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The comparison between the effects of aspirin and clopidogrel monotherapy on postoperative bleeding in diabetic patients after off-pump coronary artery bypass surgery

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There is limited data about the bleeding complication of antiplatelet therapy after coronary artery bypass graft (CABG) operations focused on diabetic patients. Herein, we aimed to evaluate the effects of aspirin and clopidogrel monotherapies on postoperative bleeding in these patients. A total of 165 diabetic patients who underwent isolated off-pump beating heart coronary artery bypass (OPCAB) operation were evaluated, 84 patients were included in this retrospective study. Patients were divided into groups according to the type of antiplatelet regime. Chest tube drainage amounts and the amount of blood product transfusions were evaluated. Acetylsalicylic acid (ASA) - group included 42 aspirin monotherapy and Clopidogrel - group included 42 clopidogrel monotherapy patients after propensity matching. The mean drainage amount in ASA - group was 670.24 $\pm$ 185.46 mL, in Clopidogrel - group was 921.43 $\pm$ 167.53 mL ($p <$ 0.001). More packed red blood cell (PRBC) and fresh frozen plasma (FFP) units were needed in the Clopidogrel - group than in the ASA - group (2.05 $\pm$ 1.13 vs. 0.83 $\pm$ 0.93 units of PRBC, and 1.90 $\pm$ 0.58 vs. 1.05 $\pm$ 0.58 units of FFP, respectively, $p <$ 0.001). In conclusion, clopidogrel had a stronger effect on bleeding in diabetic patients than aspirin after OPCAB surgery.

Keywords

Coronary artery bypass; Postoperative hemorrhages; Platelet aggregation inhibitors; Diabetes complications; Aspirin; Clopidogrel

1. Introduction

Diabetes mellitus and coronary artery disease are both systemic diseases and their concomitance has a worse prognosis than their individual existence [1]. Older age, preoperative lower hemoglobin, preoperative higher creatinine levels, postoperative thrombocytopenia lower left ventricle ejection fraction (LVEF) are significantly related with postoperative bleeding after OPCAB surgery [2, 3]. Diabetes is also accepted as one of the major risk factors for bleeding and major adverse cardiovascular events in the risk scoring systems [4, 5].

Antiplatelet therapy is recommended in both American and European guidelines of CABG surgery in the postoperative period to improve the graft patency after OPCAB surgery [6, 7].

There are many studies conducted on the postoperative results of OPCAB surgery but there are limited data about the early postoperative outcomes in regard to postoperative hemorrhage. Also, these data are not focused on diabetic patients [8–12].

Herein, we aimed to compare the effects of clopidogrel and aspirin on postoperative bleeding in diabetic patients undergoing OPCAB surgery.

2. Methods

2.1 Patient population

The patients who underwent isolated OPCAB operation between the dates of April 2014–August 2018 in the same health center were evaluated in this retrospective study. Fasting plasma glucose $\geq$126 mg/dL, 2-h plasma glucose $\geq$200 mg/dL during 75-g oral glucose tolerance test, A1c $\geq$6.5% were accepted as diabetes mellitus [13]. Patients who had received an antiplatelet or anticoagulant therapy other than clopidogrel or aspirin in the last six months before the operation, who had preoperative thyroid gland dysfunction, hematologic disorder, hereditary coagulopathy, and who underwent reoperations were not included. Also, the operations which were done without left internal mammary artery harvesting were excluded.

Patients were divided into groups according to the type of antiplatelet therapy they had received. In elective operations, clopidogrel and/or aspirin therapies were ceased three to five days before the operation and low molecular weight heparin (LMWH) was administered once a day until the operation day. In emergent situations such as ongoing chest pain and ischemia signs in electrocardiography despite the medical therapy, the patient underwent emergency CABG operation in six hours after the onset of the chest pain. Clopidogrel or aspirin therapies were continued on the first postoperative day.

Table 1. UDPB classification according to postoperative chest tube blood loss.

Bleeding definition	Blood loss within twelve hours (mL)
Class 0 (insignificant)	<600
Class 1 (mild)	601–800
Class 2 (moderate)	801–1000
Class 3 (severe)	1001–2000
Class 4 (massive)	<2000

Patients were classified according to the blood loss through the chest tubes as defined in Universal Definition of Perioperative Bleeding in adult cardiac surgery (UDPB) [14] (Table 1). The total blood product transfusions including PRBC and FFP which were done in the postoperative period were evaluated. Local institutional approval for the study execution and data usage was taken.

2.2 Operative technique

The general anesthesia induction was done with intravenous injection of fentanyl 10 microgram/kg, midazolam 0.1 mg/kg, and rocuronium 1 mg/kg following the electrocardiography and invasive blood pressure monitoring. The patient was intubated after the establishment of general anesthesia and ventilated with 300–400 mL tidal volume. Also, methylprednisolone 1 mg/kg and intravenous pheniramine were administered to prevent adverse drug reactions after protamine administration.

The activated clotting time was maintained over 300 seconds with the administration of 300 IU/kg unfractionated heparin before the median sternotomy and additional doses were administered if necessary throughout the operation. Left internal mammary artery and saphenous vein grafts were harvested in a standard fashion. Intravenous infusions of magnesium (1 amp) and lidocaine 1 mg/kg were administered throughout the graft harvesting period as a standard protocol to prevent arrhythmias. The patient body temperature was kept between 34–36 °C, mean arterial blood pressure was kept between the ranges 60–90 mmHg and the heart rate was kept between the ranges 60–80 beats/min with esmolol infusion if necessary. The protocol of esmolol administration was 1 mg/kg initial bolus dose intravenous infusion over 30 seconds, then followed by 0.15–0.3 mg/kg/min intravenous infusion adjusted according to the heart rate. Heparin effect was neutralized with 50–100 IU/kg protamine administration after the completion of all anastomoses.

2.3 Statistical analysis

The statistical analysis of the data was done with the Statistical Package for the Social Sciences (SPSS 16.0 Inc., Chicago, IL, USA) software. Categorical data were reported as numbers and percentages. Continuous data were reported as means ± standard deviation (SD). The non-parametric data of the groups were tested with Spearman's correlation, chi-square, and Fisher's exact tests and parametric data were tested with independent samples *t*-test. Propensity scores were calculated using logistic regression analysis. The area under the receiver-operating characteristic (ROC) curve (C-index) was 0.716 and Hosmer-Lemeshow goodness-of-fit chi-square value was 6.15 and $p = 0.630$ which indicated that the propensity score model was adequate and well-calibrated. p value alpha for UDPB groups analysis was calculated with Bonferroni correction and accepted significant at $p < 0.0063$ level. Multiple linear regression analysis was performed to evaluate the significance of predictors for postoperative drainage amount. Other p values < 0.05 were considered statistically significant.

3. Results

A total of 503 patients were identified who underwent isolated OPCAB surgery. Among these patients, 165 diabetic patients were evaluated for the preoperative characteristics. There were significant differences between the groups regarding the variables previous MI, chronic obstructive pulmonary disease, hypertension, and preoperative ejection fraction before the propensity matching. The patient groups were adjusted according to the propensity scores using one-to-one matching ratio and nearest neighbor algorithm. A total of 84 patients were selected. ASA - group included 42 (50%) aspirin monotherapy and Clopidogrel - group included 42 (50%) clopidogrel monotherapy patients after propensity score matching (Fig. 1). The main preoperative characteristics of the patients are presented in Table 2. Two groups were matched for all the preoperative data.

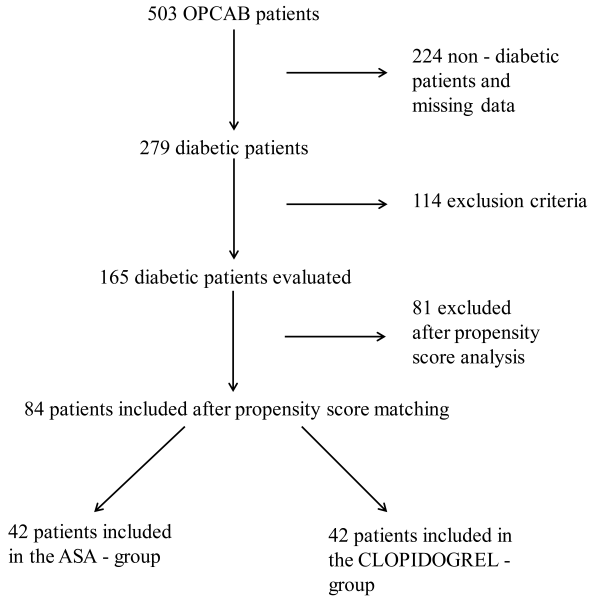

Fig. 1. Flow diagram of patient selection. A total of 503 patients were enrolled. Down arrows indicate the flow of the patient selection process and the number of patients included in each step. Side arrows indicate the number of patients excluded in the process. OPCAB, Off-pump coronary artery bypass; ASA, Acetylsalicylic acid.

Table 2. Preoperative data (propensity matched).

	ASA - group (n = 42)	Clopidogrel - group (n = 42)	*p* value
Age (Mean ± SD)	63.14 ± 7.54	63.21 ± 6.74	0.964
Male n (%)	29 (69.04)	30 (71.42)	0.943
BMI (Mean ± SD)	31.31 ± 2.95	30.27 ± 4.78	0.238
BSA (Mean ± SD)	2.09 ± 0.07	1.98 ± 0.05	0.159
Preoperative EF (%) (Mean ± SD)	54.62 ± 5.66	52.71 ± 6.93	0.172
Fasting plasma glucose (mg/dL) (Mean ± SD)	170.05 ± 45.19	174.38 ± 71.45	0.741
Hemoglobin A1c (%) (Mean ± SD)	7.11 ± 1.56	7.66 ± 1.81	0.140
Hemobiology and platelet indices (Mean ± SD)			
Hemoglobin (g/dL)	12.01 ± 1.63	11.34 ± 2.03	0.098
Hematocrit (%)	36.39 ± 4.25	34.68 ± 5.38	0.110
Platelet count (10^9/L)	192.88 ± 45.41	202.67 ± 40.95	0.303
PDW (fl)	14.92 ± 2.10	14.59 ± 2.23	0.480
MPV (fl)	11.44 ± 0.86	11.21 ± 1.13	0.302
P-LCR (%)	35.51 ± 5.86	34.46 ± 5.66	0.407
PCT (10^9/L)	0.21 ± 0.04	0.22 ± 0.03	0.122
Previous myocardial infarction n (%)	42 (100)	42 (100)	1.000
Emergency surgery n (%)	5 (11.90)	4 (9.52)	1.000
COPD n (%)	24 (57.14)	21 (50.00)	0.512
Hypertension n (%)	24 (57.14)	24 (57.14)	1.000
Hyperlipidemia n (%)	6 (14.28)	3 (7.14)	0.483
Renal dysfunction n (%)	3 (7.14)	3 (7.14)	1.000

ASA, Acetylsalicylic acid; BMI, Body mass index; BSA, Body surface area; EF, Ejection fraction; PDW, Platelet distribution width; MPV, Mean platelet volume; P-LCR, Platelet large cell ratio; PCT, Plateletcrit; COPD, Chronic obstructive pulmonary disease.

Table 3 presents the postoperative data of the groups. The mean ± SD of postoperative drainage amount, mechanic ventilator support times, intensive care unit stay times, PRBC and FFP units transfused were significantly higher in the Clopidogrel - group ($p < 0.001$, $p = 0.010$, $p = 0.047$, $p < 0.001$ and $p < 0.001$, respectively). Also, there was a significant difference in the UDPB classification of the groups so a Bonferroni correction was conducted. According to the new calculated alpha, there were significantly more ASA - group patients in Class 0 and more Clopidogrel - group patients in Class 2 ($p < 0.0001$, $p = 0.0001$, respectively). All other postoperative data were similar between the groups.

In the multiple regression analysis body mass index and body surface area were found to be independent predictors for postoperative drainage amount in both groups (Table 4).

4. Discussion

The results of this study present that the postoperative hemorrhage amount and the need for PRBC transfusion after OPCAB surgery are higher in the diabetic patients receiving clopidogrel monotherapy before surgery than the patients receiving aspirin monotherapy. Also, body mass index and body surface area had significant effects on the postoperative bleeding volumes.

In the practice guidelines for perioperative blood management published in 2015, it is stated that platelet transfusion is rarely indicated in patients with platelet count >100 × 10^9/L. Also, in the same guidelines, undergoing cardiopulmonary bypass surgery and administration of potent antiplatelet drugs are suggested as indications for platelet product transfusion despite normal platelet count but there is no sufficient scientific evidence to apply these criteria [15]. All patients in this study had platelet count in the normal value range so no indication was found to transfuse platelet products.

There are different ideas about postoperative management of the patients receiving clopidogrel and aspirin before CABG surgery. In some studies, it was suggested that platelet transfusion would be needed in the postoperative period in these patients although it had been stated as opposite in the other studies [15, 16]. The main concept in our clinic is to keep the total blood product transfusions as low as possible so any blood transfusion is made if it is mandatory and the hematocrit level <25%.

In the European Society of Cardiology (ESC) guidelines published in 2017, the use of risk scoring systems such as DAPT (Dual Antiplatelet Therapy) – score [4] and PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) score [17] was recommended to evaluate the benefits and risks of DAPT therapy (class of recommendation Class IIb, evidence level A) but their value was not clearly identified in improving patient outcomes because none of these risk prediction models were tested in randomized controlled trials [18]. The vein graft patency is possibly

Table 3. Postoperative data (propensity matched).

	ASA - group (n = 42)	Clopidogrel - group (n = 42)	*p* value
Postoperative drainage (Mean ± SD) (mL)	670.24 ± 185.46	921.43 ± 167.53	<0.001
UDPB n (%)			
Class 0	21 (50.00)	3 (7.14)	<0.0001
Class 1	15 (35.71)	10 (23.81)	0.232
Class 2	6 (14.29)	23 (54.76)	0.0001
Class 3	0	6 (14.29)	0.011
ABP (mmHg) (Mean ± SD)			
Systolic	112.55 ± 12.11	115.07 ± 11.38	0.328
Diastolic	72.62 ± 10.02	74.45 ± 10.43	0.414
SVG n (%)			
≤2 grafts	33 (78.57)	33 (78.57)	1
>2 grafts	9 (21.43)	9 (21.43)	
MVS time (hours) (Mean ± SD)	5.00 ± 0.66	5.64 ± 1.41	0.01
ICU stay time (hours)	13.29 ± 0.80	24.29 ± 35.40	0.047
In-hospital stay time n (%)			
≤7 days	39 (92.86)	36 (85.71)	0.29
>7 days	3 (7.14)	6 (14.28)	
Inotropic support n (%)	33 (78.57)	27 (64.29)	0.147
IABP n (%)	3 (7.14)	3 (7.14)	1
Postoperative revision n (%)	6 (14.29)	9 (21.43)	0.393
PRBC units transfused (Mean ± SD)	0.83 ± 0.93	2.05 ± 1.13	<0.001
FFP units transfused (Mean ± SD)	1.05 ± 0.58	1.90 ± 0.58	<0.001
Mortality n (%)	2 (4.76)	4 (9.52)	0.984

UDPB, Universal definition of perioperative bleeding; ABP, Arterial blood pressure; LIMA, Left internal mammary artery; SVG, Saphenous vein graft; MVS, Mechanical ventilator support; ICU, Intensive care unit; IABP, Intra-aortic balloon pump; PRBC, Packed red blood cell; FFP, Fresh frozen plasma.

improved with DAPT after CABG but the quality of the data is weak [19].

In the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for Coronary Artery Bypass Graft Surgery, preoperative aspirin (100 mg to 325 mg daily) administration and clopidogrel cessation for at least five days before the surgery were recommended to CABG patients. In the patients who undergo urgent CABG, clopidogrel was recommended to be discontinued for at least 24 hours before the surgery. The class of these recommendations were class I and the level of evidence was B. Oral aspirin administration was recommended within six hours postoperatively and to be continued indefinitely (class I recommendation and level of evidence A) to improve the graft patency. Clopidogrel was recommended as alternative to aspirin if the patient was allergic or intolerant to aspirin (class IIA, level of evidence A) [6].

In the 2016 ACC/AHA guidelines, in patients being treated with DAPT after coronary stent implantation or receiving DAPT because of an acute coronary syndrome (ACS) who undergo CABG surgery, resuming and continuation of the $P2Y_{12}$ inhibitor therapy postoperatively until the end of the therapy, was recommended (class I recommendation). Also in patients with stable ischemic heart disease, DAPT for 12 months postoperatively was recommended to improve graft patency (class IIb recommendation) [7]. Also major bleeding was reported to be more frequent with DAPT after surgery [20].

Both of these guidelines recommend aspirin and clopidogrel treatment postoperatively in the CABG patients with careful assessment of the bleeding risks. We think that, the results of this study support these recommendations.

It is possible to confirm the "obesity paradox" for the postoperative bleeding according findings of this study. The "obesity paradox" is first described in 1999 for obese and overweight hemodialysis patients which states that high body mass index (BMI) is associated with lower morbidity and mortality [21]. Moscarella *et al.* [22] also confirmed the obesity paradox in ACS patients who underwent primary percutaneous coronary intervention (PCI) after ST segment elevated myocardial infarction (STEMI). On the contrary, Calabrò *et al.* [23] rejected the obesity paradox and found no relation between the BMI and adverse outcomes in ACS patients. In this study, mean BMI levels of the groups were at obesity and overweight levels and it was slightly higher in Clopidogrel – group. Also BMI was found to be one of the independent predictors for postoperative bleeding.

Lower body surface area was reported to be a predictive factor for postoperative blood loss and blood product transfusion [24]. The data of the current study is consistent with the aforementioned study.

Table 4. Multiple regression analysis of predictors for postoperative drainage between the groups.

	ASA- group				Clopidogrel - group			
			95.0% Confidence Interval for B				95.0% Confidence Interval for B	
	B[α]	*p* value	Lower Bound	Upper Bound	B[β]	*p* value	Lower Bound	Upper Bound
Age	−5.11	0.699	−32.07	21.86	3.25	0.234	−2.25	8.76
BMI	11.91	0.028	1.41	22.41	20.65	<0.001	10.52	30.78
BSA	759.84	0.020	130.25	1389.43	1095.90	<0.001	624.71	1567.10
FPG	−0.45	0.391	−1.52	0.61	−0.11	0.610	−0.57	0.34
Hemoglobin A1c	17.76	0.243	−12.87	48.40	−13.66	0.158	−33.01	5.69
Preoperative EF	−4.90	0.299	−14.41	4.62	−4.98	0.151	−11.89	1.94
Preoperative Hemobiology								
Hemoglobin	27.60	0.651	−96.66	151.87	−47.60	0.205	−123.02	27.82
Hematocrit	−7.30	0.755	−55.11	40.51	16.74	0.253	−12.75	46.23
Platelet count	−0.45	0.416	−1.58	0.67	−0.21	0.504	−0.86	0.43
MPV	64.59	0.219	−41.11	170.28	−17.98	0.129	−41.55	5.59
PDW	−12.96	0.479	−50.12	24.21	−5.32	0.369	−17.30	6.67
PLCR	−0.43	0.960	−17.80	16.94	0.49	0.848	−4.71	5.69
PCT	−553.80	0.394	−1869.63	762.03	−812.57	0.038	−1574.78	−50.37
Systolic ABP	1.32	0.460	−2.30	4.94	1.56	0.250	−1.17	4.29
Diastolic ABP	0.21	0.921	−4.16	4.58	−1.65	0.278	−4.73	1.42

BSA, Body surface area; FPG, Fasting plasma glucose; EF, Ejection fraction; PDW, Platelet distribution width; MPV, Mean platelet volume; P-LCR, Platelet large cell ratio; PCT, Plateletcrit; ABP, Arterial blood pressure; MVS, Mechanic ventilator support; ICU, Intensive care unit.

[α] Adjusted R square = 0.658, F = 5.644, $p < 0.001$; [β] Adjusted R square = 0.833, F = 12.989, $p < 0.001$.

Many factors such as postoperative renal dysfunction requiring hemodialysis, poor left ventricle ejection fraction (LVEF), perioperative MI, sepsis, diabetes, age, etc. are related with prolonged internsive care unit (ICU) stay [25–28]. But Silberman *et al.* [27] did not find bleeding related with prolonged ICU-stay times. Also Tunç *et al.* [28] reported that blood product transfusions both intraoperative and in the first 24 hrs postoperatively were not related with prolonged ICU stay. On the other hand, Al-Attar *et al.* [29] found significantly increased ICU stay times in cardiac surgery patients in case of postoperative bleeding and revision surgery. These studies were conducted on various cardiac surgery patient groups, not on isolated OPCAB patients.

In their study Cislaghi *et al.* [30] reported that redo surgery, CPB time longer than 91 mins, more than four units of RBC or FFP intraoperatively and LVEF ≤30% were independent predictors for prolonged mechanical ventilator support (PMVS) but not bleeding. On the contrary, Yende *et al.* [31] found that postoperative bleeding was the cause of failure of extubation within eight hours postoperatively in the 10.2% of their patient cohort. These studies also include various cardiac surgery patient groups, not only isolated OPCAB patients.

The postoperative bleeding resulted in prolonged MVS and ICU—stay times in this study. This result is valuable because the patient cohort is very specific to diabetic isolated OPCAB patients.

5. Limitations of the study

The presence of any hereditary coagulation disorder was an exclusion criterion for the study but it was not identified in some patients because the determination tests were unavailable. Management of postoperative bleeding was carried out by the same surgery team.

6. Conclusions

Clopidogrel monotherapy has a stronger effect on postoperative bleeding than aspirin monotherapy in diabetic patients after OPCAB surgery. More studies should be conducted to clarify the physiologic and biochemical mechanisms of this effect. Also, body mass index and body surface area are independent predictors of postoperative bleeding in these patients.

Abbreviations

ASA, Acetylsalicylic acid; ACS, Acute coronary syndrome; ACT, Activated clotting time; CABG, Coronary artery bypass graft; CAD, Coronary artery disease; CPB, Cardiopulmonary bypass; DAPT, Dual antiplatelet therapy; DM, Diabetes mellitus; FFP, Fresh frozen plasma; LIMA, Left internal mammary artery; MI, Myocardial infarction; OPCAB, Off-pump coronary artery bypass; PCI, Percutaneous coronary intervention; PMVS, Prolonged mechanical ventilator support; PRBC, Packed red blood cell; STEMI, ST-elevation myocardial infarction; SD, Standard deviation; LVEF, Left ventricle ejection fraction.

Author contributions

LA, Designed the study, analyzed the data. EÇ, Collected the data. LA and EÇ, Wrote the manuscript.

Ethics approval and consent to participate

No informed consent was obtained because of the retrospective nature of data collection from hospital records in the study. The institutional approval number is 2017/3056.

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Conflict of interest

The authors declare no conflict of interest.

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