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Association of Plasma Fibrinogen and Thromboelastography With Blood Loss in Complex Cardiac Surgery

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Abstract

Postoperative coagulopathic bleeding is common in cardiac surgery and is associated with increased morbidity and mortality. Ideally, real-time information on in-vivo coagulation should be available. However, up to now it is unclear which perioperative coagulation parameters can be used best to accurately identify patients at increased risk of bleeding. The present study analyzed the associations of perioperative fibrinogen concentrations and whole blood viscoelastic tests with postoperative bleeding in 89 patients undergoing combined cardiac surgery procedures. Postoperative bleeding was recorded until 24 hours after surgery. Regression analyses were performed to establish associations between blood loss and coagulation parameters after cardiopulmonary bypass including a prediction model with known confounding factors for bleeding. Coagulation tests show large changes over the perioperative course with the strongest coagulopathic deviations from baseline after cardiopulmonary bypass. After adjustment for multiple confounders, viscoelastic clot strength instead of fibrinogen concentration showed a similar performance for 24 hour blood loss and a better performance for 6 hour blood loss. This makes intraoperative viscoelastic testing a useful tool to strengthen early clinical decision-making with the potential to reduce perioperative blood transfusions.

Keywords

postoperative blood loss, cardiac surgery, fibrinogen, viscoelastic testing

Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) is associated with coagulopathy and bleeding.[1] Patients with increased perioperative blood loss are at risk for postoperative morbidity and mortality.[2-5] The etiology of coagulopathy in cardiac surgery patients is multifactorial and varies according to the surgical phase (i.e. preoperative, intraoperative, postoperative). Relevant and immediately available information about perioperative hemostasis is necessary to target interventions that reduce bleeding. Ideally, real-time information on in-vivo coagulation should be available. However, up to now it is unclear which perioperative coagulation parameters can be used to accurately identify patients at increased risk of postoperative bleeding.

Plasma fibrinogen is a key coagulation factor[6] that has been associated with blood loss in cardiac surgery patients.[7-9] The Clauss fibrinogen assay is considered the gold standard to determine the plasma fibrinogen concentration, but the long turn-around time makes this test less suitable for timely clinical decisions. Point of care (POC) viscoelastic tests are available in the operating theatre for real time in-vitro coagulation assessment to guide patient blood management.[10,11] The use of POC viscoelastic testing has been associated with a reduction of inappropriate blood transfusions in cardiac surgery.[11,12] It remains, however, unclear whether this reduction was due to the use of POC viscoelastic testing or other factors such as

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behavioral changes.[13] Thus, the additional value of POC viscoelastic tests for postoperative bleeding in cardiac surgery patients is still unclear.

The present study aimed to analyze the associations of perioperative fibrinogen concentrations and POC viscoelastic tests with postoperative blood loss in patients undergoing complex cardiac surgery.

Patients and Methods

Study Design

Recently, we studied the effects of perioperative platelet function on postoperative blood loss.[14] This was a prospective observational single center cohort study in patients undergoing elective surgery for combined coronary artery disease (CABG) and valvular heart disease or isolated multiple heart valve disease at a large tertiary hospital for cardiac surgery between april 1st 2015 and may 1st 2016. Ethical approval was provided by the local ethics committee (Medical Ethics Research Committee United, no. NL51434.100.14). One-hundred patients gave informed consent upon hospital admission. The study was performed in accordance with the Declaration of Helsinki. Now, we analyzed in the same population fibrinogen concentrations and results of viscoelastic testing. In short, routine laboratory coagulation tests and viscoelastic coagulation tests were performed at 4 perioperative time points with the intention to investigate their usefulness for the prediction of postoperative blood loss. For detailed information on clinical management and study methods we refer to our recent publication.[14]

Data Collection and Study Procedures

Data regarding medical history, preoperative drug therapy and perioperative care was collected from electronic medical records by a member of the study team. Blood samples for coagulation tests were collected in all patients at 4 time points: (i) at baseline after induction of anesthesia, (ii) during CPB after initiation of rewarming from hypothermia, (iii) after CPB decannulation and administration of protamine and (iv) after arrival at the ICU. Routine coagulation assays were performed at the hospital laboratory and included: platelet count (PC), Clauss fibrinogen (STA-R Evolution analyzer, Diagnostica STAGO, Asnières sur Seine, France), protrombin time (PT), and Cephotest. Cephotest is a heparin-sensitive aPTT and expressed as ratio prolongation compared to a normal pool aPTT. Whole blood for routine coagulation assays was sampled 3.2% sodium citrate tubes (BD Vacutainer). Viscoelastic Point of Care (POC) thromboelastography (TEG) assay (TEG 5000-analyzer, Haemonetics Inc., Braintree, MA, USA) was performed in non-anticoagulated whole blood at the operating theatre by a research professional within 5 minutes after sampling. Viscoelastic assays were performed with plain kaolin activated TEG at time points i, iii, iv and kaolin activated TEG with 2 IU heparinase at time point ii. Plain kaolin activated TEG data were collected as part of the study and were not available for the attending anesthetist or surgeon. Viscoelastic POC parameters included: kaolin initiated clotting time (R; min.), initial clot kinetics with K time (K; min), propagation rate of coagulation (angle; degrees) and clot strength with maximum amplitude (MA; mm).

Blood Transfusion and CPB Management

Blood transfusion was performed according to our local transfusion protocol with an intraoperative transfusion trigger for red blood cell (RBC) transfusions (hematocrit <0.20 l/l during CPB or <0.25 l/l after CPB). The RBC transfusion trigger on the intensive care unit (ICU) was a hemoglobin value (Hb) of less than 4.4 mmol/l (7.1 g/dl). Intraoperative transfusion of blood products to treat coagulopathy were based on kaolin-heparinase (ii) TEG parameter R time less than 10 minutes or α-angle less than 45° for plasma and MA less than 45 mm for platelet concentrate. The postoperative decision to transfuse was left to the discretion of the ICU team. Coagulopathy after ICU arrival was defined as bleeding (>300 ml during 1st hour and >150 ml during 2nd-3th hours) in combination with coagulopathy. Postoperative triggers for platelet and/or plasma blood transfusion were low PC (<$100x10^9$/l) or extended cephotest (>1.4) with clinical signs of coagulopathy. Coagulation factor concentrates were no part of the hemostasis management during the study period. Intra-operative cell salvage (CS) was routinely used during surgery. The volume of transfused autologous blood was registered as CS reinfused.

During surgery all patients were anticoagulated with 300 IU/kg intravenous unfractionated heparin before CPB to achieve a kaolin activated clotting time (ACT target > 400 s) and patients were cooled to a rectal temperature of 32°C to 34°C. Additional heparin was given when needed to keep ACT above target. After CPB, heparin was reversed with protamine sulfate; 0.75 mg for every 100 U of total heparin dose administered during CPB. Tranexamic acid (1-2 g) was administered to all patients.

Outcomes

The primary outcome measure was chest tube drainage volume (ml blood loss) at 24 hours after cardiac surgery. Secondary outcome parameters were blood loss after 6 hours, reoperation for bleeding until 24 hours after surgery, and hospital mortality.

Statistical Analysis

As data from a previous study was used,[14] no formal sample size calculation was performed for this study. Normal distribution of variables was assessed with visual inspection of the histograms. Continuous data are presented as mean and standard deviation or median and interquartile range (IQR) for normally and non-normally distributed data. Categporical data are described as numbers and percentages. The Student's t-test and the Mann-Whitney U-test were used to compare independent continuous variables between groups for normally and non-normally distributed variables respectively. No adjustment

for multiple testing was performed. Percentage of change for coagulation parameters between baseline and nadir values were calculated.

The correlation between TEG and fibrinogen and the correlation between coagulation parameters and postoperative blood loss were explored using Pearson's correlation coefficient. The association between blood loss and TEG after CPB was explored using linear regression analysis including a multivariable model with a priori selected confounding factors that were based on previously described risk factors for blood loss after cardiac surgery, including gender, body mass index, eGFR-MDRD4 (estimated glomerular filtration rate by modification of diet in renal disease 4 variable equation), baseline hemoglobin and CPB time.[15-19] All analyses were repeated using fibrinogen as the coagulation parameter. No interactions were investigated. To assess the discriminatory ability of coagulation parameters for postoperative blood loss, overall model performance was reported by the coefficient of determination R^2. R^2 ranges from 0 to 1, with higher values indicating better model performance.

For statistical analysis IBM SPSS software version 24.0 for Windows was used (IBM Corp., Armonk, NY, USA). A P value <0.05 was considered statistically significant.

Results

Study Population and Outcomes

In the present study ten patients with a P2Y12 inhibitor were excluded, and 1 patient was excluded because information on postoperative blood loss was missing. As a result, 89 patients were included in the analysis. Baseline characteristics of the study population are presented in Table 1. Sixty-two (69.7%) patients were male, median age was 73 [68-77] years, and the most commonly performed surgical procedure was CABG combined with single valve surgery. Median postoperative blood loss was 270 [190-400] ml after 6 hours and 540 [430-730] ml after 24 hours. Forty two patients (47.2%) received one or more allogeneic blood transfusions during surgery (Table 2). Postoperative hospital mortality was 3.4% (n=3).

Table 1. Baseline Patient and Surgery Characteristics.[a]

	Frequency (n)	Missing
Patient characteristics		
Male gender, n (%)	62 (70)	0
Age (yr)	73 [68-77]	0
Body mass index (kg m^{-2})	26 [25-29]	1
Diabetes mellitus, n	13	1
Hypertension, n	42	0
Hypercholesterolemia, n	36	5
Smoking, n	25	0
Acetylsalicylic acid, n (%)	49 (55)	0
Laboratory		
Hemoglobin (mmol/l)	7.5 [6.8-8.1]	0
eGFR-MDRD4 (ml/min/1.73m^2)	57 ± 7	0
Type of surgery		
CABG + single valve	66	0
CABG + multiple valve	9	0
Multiple valve surgery	14	0
Number of grafts, median (range)	1 (4)	0
Procedural characteristics		
Volume CS reinfused (ml)	500 [300-790]	0
CPB time (min)	150 [120-180]	0
Lowest body temperature (°C)	34.8 [34.1-35.6]	2
Temperature at ICU arrival (°C)	35.9 [35.5-36.2]	2

Abbreviations: CABG; coronary artery bypass graft, CPB; cardiopulmonary bypass, CS; cell salvage, eGFR-MDRD4; glomerular filtration rate, ICU; intensive care unit.
[a]Values are median [IQR], mean ± or number (percentage).

Table 2. Allogeneic Blood Transfusions.

	Intra-operative			Post-operative			Total	
Transfusion	N	%	Median [IQR]	N	%	Median [IQR]	N	%
RBC	36	40	2 [1-2]	8	9	1 [1 -1]	38	43
Plasma	13	15	2 [2-3]	4	4	2 [2-3]	16	18
TC	16	18	1 [1-1]	7	8	1 [1-1]	23	26
Total	42	47	2 [1-3]	16	18	1 [1-2]	49	55

Abbreviations: RBC; red blood cells, TC; thrombocyte concentrate with transfusion; N; number of patients, %; percentage of patients and Median number of units in transfused patients.

Fibrinogen Concentrations and TEG Results

Perioperative plasma fibrin ogen concentrations are presented in Table 3. In all patients plasma fibrinogen concentrations were lower during surgery compared to baseline. The maximum relative decrease in fibrinogen concentration was 41 [36-48] % with the lowest fibrinogen concentration occurred after CPB (1.7 [1.5-2.2] g/l). At ICU arrival, the median fibrinogen concentration was 1.8 [1.6-2.3] g/l and below lower reference limit of 2.0 g/l in 56% of patients.

Perioperative POC TEG results are presented in Table 3. TEG values deviated strongest from baseline after CPB. The maximum relative decrease after CPB was 16 [12-21] % for TEG-MA and 8 [0-16] % for TEG-angle. The correlations between fibrinogen and TEG values are presented in supplementary Table A. From all TEG variables, plasma fibrinogen concentrations were best correlated with TEG-MA, with the highest correlations at baseline (r=0.693, P<0.001) and after CPB (r=0.688, P <0.001).

Coagulation Tests and Postoperative Blood Loss

The correlations between coagulation test results and postoperative blood loss are presented in supplementary Table B. At all perioperative time points, the fibrinogen concentration was correlated with 24 h blood loss. The strongest correlation was present after ICU arrival (r=-0.291, P=0.007). The correlation between fibrinogen and 6 h blood loss was only significant after ICU arrival. Several TEG values were correlated with postoperative blood loss. After CPB, TEG-MA was correlated with 6 h and 24 h blood loss (r=-0.324, P=0.004 and

Table 3. Results of Routine and Viscoelastic Coagulation Assays.

	Baseline	CPB	Post-CPB	ICU
Laboratory				
Platelet count (x10^9/l)	193 [160-222]	125 [105-158]	90 [72-112]	112 [93-136]
PT (s)	15 [14-16]	23 [21-26]	22 [20-24]	19 [18-21]
Cephotest	1.0 [1.0 -1.0]	6.0 [6.0-6.0]	1.3 [1.2 -1.4]	1.2 [1.1 -1.3]
Fibrinogen (Clauss; g/l)	3.1 [2.7-3.6]	1.8 [1.6-2.3]	1.7 [1.5-2.2]	1.8 [1.6-2.3]
TEG assay				
R (min)	7.1 [6.0-8.4]	7.0 [5.8-8.4]	7.4 [6.3-10.2]	6.3 [5.2-7.5]
K (min)	1.6 [1.4 -1.8]	1.8 [1.5-2.2]	2.1 [1.8-2.7]	1.9 [1.6-2.2]
Angle (°)	67 [63-71]	64 [59-69]	60 [56-66]	63 [58-68]
MA (mm)	70 [67-73]	59 [56-63]	58 [54-62]	60 [57-65]

Abbreviations: PT, protrombin time; INR, international normalized PT ratio; TEG, thromboelastography; R, kaolin initiated clotting time; K, clot kinetics; MA, clot strength with maximum amplitude.

Table 4. Adjusted Associations for Fibrinogen Concentration and Clot Strength With Postoperative Blood Loss.

	Multivariable model							
	6 h blood loss				24 h blood loss			
	Fibrinogen		TEG-MA		Fibrinogen		TEG-MA	
	B	*P*	B	*P*	B	*P*	B	*P*
Gender	120.50	0.002	115.10	0.002	175.0	0.004	147.45	0.010
BMI	-9.61	0.018	-11.17	0.004	-13.60	0.029	-14.82	0.014
eGFR	2.18	0.315	2.97	0.141	3.10	0.351	4.59	0.147
Hb	18.50	0.331	6.38	0.760	18.93	0.516	8.10	0.805
CPB time	-0.27	0.413	-0.19	0.532	-0.31	0.532	-0.30	0.537
Fibrinogen Post CPB	-53.28	0.104			-107.65	0.033		
TEG-MA Post-CPB			-7.43	0.005			-9.28	0.022
R^2 model	0.278	<0.001	0.345	<0.001	0.271	<0.001	0.268	0.001

Abbreviations: B, unstandardized B; BMI, body mass index; CPB time, cardiopulmonary bypass time (min); eGFR, estimated glomerular filtration rate by modification of diet in renal disease 4 variable equation (ml/min); Hb, hemoglobin at baseline (mmol/l); TEG-MA, thromboelastography maximum clot strength.

r=-0.267, P=0.017, respectively). At ICU arrival, TEG MA was no longer associated with postoperative blood loss.

After adjustment for confounders, fibrinogen and TEG-MA after CPB had the strongest association with postoperative blood loss (Table 4). Compared to fibrinogen, TEG-MA after CPB showed the best model performance for 6 h blood loss (R^2 =0.345 compared to 0.278 for fibrinogen). Model performance for 24 h blood loss was similar between TEG-MA and fibrinogen (R^2 =0.268 compared to 0.271 for fibrinogen).

Comment

This observational study in patients undergoing complex cardiac surgery showed that perioperative fibrinogen concentrations were associated with postoperative blood loss. After adjustment for multiple confounders, the strongest association between blood loss and fibrinogen was present after CPB. A multivariable model that included viscoelastic clot strength instead of fibrinogen concentration after CPB showed a similar performance for 24 h blood loss and a better performance for 6 h blood loss.

The results of our study including intraoperative coagulation tests before, during and after CPB and postoperative tests after ICU arrival provides a better understanding of the variations in perioperative TEG and fibrinogen levels. We confirmed that perioperative fibrinogen concentrations are associated with blood loss after cardiac surgery.[8,20,21] In contrast to prior reports, we demonstrated that fibrinogen concentrations in the final surgical phase (after CPB) were best associated with 24 hour blood loss, after adjustment for multiple risk factors for postsurgical bleeding.[7,9,22-24] Furthermore, our data illustrated that coagulation test results show large changes over the perioperative course and that the strongest deviations from baseline were present after CPB. As a result, one could advocate to perform multiple coagulation assays to monitor hemostatic conditions after CPB. However, only TEG MA and plasma fibrinogen were significantly correlated with postoperative blood loss. The adjusted value of TEG MA instead of fibrinogen concentration after CPB was higher for 6 h blood loss and the performance was similar for 24 h blood loss.

Viscoelastic tests measure multiple components of hemostasis, which allows for a rapid assessment of hemostasis. The

results of our study confirmed that TEG MA after CPB was correlated with postoperative blood loss.[25,26] In comparison, another study showed that post CPB rotational thromboelastometry (ROTEM) was best associated with blood loss after including significant covariates (model performance R^2 0.275).[27] While it is difficult to compare studies due to variations in study design, and although TEG and ROTEM values are not interchangeable, both studies demonstrated that post CPB POC coagulation testing can be used to predict postoperative blood loss. As a result, intraoperative viscoelastic testing is a useful tool to strengthen early clinical decision-making and has the potential to reduce perioperative blood transfusions with consequently blood product cost savings.[28-30]

The following limitations should be considered. The data were prospectively and consecutively collected, but our sample size is limited. Furthermore, our patients had relatively low volumes of blood loss. Although different fibrinogen concentrations were correlated with blood loss, a linear relation cannot be assumed because hemostasis depends on a series of complex interactions between both cellular and protein components of coagulation.[31] Similar to previous literature reports, our models have rather low R^2 values, suggesting that while adjusted for known confounding risk factors for blood loss, much of the variation in blood loss is related to unobserved characteristics. Each surgical procedure is distinctively unique with several decisions and interventions that influence blood loss.

In conclusion, perioperative fibrinogen concentrations are associated with blood loss after cardiac surgery and a model including viscoelastic clot strength or plasma fibrinogen concentration after CPB can be used to predict postoperative blood loss. However, perioperative coagulopathy is characterized by constantly changing derangements of coagulation that can only be partly assessed with a single coagulation test.

Since TEG became daily routine during cardiac surgery in our hospital, the maximum clot strength after CPB has become the fastest and most useful parameter for guiding our hemostatic management until now. In the future, an improved understanding of the multiple features of coagulation dynamics may lead to new monitoring strategies and ameliorated standardization of global hemostasis assays to further support clinical decision making.

Trial registry number: This study has been registered in the Nederlands (Dutch) Trial Register with number NTR 4984.

Declaration of Conflicting Interests

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Supplemental Material

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