

Association Between Platelet Count and Postoperative Blood Loss in Patients Undergoing Cardiac Surgery With Cardiopulmonary Bypass and Fresh Frozen Plasma Administration Guided by Thromboelastometry

Junko Ichikawa, MD; Yoshiko Osada, MD; Mitsuharu Kodaka, MD;
Keiko Nishiyama, MD; Makiko Komori, MD

Background: Coagulopathy after cardiopulmonary bypass (CPB) is caused by multiple factors, including reduced coagulation factors and a low platelet count.

Methods and Results: In this study, we undertook a post hoc analysis to identify factors associated with increased postoperative blood loss in 97 patients undergoing cardiac surgery with CPB, with fresh frozen plasma administered according to a ROTEM-guided algorithm. We identified 24 patients for the top quartile of postoperative blood loss, >528 mL and defined as having excessive blood loss. Using Spearman's rank correlation test and multivariable linear regression, we reanalyzed the participants' demographic, surgical and anesthetic variables, laboratory test results, blood loss, and transfusion data. Univariate analysis indicated that patients who experienced higher postoperative blood loss received a significantly higher heparin dose, had a higher requirement for fresh frozen plasma transfusion during surgery, and had a significantly lower hematocrit and platelet count at the end of surgery compared with patients without excessive blood loss. Multivariate analysis showed that platelet count at the end of surgery (odds ratio 0.780, 95% confidence interval 0.629–0.967; $P=0.024$) was an independent factor for excessive blood loss.

Conclusions: Low platelet count at the end of surgery was associated with excessive postoperative bleeding during cardiac surgery with CPB.

Key Words: Cardiopulmonary bypass; Postoperative blood loss; Rotational thromboelastometry; Thrombocytopenia

The use of supplemental point-of-care (POC) coagulation tests is recommended during cardiac surgery with cardiopulmonary bypass (CPB) because they optimize blood product management, thereby avoiding excessive blood loss.^{1–4} Rotational thromboelastometry (ROTEM) permits rapid viscoelastic evaluation of clot formation in whole blood.⁵ The technique uses a variety of activators and inhibitors to assess clot formation, thrombin generation and fibrinolysis. We previously reported that introduction of a ROTEM-guided protocol for administering fresh frozen plasma (FFP) during cardiac surgery reduced postoperative blood loss and overall blood product use compared with blood product use based solely on clinicians' experience.⁶ Fibrinogen is the first coagulation factor to fall below a critical threshold during massive hemorrhage.^{7–9} The prompt and appropriate administration of FFP and/or fibrinogen concentrate based on POC measurements is associated with decreased perioperative bleeding.¹⁰ It is important to achieve a well-balanced postoperative coagulation status before discharging the patient from the oper-

ating room.

However, some participants in our study still experienced excessive postoperative bleeding despite being treated according to the ROTEM algorithm. The algorithm did not specify the conditions for platelet transfusion. Instead, decisions to transfuse platelet concentrate were based on whether the patient had thrombocytopenia preoperatively and/or visual confirmation of the presence of empirical microvascular bleeding. Timely availability of platelets is often an issue in Japan, even though lower platelet count and function is associated with increased blood loss, transfusion of blood products and transfusion-associated adverse events.¹¹

The aim of this study was to examine the relationship between excessive postoperative bleeding and, specifically, the platelet count using logistic regression analysis in a post hoc analysis of participants in our study managed according to the ROTEM protocol. A better understanding of these relationships could help us predict substantial postoperative blood loss and thus further improve management

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Department of Anesthesiology, Tokyo Women's Medical University Medical Center East, Tokyo, Japan

Mailing address: Junko Ichikawa, MD, Department of Anesthesiology, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu, Arakawa-ku, Tokyo 116-8567, Japan. E-mail: htwwx872@yahoo.co.jp

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of coagulopathy in addition to that achieved with the ROTEM-based FFP transfusion protocol.

Methods

Ethics Committee Approval

This study was a post hoc analysis of our previous prospective, observational study that assessed the effectiveness of ROTEM-guided coagulation management on blood loss and transfusion requirements between April 2013 and December 2015 at Tokyo Women's Medical University Hospital East, Tokyo, Japan. The original study was approved by the local ethics committee (reference no. 2775, Shunichi Miyazaki, Chair of Tokyo Women's Medical University). Written informed consent was given by each participant.

Study Population

Consecutive patients undergoing cardiac surgery with CPB during the study period were enrolled. Exclusion criteria were a history of coagulopathy, liver dysfunction, reoperation, abnormal preoperative coagulation profile (international normalized ratio ≥ 1.3 , activated partial thromboplastin time >40 s) and/or recent exposure to anticoagulant and/or antiplatelet agents that should have been suspended preoperatively.

Study Protocol

The research database compiled during the original study comprised participants' demographic and clinical characteristics, including age, sex, height, weight and complications; surgical variables including aortic cross-clamp and CPB times; intraoperative and postoperative blood loss in the first 24 h after ICU admission; and transfusion data.

Transfusion of packed red blood cells (PRBCs) was indicated when the hematocrit dropped below 20% during CPB and below 30% after extracorporeal circulation. Occasionally, despite a hematocrit of $>30\%$, PRBCs were transfused when the patient's clinical condition dictated it, or in accordance with the surgeon's instructions. Platelet transfusion was performed in cases of preoperative thrombocytopenia and/or clinically relevant diffuse bleeding after heparin reversal. FFP was administered based on the ROTEM results, measured approximately 20 min before aortic de-clamping. For the extrinsic test (EXTEM), tissue factor was used to trigger coagulation, with the results reflecting thrombin-mediated platelet activation and fibrin polymerization. For FIBTEM, cytochalasin D is added to the EXTEM test to inhibit the contribution of platelets to fibrin clot formation. A FIBTEM maximum clot firmness (MCF) of ≤ 9 mm was set as the threshold for FFP administration to achieve a FIBTEM MCF target of ≥ 10 mm. A transfusion of FFP 3–4 mL/kg was administered for a targeted increase in the FIBTEM MCF of 1 mm. If bleeding continued, further FFP was transfused.

Other Hemostatic Measurements

Routine arterial catheters were used for blood sampling: (1) before induction of anesthesia (baseline); (2) shortly after starting CPB; (3) approximately 20 min before aortic de-clamping; and (4) at the end of surgery. Complete blood counts and coagulation studies, including prothrombin time, activated partial thromboplastin time, and the concentrations of fibrinogen, fibrinogen degradation products and D-dimer, were measured by the central

hematology laboratory according to our institution's protocols. Complete blood counts were performed using the LH 780 (Beckman, Brea, CA, USA), and coagulation studies were performed using an ACL TOP device (Instrumentation Laboratory, Bedford, MA, USA). Plasma antithrombin activity was measured by a commercial, automated coagulation laboratory (ACL TOP 500CTS). Prothrombin fragment F1+2 (F1+2) and the thrombin-antithrombin complex (TAT) were measured with Enzygnost F1+2 monoclonal kits (Siemens Healthcare Diagnostics, Munich, Germany) and HISCL commercial assay kits (Sysmex, Kobe, Japan), respectively. Anti-Xa heparin concentration was measured in the laboratory using an automated chromogenic assay (>0.1 U/mL).

Anesthesia, Hemostatic Strategy and CPB

All patients underwent normothermic CPB using a membrane oxygenator and biocompatible circuits (Capiox, RX-15 or 25; Terumo Corporation, Tokyo, Japan). When the body surface area was <2.08 m², the extracorporeal circuit was primed with 550 mL sodium bicarbonate, 30 g mannitol, and 5 mg betamethasone per kilogram body weight. When the body surface area was ≥ 2.08 m², the circuit was primed with 800 mL bicarbonate solution.

We used Hepcon HMS for all patients based on the manufacturer's protocol (LEO Pharma, Ballerup, Denmark). The dose of porcine heparin was calculated based on each patient's estimated blood volume and the pump priming volume to achieve a target activated clotting time (ACT) of 450 s. Because the calculation of a patient's blood volume based on the body surface area is approximate, a 3,000–5,000 IU loading dose of heparin was added to the CPB pump prime. Heparin was reversed by administering protamine sulfate based on a heparin-protamine titration technique using the Hepcon HMS.

All patients received 1 g tranexamic acid intravenously before heparin administration and blood sampling for measurement. A second intravenous dose of 1–2 g was administered only if the CPB was prolonged (>140 min).

Statistical Analysis

Data are presented as the mean \pm standard deviation (SD) or the median and 25th and 75th percentiles for continuous variables and as the number (proportion, %) for categorical variables. Continuous variables were examined for a normal distribution using the Shapiro-Wilk test. We subdivided our patient population into 2 groups based on the amount of blood lost. Patients who experienced excessive blood loss formed the group with the top quartile for postoperative blood loss. Patient-related, surgical, anesthetic, and laboratory variables of the 2 groups were compared with the unpaired t test or the Wilcoxon ranked sum test for continuous variables and Fisher's exact test for categorical variables. The independent relationships between all clinically relevant and statically significant variables ($P < 0.05$ in the univariate analysis) and the amount of postoperative blood loss were identified using a multivariate logistic regression analysis, with excessive bleeding as the dependent variable and other variables as independent variables. The association between excessive blood loss and the platelet count was the principal relationship of interest. The criterion for rejection of the null hypothesis was $P < 0.05$. All statistical analyses were performed using SPSS software (version 22.0; SPSS, Chicago, IL, USA).

Table 1. Demographic, Surgical and Anesthetic Characteristics of Each Group of Patients

Parameter	Patients with high blood loss (n=24)	Patients without high blood loss (n=73)	P value
Mediastinal blood loss for 24 h (mL)	740±256	264±105	<0.0001
Age (years)	70.6±13.8	67.9±12.9	0.380
Weight (kg)	54.5±10.2	59.3±13.4	0.110
Height (cm)	159.5±9.7	158.1±9.5	0.543
Operative procedure			
Valve repair/replacement (n, %)	14 (58.3)	50 (68.5)	0.457
Aortic surgery (n, %)	3 (12.5)	9 (12.3)	0.999
Deep hypothermic circulatory arrest (n, %)	2 (8.3)	7 (9.6)	0.608
Combined operations (n, %)	6 (25.0)	5 (6.8)	0.025
CPB time (min)	138.3±56.9	129.8±62.1	0.565
ACC time (min)	106.5±50.8	97.2±48.3	0.426
Operation time (min)	263.5±75.5	244.3±61.8	0.342
Medical history			
Myocardial infarction	2 (8.3)	7 (9.6)	0.999
Hypertension	9 (37.5)	24 (32.9)	0.804
Diabetes	5 (20.8)	10 (13.7)	0.515
Arrhythmia	6 (25.0)	12 (16.4)	0.372
Renal insufficiency (serum creatinine >2.0 mg/dL)	5 (20.8)	15 (20.5)	0.999
Anticoagulation			
Blood heparin concentration after starting CPB (IU/mL)	3.1±1.0	3.0±0.9	0.664
Blood heparin concentration before ending CPB (IU/mL)	3.5±1.2	3.2±1.3	0.292
Initial heparin dose (IU/kg)	271±100	237±67	0.061
Total heparin dose (IU/kg)	471±165	398±121	0.022
Total protamine dose (mg/kg)	1.6±0.5	1.6±0.5	0.665
Intraoperative blood loss (mL)	547±373	536±810	0.954
Hemoglobin at the end of surgery (g/dL)	11.2±1.0	11.0±1.4	0.556
Transfusion-related data during surgery			
PRBCs transfused (mL)	1,030±449	808±214	0.082
Patients transfused with PRBCs (n, %)	21 (87.5)	64 (87.7)	0.614
FFP transfused (mL)	659±265	645±569	0.336
Patients transfused with FFP (n, %)	19 (79.2)	29 (39.7)	0.001
Platelets transfused (units)	20 (20)	20 (20)	0.081
Patients transfused with platelets (n, %)	4 (16.7)	9 (12.3)	0.406
Transfusion-related data after surgery			
PRBCs transfused (mL)	549±282	341±110	0.164
Patients transfused with PRBCs (n, %)	13 (54.2)	16 (21.9)	0.003
FFP transfused (mL)	686±431	383±140	0.031
Patients transfused with FFP (n, %)	12 (50.0)	7 (9.6)	<0.001
Platelets transfused (units)	20 (20)	20 (20)	0.141
Patients transfused with platelets (n, %)	2 (8.3)	1 (1.4)	0.153

Data are presented as the mean±standard deviation or the median (interquartile range) for continuous variables, and number (proportion, %) for categorical variables. ACC, aortic cross-clamping; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; PRBC, packed red blood cells.

Results

From a total of 116 participants, 19 were excluded from the analysis (14 met ≥1 of the predefined exclusion criteria, 2 required surgical re-exploration and 3 had missing data). Consequently, the data of 97 patients undergoing cardiac surgical procedures requiring CPB were included in our final analysis. The estimated post-CPB blood loss during the first 24 postoperative hours was negatively skewed with a median of 300 mL (25th and 75th percentiles of 210 and 528 mL, respectively) and a mean of 382 (±SD 258 mL). After log transformation, blood loss was normally distributed (mean 2.22±SD 0.14). The highest quartile for blood

loss was defined by postoperative hemorrhage >528 mL during the first 24 postoperative hours (24 patients were included in this group). Although there were no deaths among those who experienced excessive bleeding, 2 patients required surgical re-exploration because >1,500 mL blood was drained during the first 3 h after ICU admission, and they were excluded from the study.

The patients' characteristics, and the surgical and anesthetic variables of each group, are shown in **Table 1**. The results of laboratory tests are shown in **Table 2**. A significantly higher proportion of patients who experienced higher postoperative blood loss underwent combined surgical procedures and required FFP transfusion during surgery

Table 2. Laboratory Parameters and Their Relationship With Blood Loss During Surgery

Parameter	ROTEM	Controls	P value
	Patients with high blood loss (n=24)	Patients without high blood loss (n=73)	
After induction of anesthesia			
Hematocrit (%)	35.8±5.3	37.6±6.1	0.210
Platelet count (10 ⁹ /L)	15.9±6.9	18.6±6.6	0.090
PT (s)	12.8±2.1	12.4±1.2	0.172
APPT (s)	33.1±6.7	32.9±4.3	0.447
Antithrombin activity (U/mL)	87.6±18.6	94.9±17.6	0.089
Fibrinogen (mg/dL)	330.9±125.3	360.6±104.2	0.260
Fibrin degradation products (μg/mL)	4.7 (2.5–7.8)	3.8 (2.5–5.8)	0.633
D-dimer (μg/mL)	0.8 (0.5–2.7)	0.8 (0.5–2.1)	0.751
TAT (pmol/L)	4.9 (3.5–10.3)	6.6 (3.6–13.8)	0.406
Prothrombin fragment 1+2 (pmol/L)	290 (144–568)	279 (172–417)	0.988
Pre-CPB			
Hemoglobin (g/dL)	8.0±1.1	8.3±1.4	0.380
Hematocrit (%)	24.4±3.4	25.9±6.8	0.301
Platelet count (10 ⁹ /L)	9.8±3.5	12.6±9.2	0.160
Fibrinogen (mg/dL)	166.3±76.5	198.3±106.8	0.178
Antithrombin activity (U/mL)	53.3±8.0	56.0±15.0	0.407
Fibrin degradation products (μg/mL)	3.0 (2.5–4.8)	3.0 (2.5–4.7)	0.969
D-dimer (μg/mL)	0.5 (0.5–1.9)	0.7 (0.5–1.6)	0.539
TAT (pmol/L)	12.9 (8.4–22.5)	13.5 (9.2–23.0)	0.614
Prothrombin fragment 1+2 (pmol/L)	538 (231–837)	495 (353–789)	0.576
End of CPB			
Hemoglobin (g/dL)	9.0±0.8	9.1±1.2	0.882
Hematocrit (%)	26.7±2.4	27.1±3.7	0.634
Platelet count (10 ⁹ /L)	9.4±3.5	10.8±4.2	0.131
Fibrinogen (mg/dL)	173.2±86.6	184.5±85.7	0.593
Antithrombin activity (U/mL)	52.1±14.1	56.9±12.2	0.125
Fibrin degradation products (μg/mL)	5.4 (3.3–10.1)	4.6 (3.1–9.1)	0.533
D-dimer (μg/mL)	1.9 (0.7–4.3)	1.5 (0.7–3.3)	0.698
TAT (pmol/L)	41.9 (14.8–60.0)	30.0 (19.5–60.0)	0.701
Prothrombin fragment 1+2 (pmol/L)	818 (540–1,200)	961 (695–1,200)	0.62
End of surgery			
Hemoglobin (g/dL)	9.9±0.7	10.4±1.2	0.066
Hematocrit (%)	29.5±2.3	32.1±3.3	0.031
Platelet count (10 ⁹ /L)	8.9±3.0	11.0±3.6	0.018
PT-INR	1.3 (1.3–1.4)	1.3 (1.2–1.4)	0.285
PT (s)	15.6±2.1	14.6±1.8	0.715
APPT (s)	40.7±9.5	38.6±6.5	0.721
Fibrinogen (mg/dL)	240.1±72.8	253.0±76.6	0.497
Antithrombin activity (U/mL)	62.8±9.3	65.5±12.4	0.358
Fibrin degradation products (μg/mL)	7.3 (4.0–10.8)	6.0 (4.1–10.7)	0.831
D-dimer (μg/mL)	1.8 (0.9–5.1)	2.0 (1.2–3.3)	0.856
TAT (pmol/L)	60.0 (49.7–60.0)	50.6 (35.8–60.0)	0.252
Prothrombin fragment 1+2 (pmol/L)	1,200 (1,080–1,200)	1,200 (1,035–1,200)	0.574

Data are mean±standard deviation or the median (interquartile range) for continuous variables. APTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; INR, international normalized ratio; PT, prothrombin time; TAT, thrombin-antithrombin complex.

($P=0.025$ and $P=0.001$, respectively, **Table 1**). Patients who experienced excessive postoperative bleeding also received a significantly higher dose of heparin ($P=0.022$, **Table 1**) and had a significantly lower hematocrit and platelet count at the end of surgery ($P=0.031$ and 0.018 , respectively, **Table 2**), compared with patients without excessive blood loss.

The multivariate analysis, which included variables with $P<0.05$ in the univariate analysis, showed that the platelet count at the end of surgery was independently associated with lower postoperative blood loss (odds ratio (OR) 0.780, 95% confidence interval (CI) 0.629–0.967, $P=0.024$, **Table 3**). The OR value, 0.780, was equivalent to an increase in the platelet count of $1 \times 10^4/\mu\text{L}$. The requirement for

Table 3. Multivariate Analysis for Statistically Significant Variables Influencing Postoperative Blood Loss in the Univariate Analysis (P<0.05)

Parameters	OR	95% CI	P value
Requirement for intraoperative FFP transfusion (n, %)	3.367	0.960–11.815	0.058
At the end of surgery			
Platelet count (for every $1 \times 10^9/L$ increase)	0.780	0.629–0.967	0.024
Hematocrit (for every 1% increase)	0.880	0.733–1.056	0.169
Total heparin dose (for every 100 IU increase)	1.008	0.997–1.020	0.159

CI, confidence interval; FFP, fresh frozen plasma; OR, odds ratio.

intraoperative FFP transfusion (OR 3.367, 95% CI 0.96–11.815, $P=0.058$) and total heparin dose (OR 1.008, 95% CI 0.997–1.02, $P=0.159$, where a value of 0.1 mL of the dose was equivalent to an increase of 100 IU of heparin) were negatively associated with postoperative blood loss. No significant relationship was observed in the multivariate analysis between blood loss and the volume of FFP transfused. Although combined procedures (defined as any procedure other than isolated coronary artery bypass grafting, valve surgery or repair of a septal defect) were a significantly higher proportion among the patients with excessive blood loss group, it was removed from the multivariate analysis because of the ambiguous definition.

Discussion

Coagulopathy after CPB is caused by many factors, including disturbed hemostatic function caused by hemodilution, coagulation factor depletion, platelet dysfunction, heparin rebound and activation of the fibrinolytic system.^{11–14} In this study, a low platelet count at the end of surgery was associated with greater postoperative blood loss, even when FFP was administered according to the ROTEM protocol. These findings suggest that ROTEM-guided FFP transfusion alone is not sufficient to guide the overall hemostatic strategy and maintenance of the platelet count would further improve coagulation management. In contrast with the findings of other studies,^{9,15} however, the change in fibrinogen concentration and absolute fibrinogen concentration in this study did not contribute significantly to postoperative blood loss. Taken together, our findings suggested that the ROTEM-guided use of FFP accurately predicted coagulopathy, allowing for correction and maintenance of the fibrinogen concentration in this patient population.

This was not a novel finding that low platelet count at the end of surgery was associated with high postoperative blood loss. Indeed, it is well recognized that patients with thrombocytopenia¹⁶ or platelet dysfunction^{17–19} are at markedly higher risk for postoperative blood loss. Importantly, the patients in this study, who were undergoing elective cardiac surgery with ROTEM-based coagulation management, had demographic characteristics and pre-CPB and post-CPB coagulation function that were not significantly associated with blood loss, whereas a low platelet count after hemostatic therapy at the end of surgery was associated with excessive loss.

Platelet counts in this study decreased by approximately 30–40% during CPB and were still low even after platelet transfusion at the end of surgery. This phenomenon could be attributed to a combination of increased platelet consumption caused by coagulation activation, hemodilution,

adherence to the CPB circuit surface or accelerated clearance caused by thrombin-mediated activation.²⁰ We found that each $10 \times 10^9/L$ increase in platelet count at the end of surgery was associated with an OR of 0.780 (95% CI 0.629–0.967), and a likelihood of excessive postoperative blood loss ($P=0.024$). This finding concurs with a study conducted by Orlow and colleagues,²¹ who reported that each $10 \times 10^9/L$ increase in collagen-activated functional platelet count during rewarming and after protamine administration was associated with relative risks of 0.89 and 0.87, respectively, for high blood loss.

Laboratory test results, including a complete blood count, are not available immediately, and POC devices are a useful, rapid and accurate means of predicting thrombocytopenia. A ROTEM device predicts the platelet count by calculating the platelet component of coagulation based on clot elasticity,²² which reflects the force with which the blood clot resists rotation within the device.²³ In this study, after logarithmic transformation of the platelet count and linear regression analysis using the maximum clot elasticity (MCE) in EXTEM as the dependent variable (y) and \log_{10} [platelet count] as the independent variable (x), positive correlations were found (MCE prediction equation $y=27.02+95.93x$, $R^2=0.310$, $P<0.001$). The platelet component reflected by MCE EXTEM–MCE FIBTEM was also related to the logarithm of the platelet count described by the following equation: MCE EXTEM–MCE FIBTEM $y=15.05+94.29x$ ($R^2=0.254$, $P<0.001$).

A previous report that there was only a moderate correlation between platelet count and platelet aggregation during cardiac surgery further supports the concept that the platelet count alone is not an adequate means of assessing platelet function.²⁴ Monitoring the platelet count in parallel with platelet function, the latter measured by techniques such as impedance aggregometry, modified viscoelastometry or flow cytometry, would allow prompt and appropriate treatment to avoid coagulopathy at the end of surgery. The platelet-mapping assay is a modification of thromboelastography, which measures clot strength as a reflection of platelet function, and detects the reduction in percentage platelet aggregation in the presence of collagen, adenosine diphosphate or arachidonic acid. It was designed to be used for evaluating multiple platelet receptors and the role of altered receptor activity. Weitzel et al reported that platelet aggregation as measured using collagen predicted postoperative bleeding following CPB with a sensitivity of 83% and a specificity of 68%.²⁵

In the present study, optimizing the heparin dose to achieve a target ACT based on the heparin dose-response technique and calculation of the protamine dose by using the protamine titration technique led to higher doses of heparin and lower doses of protamine relative to the heparin

dose.^{26,27} Administration of a protamine dose lower than that of a fixed-dose regimen might avoid the potential toxicity of protamine,^{28,29} which inhibits thrombin-induced platelet aggregation and might restore platelet reactivity to thrombin, which is depressed during CPB. However, a lower protamine dose might also increase the risk of bleeding caused by residual circulating heparin, which is a result of incomplete heparin reversal after neutralization³⁰ or heparin rebound³¹ and characterized by heparin reactivation following initial adequate neutralization. Heparin rebound occurs because not all the heparin is bound to, and thus cleared by the protamine.³² In this situation there is a proportion of heparin that is bound non-specifically to plasma proteins and vascular cells, thereby leaving a heparin reservoir.³³ Another factor is the difference in the pharmacokinetic half-lives of protamine and heparin.³⁴

In our previous study,³⁵ the blood heparin concentration was elevated in all patients 2 h after protamine neutralization despite administration of heparin doses calculated by the Hepcon HMS. In the same study, approximately 70% of patients exhibited positive heparin results when assayed a few minutes after the administration of protamine, indicating incompletely reversed heparin, and the remaining 30% exhibited true heparin rebound. However, the peak heparin level of 0.18 ± 0.07 U/mL at 4 h after protamine administration did not significantly correlate with the total blood loss during the first 24 h after surgery. This might be consistent with our finding in the present study that a significantly larger intraoperative heparin dose was observed in patients with excessive blood loss but was not associated with postoperative blood loss.

Use of the Hepcon HMS is a safe and expedient method of neutralizing active circulating heparin in patients following CPB and reducing excessive postoperative blood loss associated with incompletely reversed heparin and/or heparin rebound.

In this study, thrombin generation measured by F1+2 and TAT at baseline did not differ significantly between the groups. It has previously been reported that patients with low preoperative thrombin generation were more susceptible to developing CPB-associated coagulopathy than those with higher preoperative thrombin generation for greater hemostatic reserve.^{36,37} Despite maintaining what is generally considered to be adequate anticoagulation with heparin to maintain an ACT of 450 s during cardiac surgery, we found increased plasma concentrations of F1+2 and TAT at the end of surgery in both groups, with no significant difference between the groups. Thrombin formation is the key regulatory step in hemostasis and thrombosis, as well as activating coagulation factors V, VIII, XI and XIII, and converting fibrinogen to fibrin.^{38,39} Stimulation of thrombin receptors on the platelet surface results in platelet activation and aggregation.⁴⁰ In addition to its prothrombotic role, thrombin is capable of modifying the thrombotic response by triggering the release of tissue plasminogen activator from the endothelial surface. However, excessive thrombin formation during CPB would deplete plasma coagulation factors, and cause platelet dysfunction and hyperfibrinolysis, all of which have been observed during cardiac surgery. In this study, significantly increased thrombin formation was observed in both groups but was not associated with postoperative blood loss.

Study Limitations

First, our definition of excessive postoperative blood loss

was relatively small (528 mL) because ROTEM-based FFP administration substantially reduces perioperative blood loss. This study was performed preliminarily to identify a patient population that has an increased risk of bleeding despite the use of thromboelastometry guidance to inform blood management strategy. Blood loss from the end of CPB until operating room discharge was not included in postoperative blood loss because it was included in the intraoperative blood loss. Second, the sample size was relatively small, and the scope of laboratory variables measured was limited. Our results may have been influenced by potentially biasing or unmeasured confounding factors, illuminating associations, rather than cause and effect relationships, in what is a snapshot of a complex, dynamic association between coagulation status and postoperative blood loss. Consequently, our findings may not be generalizable to other practices. Further study is required to confirm our results.

In conclusion, our post hoc analysis of 97 patients undergoing cardiac surgery with CPB and who were administered FFP based on a ROTEM-guided algorithm found that low platelet count at the end of surgery was associated with high postoperative blood loss. These findings may help identify patients at risk of excessive postoperative bleeding and could inform the development of broader, more comprehensive blood management strategies using the ROTEM-based FFP transfusion protocol. The validity and generalizability of our findings should be assessed in larger, multicenter studies.

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