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Original Article

A retrospective study on the effects of diabetes mellitus on perioperative fibrinogen and bleeding amount in coronary artery bypass surgery patients

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Abstract
Aim: In this study, the effects of changes in the coagulation system of diabetic patients that undergo heart surgery on postoperative bleeding amount and complications was investigated.
Material and Methods: A total of 106 patients (35 females, 71 males) were retrospectively examined in the study. Patients were divided into two groups: diabetic (Group D, n = 47) and non-diabetic (Group C, n = 59). Preoperative and postoperative hematologic values, postoperative bleeding, and transfusion amounts of all groups were recorded.
Results: Preoperative and postoperative fibrinogen and C-reactive protein (CRP) values in Group D were significantly higher compared to those in Group C ($p< 0.05$ and $p< 0.01$, respectively). Postoperative bleeding amount, erythrocyte, and fibrinogen transfusion need were found to be significantly lower in Group D compared to Group C ($p = 0.04$, $p = 0.01$, and $p< 0.001$, respectively).
Conclusion: Diabetic patients had decreased amount ofpostoperative bleeding, possibly due to a thrombotic tendency caused by chronic inflammation related to diabetes mellitus.

Keywords: Diabetes Mellitus; Cardiopulmonary Bypass; Fibrinogen; Bleeding Amount.

INTRODUCTION

Many factors in heart surgeries that are performed with cardiopulmonary bypass (CPB) can disrupt the balance of the coagulation system. Hemodilution, platelet dysfunction, perioperative antithrombotic agent use, surgical trauma, and hypothermia are among these factors (1,2). For these reasons, there is both the risk of thromboembolic events and bleeding risk after heart surgery.

Bleeding is observed very often after cardiac surgery. It progresses so severely that re-exploration is needed in the early period after surgery in about 2-6% of patients (3). Like postoperative bleeding itself, blood products given for its treatment have also been shown to increase mortality and morbidity (4). Therefore, it is a difficult process to enable bleeding control without inducing thromboembolic events in the early postoperative period (5).

In patients with diabetes mellitus (DM) for whom cardiac surgery is planned, it is a predisposing factor for both heart and vascular diseases and a risk factor for complications observed after CPB (6). Neuroendocrine changes occurring during CPB and inflammation further disrupt the microvascular endothelial dysfunction that already exists in diabetic patients (7,8). Therefore, tendency for thrombosis in these patients can affect the postoperative bleeding amount and development of thromboembolic events.

Hemostasis balance in diabetic patients is disrupted in favor of proinflammation and procoagulation. Reasons for this condition are increased levels of some coagulation factors and the negative effect on the fibrinolytic system that leads to coagulation9. Many factors contribute to the prothrombic condition reported for DM, including chronic inflammation, increased oxidative stress, decreased expression of protective endothelial factors, and disrupted fibrinolysis (10).

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Due to the reasons explained above, little bleeding after cardiac surgery and even an increase in thromboembolic events can be expected. On the other hand, another reason shown to be related to postoperative bleeding is postoperative fibrinogen plasma concentration (11,12). We aimed to examine the effect of preoperative fibrinogen level in the presence of dilutional coagulopathy that develops as a result of CPB on postoperative bleeding and thromboembolic events in diabetic patients.

MATERIAL and METHODS

Once approval was obtained from the Local Ethics Committee of RecepTayyipErdoğan University (No: 2018/17), a total of 106 patients that underwent coronary artery surgery between March 2015 and December 2017 were examined retrospectively. Patients that underwent surgery again for valve surgery, ventriculotomy, emergency surgeries, off-pump bypass, and surgical reasons except for coronary artery surgery were excluded from the study.

The same number of patients that had similar mortality according to the EuroSCOREwere divided into two groups before the operation: those with type 2 DM diagnosis (Group D, n = 47) and those without DM diagnosis (Group C, n = 59).

The data obtained after examining the anesthesia-surgery information, intensive care follow-up forms, and epicrises in the patient files were evaluated. Demographic characteristics, concomitant diseases in the preoperative examination, preoperative coagulation tests, ejection fraction, and EuroSCORE values were recorded.

As a result of the examinations performed, it was seen that antiplatelet treatment was ended five days before the surgery in patients, and low-molecular-weight heparin was given until the day of operation. All patients were monitored with radial artery cannulation before the five-lead electrocardiogram, peripheral and cerebral pulse oximetry, and anesthesia application. Anesthesia induction was enabled with IV 0.1 mg/kg midazolam, 3 µg/kg fentanyl, and 1 µg/kg lidocaine, and bolus dose fentanyl, midazolam, and sevoflurane were administered based on need so that bispectral index was between 40 and 60 during the anesthesia maintenance. Neuromuscular blockage was performed with 1 mg/kg rocuronium bromide and followed by bolus doses with train-of-four monitoring. Moderate hypothermia (28 °C) during the CPB was managed by cold hypothermic cardioplegia with membrane-coated oxygenator and closed reservoir and alpha-state acid-base management. During the CPB, anticoagulation was enabled with unfractionated heparin so that active coagulation time was over 400 seconds. After the CPB, protamine sulfate was administered to reverse anticoagulation so that the active coagulation time was less than 150 seconds. Furthermore, the number of vessels that underwent revascularization surgically was examined, as well as the cross clamp, CPB, and operation times.

If international normalized ratio (INR) was > 1.5, fresh frozen plasma transfusion was performed, and erythrocyte suspension transfusion was performed on patients whose chest tube drainage was 200 mL/hour for two consecutive hours and whose hematocrit level was < 24%. Bleeding over 1000 ml in 24 hours in the chest tube drainage was considered excessive bleeding, and whether or not these patients had another operation was recorded.

Additionally, length of stay in intensive care and hospital, coagulation tests, postoperative morbidity, thromboembolic event (myocardial infarction, stroke, transient ischemic attack, deep vein thrombosis, acute mesenteric ischemia), sternum complications (wound site infection, sternum separation), further surgery due to nonsurgical reasons, and the complications developed were recorded from the file and follow-up forms.

It was determined if the primary outputs, pre- and postoperative serum fibrinogen levels, were correlated with secondary outputs, pre- and postoperative C-reactive protein (CRP), coagulometry parameters, bleeding in the first 24 hours after operation, and serum fibrinogen levels of transfusion amounts.

Statistical Analysis

The SPSS 15 (Statistical Package of Social Sciences Inc., Chicago, IL, USA) program was used for statistical evaluation. The Kolmogorov-Smirnov test was used to determine the compliance of numerical data with normal distribution, in which case the data were shown as mean ± standard deviation, and evaluated with an independent-test. Categorical data were shown as number of patients (n) and percent and compared using Chi-square test. For all tests, $p < 0.05$ was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the groups are shown in Table 1. The body mass index of patients in Group D was significantly higher compared to Group C, and hyperlipidemia was more common. The preoperative fibrinogen level was significantly higher in Group D compared to Group C. Similarly, the CRP level was significantly higher in Group D compared to Group C. There were no significant differences between groups in terms of hemoglobin levels, platelet count, prothrombin time, and active partial thromboplastin times.

The postoperative data of the groups are shown in Table 2. The bleeding amount in the first 24 hours was observed to be significantly lower in Group D compared to Group C. In the first 24 hours after operation, fresh frozen plasma and erythrocyte need decreased significantly in Group D, and fibrinogen levels among the postoperative coagulation tests were observed to be significantly higher. Furthermore, the postoperative CRP level was observed to be significantly higher in Group D. There were no differences between groups in terms of postoperative platelet count, hematocrit, prothrombin time (PT), and partial thromboplastin time activated partial thromboplastin time (APTT) values. Sternal complications were seen significantly more often in the diabetic group compared to the control group. However, there were no significant differences between the two groups in terms of thromboembolic events, the length of stay in the intensive care, and discharge times from the hospital.

Table 1. Pre-operative clinical characteristics of patients

	Group C n=59	Group D n=47	p
Age (Years)	60.1±7.1	61.5±5	0.218
Female gender, n (%)	20 (33.8)	15 (31.9)	0.659
BMI (kg/m²)	27.3±3.4	32.4±3.7	0.028
Hypertension, n (%)	24 (40.7%)	23 (48.9%)	0.257
Hyperlipidemia, n (%)	31 (52.5%)	35 (74.5%)	0.009
EuroSCORE	3±085	3.17±0.81	0.920
LVEF (%)	56.5±8.7	57.1±8.5	0.989
Hematocrit (g/dL)	38.2±3.8	37±3.8	0.830
Platelet count (10³/mm³)	235±40	220±50	0.215
PT (%)	12.2±1.3	11.9±1.2	0.177
APTT (sec)	31.9±6.4	33.1±5.7	0.268
ACT (sec)	150±32.8	153.7±28.8	0.855
Fibrinogen (g/L)	3.83±0.70	4.13±0.62	0.024
CRP (mg/L)	0.579±0.31	1.01 ± 0.86	0.002

BMI (kg/m²): Body mass index (kg/m²), LVEF (%): Left ventricle ejection fraction, PT (%): Prothrombin time APTT (sec): Active partial thromboplastin time, ACT (sec): Active Coagulation Time

Table 2. Post-operative data between two groups

	Group C n= 59	Group D n= 47	p
Number of revascularizations	2.88±0.78	2.80±0.61	0.604
Pumping time (min)	87.1±27.6	96.6±34.2	0.121
Cross clamp time (min)	54.9±22.8	55.3±19.7	0.926
ACT (sec)	147.9±22.7	140.8±20.1	0.135
Hematocrit (g/dL)	30.1±1.8	29.7±1.8	0.879
Platelet count (10³/mm³)	215.6±46	234±43	0.032
PT (%)	12.3±1.4	11.8±1.2	0.147
APTT (sec)	34.64±4.3	33.9±4.9	0.121
Fibrinogen(g/L)	2.25±0.54	2.52±0.41	0.006
CRP(mg/L)	0.421±0.19	0.798±0.71	0.01
Amount of bleeding (ml)	865.5±265	730±191	0.04
FFP transfusion	2.30±0.72	1.82±0.43	<0.001
Erythrocyte	1.27±0.76	0.80±0.69	0.01
Length of stay at the intensive care (day)	2.16±0.37	2.19±0.39	0.772
Lengths of stay at the hospital (day)	11.8±9.6	12.9±9.2	0.634
Sternal complications, n (%)	2 (1.1%)	6 (2.8%)	0.039
Thromboembolic events, n (%)	3 (5.1%)	2 (4.2%)	0.289
Bleeding related to re-surgery, n (%)	5 (8.4%)	3 (6.3%)	0.312

PT (%): Prothrombin time APTT (sec): Active partial thromboplastin time, ACT (sec): Active Coagulation Time, FFP: Fresh frozen plasma

A total of 106 patients included in the study were regrouped in terms of excessive bleeding (drainage of more than 1000 ml/24 h in the chest drain). They were labeled the excessive bleeding group (n = 14) and the non-excessive bleeding group (n = 92). Even though the number of diabetic and obese patients in the excessive bleeding group was lower, it was not significant. The platelet count and fibrinogen level were observed to be significantly lower in the excessive bleeding group compared to the non-excessive bleeding group. More erythrocyte suspension and fresh frozen plasma were needed in the excessive bleeding group.

Table 3. Analysis of pre-operative and post-operative determinants of excessive bleeding on the first day

	Non excessive bleeding Group n=92	Excessive bleeding Group n=14	p
Diabetes, n (%)	41 (44.5%)	6 (42.8%)	1
Obesity (BMI>30kg/m2), n (%)	18 (19.5%)	1 (7.14%)	0.57
(Diabetes+obesity), n (%)	16 (17.3%)	1 (7.14%)	0.339
Fibrinogen(g/L)	147.9±22.7	125.8±20.1	0.027
CRP(mg/L)	0.48±0.33	0.39±0.22	0.185
EuroSCORE	3.17±0.91	3.52±0.77	0.146
Insulin user, n (%)	13 (87%)	2 (13%)	1
Oral anti-diabetic user, n (%)	30 (88%)	4 (12%)	1
Platelet count (10³/mm³)	233.7±42.8	210.7±36.2	0.043
APTT (sec)	31.05±4.9	30.94±3.62	0.125
PT (%)	12.1±0.8	11.7±0.7	0.091
Cardiopulmonary bypass time (min)	80.7±22.1	94.8±31.9	0.042
Cross clamp time (min)	53.8±28.9	59.8±25.7	0.061
Female gender, n (%)	31 (89%)	4 (11%)	0.940
Red blood cell packs transfused (Units)	0.86±0.72	1.93±0.73	<0.001
FFP transfused (Units)	2.01±0.69	2.71±0.91	0014

BMI (kg/m²): Body mass index (kg/m²), PT (%) : Prothrombin time APTT (sec): Active partial thromboplastin time, ACT (sec): Active Coagulation Time, FFP: Fresh frozen plasma

DISCUSSION

In our study, bleeding amount was found to be less in diabetic patients after CPB surgery. Recent studies were in opinion that diabetic patients were more inclined to hypercoagulation and prothrombotic conditions (9). Earlier studies associated thisprothrombotic condition withincreased incidence of thromboembolic events (13,14). However, our study found no correlation with thromboembolic events after cardiac surgery.

It was shown that diabetic patients needed more blood products in the postoperative period in isolated CPB surgery15, and they needed operation more often after bleeding (17). Even though these studies contradict our thesis, further surgery after bleeding was more related to surgical reasons, and similarly, it was suggested that diabetic patients' need for more blood products after CPB surgery might vary depending on the threshold value of the hemoglobin used. For these reasons, it would not be right to say that the amount of bleeding that occurred resulted from coagulation factors.

However, correlation between the amount of bleeding in postoperative chest tube drainage and diabetic patients was only examined in two studies in the literature. In a study conducted by Kristensen et al., even though it was shown that diabetic patients had more bleeding, the correlation between the reason for excessive bleeding and coagulation tests could not be explained (16). In another study, Bucerius et al. could not show any differences between the two groups (18). In this study, we found that, contrary to the literature, chest tube drainage was less in diabetic patients in the first 24 hours, and less erythrocyte and fresh frozen plasma were needed. We tried to explain if this condition was associated with perioperative coagulation factors such as preoperative and postoperative fibrinogen and platelet count.

The fact that diabetes caused hypercoagulopathy by affecting the primary and secondary hemostasis was reported a few times (9,14). In this study, the high serum fibrinogen level measured in both preoperative and postoperative periods in the DM group might have contributed to the low bleeding amount in the postoperative period.

Fibrinogen as an acute phase reactant plays a key role in hemostasis (19). Significant blood loss can be estimated due to preoperative and postoperative fibrinogen deficiency that requires more blood products in the postoperative period and causes excessive blood loss (20,21). Fibrinogen levels secondary to inflammation in diabetic patients that are inclined to hypercoagulation is higher (9 Furthermore, the correlation between CRP, another inflammation indicator, and fibrinogen shows that CRP contributes to hypercoagulation by increasing tissue factor release and fibrinolysis (22,23).

We could not evaluate platelet functions in our study, but it is assumed that diabetic patients have a strong association with thromboelastographic hypercoagulopathy (24). In addition to this prothrombiccondition, the fact that diabetic patients have a higher platelet count in the postoperative period could be another reason explaining the lesser amount of bleeding.

Another factor that could explain the postoperative bleeding amount is that there were more patients in the diabetic group with a BMI over (30). This could be explained by the fact that postoperative bleeding in obese patients was less due to their tendency to thrombosis (25,26). Furthermore, less bleeding was observed because the large surface area in patients with high BMI leads to exposure to less hemodilution during CPB (27).

Postoperative bleeding increases mortality and morbidity after cardiac surgery. The fact that excessive bleeding is associated with platelet dysfunction, weakened coagulation, and increased fibrinolysis, as well as the effect of factors such as BMI, gender, and genetic predisposition, shows that various systems contribute to excessive bleeding (28). Rivera et al. defined excessive bleeding as presence of more than 1000 ml blood in the chest tube drainage within 24 hours after heart surgery. They observed that excessive bleeding was higher in patients with low BMI, long PT, and low fibrinogen level (29). In our study, even though the number of obese, diabetic, and female patients was lower in the group with excessive bleeding, there was no statistically significant difference. This might be due to the low number of patients.

Because our study was retrospective and observational, strength analysis could not be performed in determining the number of samples. Furthermore, it is necessary to generalize the obtained results because this is a limited study due to its single-centered nature and low number of patients. Our study was also restricted because the HbA1c levels of the patients in the diabetic group were not recorded, and there was no intra-operative specific blood sugar regulation method and follow-up. It was reported that HbA1c and fibrinogen levels showed correlation. Furthermore, it was stated that HbA1c level is associated with postoperative thromboembolic events and mortality (30).

CONCLUSIONS

Diabetic patients are less inclined to bleeding after heart surgery due to their prothrombotic condition. According to our study, such prothrombotic condition did not cause diabetic patients to encounter more postoperative thromboembolic events or affect their discharge times. Our results show that chronic inflammation caused thrombotic condition by affecting the coagulation cascade and platelet functions. However, we believe that more comprehensive studies with larger participation will better explain the mechanism of this difference.

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