level of 200 mg/dL was attainable with a single dose of 4 g, and this level seemed to mitigate bleeding despite moderately decreased endogenous TG. A large prospective randomized study is warranted to examine the efficacy and safety of FIB therapy in high-risk cardiac surgical patients.

CONFLICT OF INTEREST

KT has received a consulting fee from ROTEM, Inc. All other authors have no conflict of interest to declare.

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