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Change in fibrinogen levels and severe postoperative bleeding in cardiac surgery

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Thromboelastography or rotational thromboelastometry, is being increasingly utilized in cardiac surgery of late. However, it is an indirect test and is not available in all centers. Low fibrinogen levels before and after cardiopulmonary bypass (CPB) have been described to be associated with postoperative bleeding in cardiac surgery. This study explored the usefulness of reduction ratio of the fibrinogen levels before CPB (preCPB) and after CPB (postCPB) in predicting postoperative hemorrhage. A retrospective, observational study of adult patients who underwent cardiac surgery with CPB between February 2014 and January 2016 was conducted, which included a total of 264 patients. The fibrinogen levels were measured twice, preCPB and postCPB, and the fibrinogen reduction ratio was acquired [(preCPB − postCPB)/preCPB]. Postoperative blood loss, which was defined as the blood collected from the chest drain for 12 hours following arrival at the intensive care unit, was considered severe if it was more than 1,000 mL. A multivariate analysis showed that fibrinogen reduction ratio, sex, and postCPB platelet count were significantly associated with severe postoperative bleeding. However, the pre- and postCPB fibrinogen levels were not significantly associated with severe bleeding. Furthermore, a fibrinogen reduction ratio of > 41.3% was independently associated with postoperative severe bleeding, with an odds ratio of 3.472 (1.483–8.162). These results suggest that the reduction ratio of pre- and postCPB fibrinogen levels may be utilized in predicting postoperative bleeding.

Keywords: Cardiopulmonary bypass, Fibrinogen, Postoperative hemorrhage

Introduction

Severe bleeding and transfusion after cardiac surgery are associated with various complications, which increase morbidity and mortality [1]. The main causes of bleeding after or during cardiac surgery include preoperative anti-thrombotic medication, residual heparin effects, surgical trauma, platelet dysfunction, dilution coagulopathy, and hypothermia; the latter three are caused by cardiopulmonary bypass (CPB) [2]. Fibrinogen is a plasma protein that is important for coagulation [3]. A low fibrinogen level after cardiac surgery is an important indicator of acquired coagulopathy. Fibrinogen levels before and after CPB are correlated with bleeding after cardiac surgery [4-6]. However, the meta-analysis revealed that the correlation between

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fibrinogen levels and bleeding is significant, but not strong [4].

Although central laboratory coagulation tests are commonly utilized in pre- and postoperative coagulation management, they have disadvantages. For example, platelets and other blood cellular components are not considered, as the test does not use the whole blood sample. The time allowed is also not enough for coping with critical condition changes in patients undergoing cardiac surgery. In contrast, the use of thromboelastography (TEG) or rotational thromboelastometry, as a point-of-care (POC) test, overcomes these drawbacks and the results are consistent with the central laboratory coagulation test results [7]. Several recent studies have examined the extent of postoperative bleeding that occurs when using TEG or fibrinogen-thromboelastometry (FIBTEM, which is for the detection of fibrinogen deficiency or fibrin polymerization disorders) [8,9]. However, these POC tests do not measure fibrinogen levels; rather, they measure the fibrinogen-based clot firmness. Therefore, fibrinogen administration based on these indirect tests could lead to complications and increased costs. In addition, these POC tests are still not available in many centers.

Therefore, the aim of this study was to determine whether the reduction ratio of fibrinogen levels before and after CPB is associated with, and predictive of, postoperative bleeding.

Materials and Methods

1. Study design and patient population

A retrospective, observational study of adult patients who underwent cardiac surgery with CPB between February 2014 and January 2016 was conducted. The Research Ethics Committee of the Pusan National University Yangsan Hospital Clinical Trial Center waived the requirement for informed consent and IRB review (05-2017-005).

The following types of cardiac surgery qualified for inclusion: coronary artery bypass grafting (CABG), valve replacement, aortic surgery (Bentall surgery, David surgery), atrial or ventricular septal defect closure, and myxoma removal surgery. Data from open-heart surgery with sternotomy and minimally invasive cardiac surgery with thoracotomy were included. Patients were excluded if they underwent surgery without CPB (e.g., off-pump CABG), had perioperative extracorporeal membrane oxygenation (ECMO) insertion, underwent reoperation due to hemorrhage within 12 hours of surgery, or died. In addition, patients with missing laboratory tests were excluded.

2. Clinical practice

Antiplatelet drugs (including warfarin and clopidogrel) were usually discontinued 4–7 days before surgery, except in cases of emergency surgery.

Anesthesia induction was performed following the cardiac anesthesia protocol of Pusan National University Yangsan Hospital using propofol, rocuronium or cisatracurium, remifentanil, and sevoflurane. Standard, bispectral index, and cerebral oximeter monitoring were undertaken, involving assessments of oxygen saturation, non-invasive blood pressure, echocardiography, and body temperature (measured at the nasopharynx and rectum). Peripheral arterial cannulation and central venous catheterization were performed. Hemodynamic parameters including arterial blood pressure, pulse pressure variation, central venous pressure, cardiac output, systemic vascular resistance, stroke volume variation, and central venous oxygen saturation were also monitored.

Most surgeries were performed with CPB under moderate hypothermia (32–34℃) or deep hypothermia (20–28℃), as required. The CPB circuit priming consisted of plasma solution A, normal saline (0.9% sodium chloride), sodium bicarbonate (NaHCO3 8.4%/20 mL), albumin (20%), and mannitol (15%). Alpha-stat pH management was performed and the target perfusion pressure was 50–70 mmHg. Anticoagulation during CPB was maintained at an activated clotting time (ACT) > 450–480 seconds using unfractionated heparin (250–300 U/kg with additional dosing as necessary). After CPB, heparin reversal was performed using protamine sulfate to sustain the ACT within 10% of the baseline and supplement it when required. No anti-fibrinolytic agent was administered during surgery. After CPB weaning, an anti-fibrinolytic agent (tranexamic acid 2 g) was administered according to the judgment of the physician and anesthesiologist. The perioperative transfusion protocol was performed using standard transfusion guidelines. Packed red blood cell transfusions were performed in stable patients with hematocrit (Hct) levels < 20% and in patients with < 30% Hct during CPB with severe bleeding or unstable hemodynamic status. Platelets, fresh frozen plasma (FFP), and cryoprecipitate were transfused according to protocol and usually based on the results of platelet count and prothrombin time-international normalized ratio (PT-INR) tests by the surgeon and anesthesiologist depending on the situation during surgery (e.g., oozing or a continuous wet condition). After the surgery, the patient was transferred to the intensive care unit (ICU).

3. Laboratory testing

Preoperative assessments included the complete blood count (CBC), PT-INR, activated partial thromboplastin time (aPTT), liver renal function test (LRFT), electrolyte levels, cardiac marker B-type natriuretic peptide (BNP) level, and an arterial blood gas analysis (ABGA). Fibrinogen levels were not measured separately before surgery.

After the induction of anesthesia, patients underwent baseline blood tests for ABGA, CBC, fibrinogen, and the ACT. During surgery, POC tests (ABGA and ACT) were performed 10–15 minutes before initiating CPB, and every 30 minutes after initiating CPB. Fibrinogen and CBC tests were performed after the aortic cross-clamping (ACC) was released and protamine (which is heparin reversal agent) was administered before CPB weaning. ABGA and ACT were performed 10 minutes later. Following this, ABGA and ACT were performed depending on the patient's condition. The CBC and fibrinogen tests took within 30 minutes and were performed by the central laboratory of the hospital. Pre-post (difference in fibrinogen between preCPB and postCPB) and fibrinogen reduction ratio [(preCPB – postCPB)/preCPB] were calculated.

4. Outcomes

Postoperative blood loss was assessed by blood volume collected via the chest tube drain during the first 12 hours in the ICU. According to the modified criteria of the Universal Definition of Perioperative bleeding, severe bleeding was defined as more than 1,000 mL during the first 12 hours in the ICU [10].

5. Statistical analysis

Patients were grouped into two based on 12-hour bleeding volume: < 1,000 mL and > 1,000 mL. Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as means and standard deviations or medians and interquartile ranges. Patient characteristics, CPB time, ACC time, postCPB laboratory tests, and fibrinogen levels before and after CPB were compared using the independent *t*-test. The Wilcoxon test was used for continuous variables and the chi-square test for categorical variables. Univariate and multivariate logistic regression analyses were performed to identify factors significantly associated with postoperative severe bleeding. The multivariate logistic regression analysis was performed on patient characteristics and coagulation parameters significantly associated with postoperative severe bleeding

Table 1. Patient characteristics and laboratory values (n = 264)

Variable	No severe bleeding (n = 232)	Severe bleeding (n = 32)	*p*-value
Female	127 (54.74)	10 (31.25)	0.021*
Age (yr)	60.64 ± 13.23	63.78 ± 13.14	0.208
Weight (kg)	61.09 ± 11.80	61.33 ± 12.32	0.913
Height (cm)	160.52 ± 9.31	163.10 ± 8.81	0.140
CPB time (min)	152.78 ± 68.41	208.12 ± 56.52	< 0.001*
ACC time (min)	107.35 ± 58.21	153.56 ± 50.22	< 0.001*
PostCPB aPTT (sec)	42.10 (37.77, 49.80)	47.25 (41.90, 53.02)	0.014*
PostCPB Hb (g/dL)	10.83 ± 1.70	11.83 ± 1.26	0.002*
PostCPB platelet ($10^3/\mu L$)	124.35 ± 50.92	92.47 ± 37.76	0.001*
PostCPB INR	1.29 (1.22, 1.43)	1.32 (1.24, 1.42)	0.518
Fibrinogen level (mg/dL)			
PreCPB	294.40 (248.80, 361.20)	311.50 (253.75, 383.38)	0.282
PostCPB	196.90 (166.75, 241.00)	172.85 (163.00, 240.18)	0.240
Pre-post	97.80 (66.00, 141.00)	136.60 (106.90, 168.15)	0.001*
Reduction ratio	32.04 ± 14.37	42.31 ± 13.52	< 0.001*
Reduction ratio > 41.3	53 (22.84)	18 (56.25)	< 0.001*

Values are presented as number (%), mean ± deviation, or median (interquartile range).
CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; aPTT, activated partial thromboplastin time; Hb, hemoglobin; INR, international normalized ratio; Pre-post, difference in fibrinogen between preCPB and postCPB; Reduction ratio, (preCPB – postCPB)/preCPB.
*$p < 0.05$.

Table 2. Multivariable analysis for association with severe postoperative bleeding

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Female	0.376	0.170–0.829	0.015	0.278	0.115–0.670	0.004*
Age (yr)	1.020	0.989–1.051	0.209			
Weight (kg)	1.002	0.971–1.033	0.913			
Height (cm)	1.030	0.990–1.071	0.141			
CPB time (min)	1.010	1.005–1.016	<0.0001	1.006	1.00–1.011	0.055
ACC time (min)	1.011	1.006–1.017	<0.0001			
PostCPB aPTT (sec)	1.003	0.990–1.016	0.674			
PostCPB platelet ($10^3/\mu L$)	0.984	0.974–0.993	0.001	0.986	0.976–0.997	0.014*
PostCPB INR	1.252	0.504–3.110	0.628			
Fibrinogen level (mg/dL)						
PreCPB	1.002	0.999–1.005	0.273			
PostCPB	0.997	0.991–1.003	0.277			
Pre-post	1.007	1.002–1.012	0.006			
Reduction ratio	1.069	1.031–1.108	<0.0001			
Reduction ratio > 41.3	4.343	2.025–9.311	<0.0001	3.472	1.483–8.126	0.004*

OR, odds ratio; CI, confidence interval; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; aPTT, activated partial thromboplastin time; INR, international normalized ratio; Pre-post, difference in fibrinogen between preCPB and postCPB; Reduction ratio, (preCPB – postCPB)/preCPB.
*$p < 0.05$.

at the univariate step. The odds ratio (OR) and 95% confidence intervals were calculated for the factors independently associated with severe bleeding. Statistical significance was defined as $p < 0.05$. All data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Between February 2014 and January 2016, 336 patients underwent adult cardiac surgery at the Pusan National University Hospital. Among them, 38 patients were missing the necessary test results. In addition, 13 patients underwent off-pump CABG, 3 patients underwent ECMO insertion, 1 patient underwent heart-lung transplantation, 16 patients underwent bleeding control within 12 hours after surgery, and 1 patient died. Thus, 264 patients were included.

Patient characteristics, CPB time, ACC time, laboratory tests are shown in Table 1 for the severe bleeding and non-severe bleeding groups. Severe bleeding occurred in 32 patients. There were significant differences between sex, CPB time, ACC time, postCPB aPTT, postCPB Hb, postCPB platelet, difference in fibrinogen levels, and fibrinogen reduction ratio of the two groups. However, preCPB and postCPB fibrinogen levels were not significantly different between the two groups. The cut-off value (41.3%) of fibrinogen reduction ratio was obtained using the best combination of sensitivity and specificity (Youden's index) and the group by cut-off value also had a significant association with severe bleeding ($p < 0.001$). The multivariate logistic analysis revealed that sex, postCPB platelet, and reduction ratio were independently related to postoperative severe bleeding. Fibrinogen reduction of more than 41.3% was independently associated with severe postoperative bleeding with an adjusted OR of 3.472 (Table 2).

Discussion

In this study, we found that the ratio of reduction in fibrinogen levels before and after CPB, platelet count after CPB, and male sex were independently associated with postoperative severe bleeding.

Previous studies reported that low pre- or postoperative (or after CPB) fibrinogen levels were correlated with postoperative bleeding; however, the correlations were weak to moderate [4]. Gielen et al. [4] reported that this relationship may be exaggerated because several studies that did not find a correlation between fibrinogen levels and postoperative bleeding were not published, which constitutes a reporting bias. Using fibrinogen levels alone are limited in clinical applications. Fibrinogen is a

glycoprotein that forms the skeleton of a blood clot and its normal level is 150–300 mg/dL (depending on the measurement method). A high fibrinogen level is observed in cardiovascular disease (> 340 mg/dL), as it is involved in the thromboembolic process and bleeding. In addition, fibrinogen is an acute-phase protein involved in the inflammatory response and may be elevated at any stage of inflammation [11,12]. Therefore, preoperative (preCPB) fibrinogen levels are frequently high in patients undergoing CPB-based cardiac surgery, especially those with ischemic heart disease or diabetes mellitus. The fibrinogen level naturally decreases after CPB weaning, as hemodilution and hypothermia result in the consumptive reduction of blood clotting factors during CPB. However, when the fibrinogen level is high at baseline, it remains high after the decrease and the criteria for compensating for fibrinogen in the treatment of bleeding are often ambiguous. Thus, we evaluated the ratio of reduction, which reflects both preoperative levels of fibrinogen and the degree of reduction during CPB. We confirmed that it was more correlated with postoperative severe bleeding than the fibrinogen levels before and after CPB. Unlike previous studies, our study showed that fibrinogen levels before and after CPB were not significantly associated with severe bleeding. Previous studies reported that preCPB or postCPB fibrinogen levels demonstrated an inverse relationship with postoperative bleeding. A meta-analysis also reported a significant correlation, although not strong. These differences in results may be due to several factors, including patient selection, the amount of reference blood loss, study design, and time of sampling. In our study, severe bleeding was characterized as over 1-L blood loss within 12 hours. Different reference blood losses may yield different results. Although not shown in our results, the postCPB fibrinogen was significantly different between the two groups when the reference blood loss was 500 mL. In addition, our study was a case-control study involving two groups and if the correlation evaluations and analyses were conducted, the results would be remarkable. We measured postCPB fibrinogen immediately after ACC release for rapid detection of postoperative severe bleeding. However, some studies measured it on patient arrival at the ICU. After surgery, the fibrinogen level increases and normalizes and the difference in the times of measurement may affect the results. The correlation between fibrinogen level and postoperative bleeding is weak to moderate and there is no significant relationship sometimes, but the difference in fibrinogen level or ratio of reduction was significant in other studies [5,13]. Therefore, the reduction ratio could be a better predictor of postoperative severe bleeding than fibrinogen levels.

Our study also showed that the platelet count after CPB was independently predictive of postoperative severe bleeding. This is consistent with previous findings that hemoglobin concentrations decreased by 30–40% and platelet counts decreased by approximately 40–50% during CPB [5,14,15]. This decrease is attributed to increased consumption by the activation of coagulation, hemodilution, and blood loss during CPB. Platelets may decrease even more because they adhere to the CPB surface and clearance increases due to thrombin-mediated activation. Therefore, the reduction of coagulation activation, minimization of hemodilution, and supplementation of platelets or fibrinogen may reduce postoperative bleeding.

Our results also revealed that male patients were more likely to develop severe bleeding than female patients. Similarly, previous studies reported that the male sex was an independent predictor of postoperative bleeding or transfusion in patients receiving CABG or cardiac surgery with CPB [16,17]. In addition, Roeloffzen et al. [18] reported that fibrin formation was faster and clot strength was higher in females than in males.

The optimal threshold for supplementing fibrinogen is not yet established. A joint statement by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists, published in 2007 and updated in 2011, included transfusion and blood conservation guidelines for cardiac surgery [19,20]. A transfusion algorithm according to the results of POC testing has been recommended and fibrinogen may be supplemented when its level is less than 80–100 mg/dL. However, a study by Karkouti et al. [14] suggested that this level is too conservative, as mass transfusions are required in more than 50% of patients even when the fibrinogen level is 200 mg/dL. Ranucci et al. [21] reported that a fibrinogen level < 220 mg/dL was independently associated with severe bleeding > 1,000 mL/12 h and a cut-off value of 115 mg/dL was proposed as a threshold for supplementation, with a target value of 280 mg/dL. They reported that these values increased to 215 and 375 mg/dL, respectively in actively bleeding patients. However, our study suggests that the absolute value of fibrinogen is not the only important marker; the ratio of reduction is also important. In our study, the cut-off value of the reduction ratio percentage for severe bleeding was 41.3%. Therefore, fibrinogen supplementation may be required when a decrease above this level is observed.

Our study had limitations. First, it is a single-center study. Each center has a different transfusion protocol. FFP or platelets administered intraoperatively contain fibrinogen and may

affect postoperative bleeding. In addition, the use of TEG, discontinuation of anticoagulants, and the use of antifibrinolytics such as tranexamic acid may affect postoperative bleeding; this outcome varies with centers. Therefore, larger multicenter studies are required to generalize our results. Second, because we did not measure the levels of specific coagulation factors other than fibrinogen and platelets, we could not evaluate their effects on postoperative bleeding. Another limitation is the definition of severe bleeding. Depending on the reference blood loss, results may vary. Although the definition of postoperative severe bleeding is arbitrary in our study, it is based on the modified criteria of the Universal Definition of Perioperative Bleeding. These criteria may be appropriate for identifying the correlations with severe bleeding.

The purpose of the present study was to determine whether the difference in fibrinogen levels before and after CPB was related to postoperative blood loss. A positive relationship would facilitate an approach that would overcome the disadvantages of POC testing and allow coagulation assessment in centers without equipment for it. The results suggest the utility of using the difference in fibrinogen levels for predicting postoperative severe blood loss in cardiac surgery with CPB. However, additional multicenter studies are required. In addition, the ratio of reduction in fibrinogen levels (rather than an absolute fibrinogen value) may facilitate the anticipation of severe bleeding in the clinical setting and prompt precautionary interventions.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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