

Can Plasma Fibrinogen Levels Predict Bleeding After Coronary Artery Bypass Grafting?

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Background: Fibrinogen is the main biomarker for bleeding. To prevent excessive postoperative bleeding, it would be useful to identify high-risk patients before coronary artery bypass grafting (CABG).

Objectives: In order to predicating bleeding after CABG, we sought to determine whether preoperative fibrinogen concentration was associated with the amount of bleeding following CABG.

Patients and Methods: A total of 144 patients (mean age = 61.50 ± 9.42 years; 65.7% men), undergoing elective and isolated CABG, were included in this case-series study. The same anesthesia technique and medicines were selected for all the patients. In the ICU, the patients were assessed in terms of bleeding at 12 and 24 hours post-operation, amount of contingent blood products received, and relevant tests. Statistical tests were subsequently conducted to analyze the correlation between preoperative fibrinogen concentration and the amount of post-CABG bleeding.

Results: The mean ± standard deviation of bleeding at 12 and 24 hours post-operation was 285.37 ± 280.27 and 499.31 ± 355.57 mL, respectively. The results showed that postoperative bleeding was associated with different factors whereas pre-anesthesia fibrinogen was not correlated with bleeding at 12 (P = 0.856) and 24 hours (P = 0.936) post-operation. There were correlations between the extra-corporal circulation time and bleeding at 12 hours post-operation ($\rho = 0.231$, P = 0.007) and bleeding at 24 hours post-operation ($\rho = 0.218$, P = 0.013).

Conclusions: Preoperative assessment of plasma fibrinogen levels failed to predict post-CABG bleeding.

Keywords: Hemorrhage; Coronary Artery Bypass; Fibrinogen

1. Background

Severe bleeding in the wake of cardiac surgery is a serious condition, as it gives rise to an increased risk of morbidity and mortality (1-3). The cause of bleeding is often dependent on numerous variables that are influenced by both surgical factors and hemostasis. Less efficient hemostasis post-surgery can be caused by increased fibrinolysis, platelet dysfunction, and coagulopathy (1, 4), as a result of exposing the patient's blood to surgical instruments or trauma, during the operation (5, 6).

To prevent excessive postoperative bleeding, it would be useful to identify high-risk patients prior to surgery. At this point in time, there is no biological marker available to identify the high-risk group. So far, commonly utilized preoperative laboratory tests, such as activated partial thromboplastin time (aPTT), prothrombin time (PT), and platelet (PLT) count, have all been able to predict postoperative bleeding after cardiac surgery accurately (7). Fibrinogen is the main protein involved in the coagulation process. Fibrinogen is converted into fibrin

by thrombin and forms a clot at the site of tissue damage to reduce blood loss and initiate repair (8). Several studies have shown an opposite correlation between the preoperative concentration of plasma fibrinogen and the amount of postoperative bleeding in coronary artery bypass grafting surgery (CABG) (9-12). However, the role of fibrinolytic inhibitors (13, 14) or anticoagulant drugs (15, 16) in cardiac surgery is still under discussion (9). The existing literature contains only a few studies on the role of preoperative plasma levels of fibrinogen as a predictor of postoperative bleeding and the results are conflicting in as much as while some researchers have found significant correlations, others have reported no such associations (8-12). A better general understanding of these issues will surely confer a better assessment of post-cardiac surgery bleeding.

2. Objectives

In order to improve understanding of the role of plasma fibrinogen in post-cardiac surgery bleeding, we sought to

determine whether preoperative fibrinogen concentration was associated with the amount of bleeding following CABG.

3. Patients and Methods

3.1. Patients

Between January 2011 and May 2011, this case-series study enrolled all of the patients referred to Baghiyatollah A'zam General Hospital who had elected for elective and isolated CABG via a cardiopulmonary bypass pump (CPB). Patients with the following conditions were excluded: age below 18 and over 75 years; abnormal tests (including PT, PTT, and BT); emergency CABG; renal failure (serum creatinine > 2 mg/dL) and known liver disorders; any previous record of repeat surgery denoting higher than normal bleeding; extracorporeal circulation time (ECC) of less than 45 minutes and more than 120 minutes; accompanying coagulation disorders; afibrinogenemia; PLT < 100,000; Aspirin (ASA) consumption within the previous three days; Plavix consumption during the previous five days; heparin consumption during the 6-hour period before the operation; and disorders that increase bleeding during the surgical operation.

The patients were visited in the ward on the night before their surgical operation and they were provided with a full explanation about the objective of the research. Written consent for the voluntary participation in the study was obtained from all the patients, and the first part of a questionnaire, encompassing the patients' demographic characteristics, medical records and accompanying diseases, surgical operation records, medical records of the consumption of ASA, heparin, and Plavix, and preoperative tests (PT, aPTT, plt, and Hb), was completed. On the morning of the operation and just prior to the induction of anesthesia, after the necessary primary measures in the operating room had been taken, the first blood sample was sent to the laboratory to measure the quantity of fibrinogen. The plasma level of fibrinogen was measured via a colorimetric procedure, and in addition turbidimetry and a Stago kit were used for the other coagulation factors.

3.2. Clinical Management and Study Design

The same anesthesia technique and medicines were selected for all of the patients. Induction of anesthesia was effected with midazolam 15-20 µg/Kg, fentanyl 10-15 µg / Kg, xylocaine 100 mg, and pancurarium 0.1 mg/kg. After ventilation and intubation, anesthesia was continued with 10 µg /Kg/h midazolam, 5 µg/Kg/h xylocaine, fentanyl 0.5 µg/Kg/h, as the maintainer. The patients received 300 units heparin against each kilogram of body weight to maintain activated clotting time (ACT) over 480 seconds. Upon CPB termination, the heparin effects were reversed by applying protamine (1 mg against each 100 unit heparin) for ACT below 130 seconds. Patients approached mod-

erate hypothermia (median 32°C).

At the end of the operation and before transfer to the Open Heart ICU, a second blood sample was taken to measure the quantity of fibrinogen. Then, the second part of the questionnaire, comprising the duration of the surgical operation, duration of aorta clamping, ECC time, minimum thermal degree experienced during the operation, number of anastomoses, and the nature and amount of the contingent blood products received during the operation, was completed. While still intubated, the patients were transferred to the open heart ICU, where they were monitored and evaluated for 24 hours with regard to bleeding (volume of blood collected in the chest bottle). The third part of the questionnaire, including information on bleeding at 12 and 24 hours post-operation, nature and amount of the contingent blood products received and relevant tests, was completed. Subsequently, the amount of fibrinogen (as reported by the laboratory) before the commencement of the operation and upon its completion were entered in a form.

3.3. Statistical Analysis

The normality of the quantitative data was measured using a Kolmogorov-Smirnov test. The categorical variables were summarized as frequencies and percentages, and the continuous variables are described as mean ± SD, unless otherwise specified. Pearson's chi-square or Fischer's exact test were employed for the categorical variables, a Student's t-test and Mann-Whitney U test were used for the numerical variables, and a Kruskal-Wallis test for the ordinal variables. Spearman's rank correlation coefficient (ρ) was drawn upon to assess the association between the measured variables and post-CABG bleeding. Multiple linear regression modeling was then performed to assess the adjusted associations between the explanatory variables and bleeding. SPSS 15 for Windows (SPSS Inc. Chicago, Illinois) was used for the statistical analyses.

4. Results

The population study consisted of 144 patients: 95 men (65.7%) and 49 women (34.3%) with a mean age of 61.50 ± 9.42 years. The minimum age was 42 and maximum 75 years. The mean preoperative quantity of fibrinogen was 333.04 ± 73.78 mg/dL, and the mean quantity of fibrinogen upon termination of the operation was 258.83 ± 56.20 mg/ dL. The mean and standard deviation of bleeding at 12 and 24 hours post-operation was 285.37 ± 280.27 and 499.31 ± 355.57 mL, respectively.

Our results indicated that age variation was correlated with bleeding during the 24-hour postoperative period ($\rho = 0.168$, $P = 0.057$). Body Mass Index was also correlated with bleeding at 12 hours post-operation ($\rho = -0.223$, $P = 0.012$) and 24 hours post-operation ($\rho = -0.182$, $P = 0.043$). The number of anastomoses was also correlated with preoperative fibrinogen concentrations ($\rho = 0.238$, $P = 0.005$). There were correlations between ECC time and bleeding

at 12 hours post-operation ($\rho = 0.231, P = 0.007$) and bleeding at 24 hours post-operation ($\rho = 0.218, P = 0.013$). There were also correlations found between bleeding at 12 hours post-operation and first-time postoperative PTT ($\rho = 0.176, P = 0.044$), first-time postoperative hemoglobin ($\rho = -0.233, P = 0.007$), second-time postoperative hemoglobin ($\rho = -0.265, P = 0.002$), and third-time postoperative hemoglobin ($\rho = -0.274, P = 0.001$). Additionally, bleeding at 24 hours post-operation was correlated with first-time postoperative hemoglobin ($\rho = -0.179, P = 0.041$), second-time postoperative hemoglobin ($\rho = -0.184, P = 0.035$), and third-time postoperative hemoglobin ($\rho = -0.232, P = 0.008$).

The results taken together showed that the amount of pre-anesthesia fibrinogen concentration was not correlated with bleeding at 12 and 24 hours post-operation ($\rho = 0.02, P = 0.8$) (Table 1).

The preoperative hemoglobin level had a significant statistical association with the blood products used during the surgical operation: The mean of the hemoglobin levels of the individuals who had received blood products (12.92 ± 1.59) was smaller by 14.34 ± 1.33 than that of the individuals who had not received blood products during their operation ($P < 0.001$). Moreover, the usage of blood products during the surgical operation had a significant association with sex ($P < 0.001$): 47% of the females and 53% of the males used blood products during cardiac surgery. In addition, the perioperative usage of blood products had no significant association with preoperative fibrinogen ($P = 0.497$) and postoperative fibrinogen ($P = 0.871$), and nor did it show any significant correlation with bleeding at 12 hours post-operation ($P = 0.856$) and bleeding at 24 hours post-operation ($P = 0.936$).

A Mann-Whitney U test revealed a significant association between sex and postoperative fibrinogen level: the postoperative fibrinogen level in the males (265.09 ± 52.43) was higher than that of the females (247.78 ± 62.12), ($P = 0.026$). Sex was significantly related to bleeding at 12 hours post-operation ($P < 0.001$) and bleeding at 24 hours post-operation ($P = 0.001$); as a result, the amount

of bleeding in the males was greater than that in the females. In addition, bleeding at 12 and 24 hours post-operation was also significantly correlated with accompanying cardiac diseases, such as myocardial infarction (MI) ($P = 0.007, P = 0.03$). In the meantime, bleeding at 12 and 24 hours post-operation was significantly associated with cigarette smoking habits ($P = 0.022, P = 0.036$): The cigarette-smoking patients had a higher amount of bleeding than did the non-smoking ones. Bleeding at 24 hours post-operation also had a significant statistical association with a past record of surgical operations ($P = 0.048$): The patients with a past record of surgical operations (233.46 ± 125) had lower amounts of bleeding than those who did not have such records (309.35 ± 267). Moreover, bleeding at 12 and 24 hours post-operation had a significant association with the postoperative usage of blood products ($P = 0.001, P = 0.004$): Those who suffered more bleeding required more blood products 12 hours after the operation.

Table 2 depicts the association between the above-mentioned variations and bleeding at 12 hours post-operation, and Table 3 demonstrates the correlation between these variations and bleeding at 24 hours post-operation.

Finally, according to the mean quantity of fibrinogen, the patients were divided into two groups and the amount of bleeding at 12 and 24 hours post-operation were examined once more. The results demonstrated no significant statistical association between the mean amount of fibrinogen and bleeding at 12 hours post-operation ($P = 0.93$) and bleeding at 24 hours post-operation ($P = 0.8$). Furthermore, the mean amount of fibrinogen was determined for all the study patients (according to their sexes separately): The mean amount of fibrinogen was 329 mg/dL in the females and 334 mg/dL in the males, and no significant statistical association was observed between them and the amount of bleeding at 12 and 24 hours post-operation.

Multiple linear regressions identified no association between fibrinogen and the other independent variables and bleeding at 12 and 24 hours post-operation.

Table 1. Correlation Between Variables and Postoperative Bleeding^a

Variable	Bleeding at 12 Hours Post-operation		Bleeding at 24 Hours Post-operation	
	ρ	P	ρ	P
Age	0.11	0.2	0.168	0.057
Body Mass Index	-0.223	0.012	-0.182	0.043
Preoperative plasma fibrinogen level	0.02	0.8	0.02	0.8
ECC, min	0.231	0.007	0.218	0.013
First-time postoperative PTT	0.176	0.044	0.13	0.13
First-time postoperative Hb	-0.233	0.007	-0.179	0.041
Second-time postoperative Hb	-0.265	0.002	-0.184	0.035
Third-time postoperative Hb	-0.274	0.001	0.232	0.008

^a Abbreviations: ECC, extracorporeal circulation; PTT, partial thromboplastin time; Hb, hemoglobin; P, P-value; ρ , Spearman's correlation coefficient.

Table 2. Associations Between Variables and Bleeding at 12 Hours Post-operation

Variable	Mean Bleeding Volume, mL	P value
Sex		< 0.001
Female (n = 49)	197.71 ± 101.6	
Male (n = 95)	336.35 ± 333.7	
MI^a		0.007
Yes (n = 12)	450.71 ± 268	
No (n = 132)	240.75 ± 127	
Smoking		0.022
Yes (n = 21)	400.94 ± 127480.1	
No (n = 123)	250.00 ± 167.6	
Past surgery history		0.048
Yes (n = 91)	233.46 ± 125	
No (n = 53)	309.35 ± 267	
Usage of blood products during surgery		0.001
Yes (n = 92)	499.17 ± 549.7	
No (n = 52)	236.85 ± 140.1	
Mean fibrinogen		0.93
> 333 (n = 66)	269.14 ± 184	
≤ 333 (n = 78)	266.09 ± 225	

^a Abbreviations: MI, myocardial infarction.

Table 3. Associations Between Variables and Bleeding at 24 Hours Post-Operation

variable	Mean Bleeding Volume, mL	P value
Sex		0.001
Female (n = 49)	348.33 ± 153.0	
Male (n = 95)	507.93 ± 424.0	
MI^a		0.03
Yes (n = 12)	405.93 ± 172	
No (n = 132)	599.23 ± 290	
Smoking		0.036
Yes (n = 21)	579.68 ± 623.7	
No (n = 123)	408.6 ± 205.7	
Past surgery history		0.14
Yes (n = 91)	383.04 ± 160.3	
No (n = 53)	465.11 ± 205.0	
Usage of blood products during surgery		0.004
Yes (n = 92)	681.36 ± 738.1	
No (n = 52)	401.59 ± 182.8	
Mean fibrinogen		0.8
> 333 (n = 66)	426.32 ± 223	
≤ 333 (n = 78)	417.46 ± 182	

^a Abbreviations: MI, myocardial infarction.

5. Discussion

The principal finding in this study was that postoperative bleeding was associated with a number of different factors, such as sex, accompanying cardiac diseases like MI, cigarette smoking, previous surgical operations, and perioperative usage of blood products, whereas pre-anesthesia fibrinogen was not correlated with bleeding at 12 and 24 hours post-operation ($P = 0.8$, $\rho = 0.02$). In recent years, several studies have reported correlations between preoperative fibrinogen concentrations and postoperative bleeding. A pilot study in 2009 reported that fibrinogen infusion reduced the amount of post-CABG bleeding. A study in 2008 demonstrated that preoperative fibrinogen concentrations, even within the normal range, was a limiting factor for postoperative hemostasis and that preoperative fibrinogen concentrations could provide useful information about postoperative bleeding and blood products transfusion. Another study in 2007 reported that low levels of preoperative fibrinogen concentration were a potential risk factor for post-CABG bleeding. Mean fibrinogen level was about normal in the patients in our study. Fibrinogen levels did not prove to be a limiting factor for postoperative hemostasis and plasma fibrinogen concentration yielded little information about the amount of postoperative bleeding.

The plasma fibrinogen level of anesthesia in our study patients correlated with preoperative platelet levels and the number of anastomoses. Furthermore, the plasma fibrinogen level was significantly higher in the men than in the women. The same correlation existed between the amount of postoperative bleeding and preoperative platelet levels and plasma fibrinogen levels before surgery in the aforementioned study in 2008 (2). Nevertheless, a study in 2010 reported a 32% decrease in the amount of postoperative bleeding in the group that received fibrinogen versus the control group.

The existing literature contains only a few studies on the role of the preoperative plasma levels of fibrinogen as a predictor of postoperative bleeding, and the results are conflicting in as much as while some researchers have found significant correlations, others have reported no such associations. About 80% of blood transfusions were carried out in the 20% 'high risk' patients undergoing cardiac surgery, so in our low risk patient subgroup, lower post-operative bleeding was predicted (8-12). Thus our results showed no such relationships.

Hemoglobin and platelet counts were significantly decreased after surgery. Also, the reduction in the amount of platelets in the studies in 2008 and 2010 was associated with increased bleeding after surgery, as was shown in an inverse linear correlation. In a study conducted in 2010, postoperative bleeding showed an inverse linear correlation with plasma fibrinogen levels before surgery and preoperative hemoglobin levels. In our study, Body Mass Index correlated with bleeding at 12 and 24 hours

post-operation. However, this correlation was not observed in a similar study in 2008. A correlation between the variables of postoperative bleeding and preoperative hemoglobin was reported in a study carried out in 2008. We found a similar correlation between postoperative hemoglobin (three times) and bleeding at 12 and 24 hours post-operation and also between first-time postoperative PTT and bleeding at 12 hours post-surgery. Pump time or ECC time correlated with bleeding at 12 and 24 hours post-surgery in our study as well. In contrast, in the 2008 study there was no correlation between this variable and the amount of bleeding.

Given the high risk that bleeding poses in cardiac surgery and the inconsistent reports in the current medical literature, further studies are necessary, particularly case-control studies or clinical trials, in order to achieve more definitive results. We also recommend that further studies with more comprehensive databases and larger sample sizes be carried out to investigate the predictive power of plasma fibrinogen levels in levels of postoperative bleeding.

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Authors' Contributions

Study concept and design: Jalali and Khaleghparast. Analysis and interpretation of data: Bakhshandeh. Drafting of the manuscript: Ghiasi, Aghaei, Ghanbari and Khaleghparast. Critical revision of the manuscript for important intellectual content: Jalali, Aghaei, Ghiasi, Ghanbari and Bakhshandeh.

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