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Clinical Investigation

Effects of Pooled Platelet Concentrate After Coronary Artery Bypass Graft Surgery in Patients With Dual Antiplatelet Therapy

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Abstract

Background: Dual antiplatelet therapy (DAPT) has become standard first-line treatment of acute coronary syndrome; however, it increases the risk of bleeding complications. The aim of this study was to investigate the benefits of pooled platelet concentrate (PPC) in reducing postoperative bleeding in patients undergoing off-pump coronary artery bypass graft (CABG) after a DAPT loading dose.

Methods: One hundred nine patients who underwent emergent CABG within the first 24 hours after receiving a DAPT loading dose were included in the study and divided into 2 groups: patients who were (group 1, n = 63) and were not (group 2, n = 46) given PPC during the surgery. The amount of bleeding in the postoperative period and the need for blood transfusions were recorded.

Results: The mean (SD) surgical drainage amounts were 475.39 (101.94) mL in group 1 and 679.34 (232.03) mL in group 2 (P = .001). The need for surgical revisions was 0% and 15.2% in groups 1 and 2, respectively (P = .002). The median (range) duration of hospitalization after surgery was 4 (4-6) days in group 1 and 6 (4-9) days in group 2 (P = .001). Total transfusions per patient were higher in group 2 than in group 1 (1 [range, 1-4] and 3 [range, 2-7] units, respectively; P = .001).

Conclusion: Perioperative PPC in patients who had received DAPT reduces postoperative bleeding, the need for blood products, and hospital stay. As a result, it has beneficial effects for early mobilization and improves patient comfort.

Keywords: Dual anti-platelet therapy; coronary artery bypass grafting; bleeding; platelet transfusion

Introduction

Dual antiplatelet therapy (DAPT) has become standard in treating acute coronary syndrome (ACS). DAPT is composed of acetylsalicylic acid and clopidogrel or ticagrelor and is used in many centers. Whereas clopidogrel is an irreversible P2Y12 inhibitor, ticagrelor is a reversible P2Y12 inhibitor drug. Because these drugs significantly affect patients with ACS, the guidelines recommend using at least 1 of these drugs with acetylsalicylic acid.[1] However, it has been reported that DAPT increases the risk of severe bleeding complications in patients undergoing coronary artery surgery with consequent blood transfusions and infection problems. Therefore, in patients undergoing elective coronary artery bypass graft (CABG), continuation of aspirin with suspension of ticagrelor or clopidogrel treatment at least 5 days before surgery is recommended.[1] In 1 study, although it was observed that pretreatment with P2Y12 receptor inhibitors had good ischemic results, the use of these drugs significantly increased the risk of bleeding in patients undergoing CABG.[2]

However, many publications have repeatedly emphasized significant blood loss in patients receiving DAPT who are undergoing CABG. Increased bleeding leads to an increased need for blood transfusions and an increase in surgical

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revisions, leading to a prolonged stay in the intensive care unit. This prolongation of the treatment process results in secondary problems such as infection and other complications. There is also morbidity associated with homologous blood products, such as transfusion reactions, wound infections, sepsis, increased hospital mortality, and decreased postdischarge survival.[3]

Patients with emergent cardiac conditions should undergo surgery immediately. Because DAPT drugs bind irreversibly to platelets, it is impossible to neutralize their effects on platelets, so using intact thrombocytes may be the most appropriate solution for this problem. The benefits of administering a new platelet suspension to these patients instead of thrombocytes affected by these drugs are still unclear.

The aim of this study was to investigate the benefits of pooled platelet concentrate (PPC) in patients who were admitted to Lokman Hekim Akay Hospital with a diagnosis of ACS and underwent CABG within 24 hours after a dual antiplatelet loading dose was given to reduce postoperative bleeding and its related complications. It was preferred to use PPC for patients who were to be given a platelet suspension because it contains platelets at a concentration 4 to 6 times higher than that in the random platelet suspensions.

Patients and Methods

After written consent was obtained from the hospital's local ethics committee, data from 1,098 patients who underwent isolated CABG in Lokman Hekim Akay Hospital between January 2019 and December 2021 were analyzed. Of these 1,098 patients, 109 patients were included who had undergone emergent CABG and had received a loading dose of 300 mg clopidogrel and 300 mg acetylsalicylic acid (DAPT) when a preliminary diagnosis of ACS was made. These patients underwent emergent CABG within the first 24 hours after receiving DAPT.

The patients were divided into 2 groups: group 1, patients given PPC during surgery (PPC group, n = 63); and group 2, patients not given PPC (non-PPC group, n = 46). The only criterion for administering PPC was that the patient had received DAPT within the previous 24 hours. The patient's preoperative platelet count and other causes were not considered as criteria. The aim was to provide PPC to all of these patients soon after the operation. In Turkey, blood and blood products are provided free of charge by the state. Because the affiliated center serves many hospitals and clinics, the PPC suspension was not available for every request; therefore, patients were allocated the 2 groups according to the availability of PPC suspension at the time of surgery. Pooled platelet concentrate production is complex, and its shelf life is far shorter than that of other blood products; however, because the PPC suspension was prepared on the same day as requested, it was transferred to the operating room at room temperature. Cold-stored PPC suspension was not used in this study.

Abbreviations and Acronyms

ACS	acute coronary syndrome
CABG	coronary artery bypass graft
DAPT	dual antiplatelet therapy
FFP	fresh-frozen plasma
Hb	hemoglobin
PPC	pooled platelet concentrate

Patients who underwent surgeries other than isolated CABG (valve surgery, etc), those with any previous cardiac surgery, and those who had previously undergone percutaneous coronary intervention and were still using an antiplatelet drug were not included in this study. In addition, patients with bleeding diathesis, previous gastrointestinal system bleeding, or chronic kidney disease requiring dialysis were excluded from this study. Patients with chronic kidney failure who had to undergo dialysis were also excluded from the study, but there were no patients who already had these problems.

Coronary artery bypass surgery with the off-pump technique was performed on all patients, with a standard median sternotomy. An intravenous dosage of 100 IU/kg of heparin was administered before left internal thoracic artery and the saphenous vein graft harvesting was completed. During surgery, stabilization devices and intracoronary shunts were used to stabilize and position the heart. After all distal and proximal anastomoses were completed, heparin was neutralized with protamine sulfate after controlling activated clotting time. At this stage, PPC infusion was given to group 1 patients immediately after protamine administration. Then, the patients in both groups underwent routine bleeding control procedures, chest tubes were inserted, and surgery was completed.

A hemoglobin (Hb) level of 8.0 mg/dL was accepted as the lower limit of normal when determining the blood

product needs of the patients. Fresh-frozen plasma (FFP) was given to patients with active bleeding. Considering the possibility of hemodilution in patients who were given FFP, blood cell counts were checked intermittently, and erythrocyte suspension was added for Hb measurements below 8.0 mg/dL. Tranexamic acid was not used in any patients.

In addition to the demographic data of all patients included in the study, data related to the amount of bleeding in the postoperative period, the length of stay in the intensive care unit, and the need for blood product transfusions were compared. As soon as the patients arrived at the intensive care unit, Hb levels and platelet counts were recorded. When calculating the total number of blood products transfused, the number of PPC suspensions administered to patients in group 1 was added to the total number of blood products transfused because PPC is also a blood product.

Statistical Analysis

At the beginning of data collection for the patients, a power analysis was conducted to determine the minimum sample size using G*Power statistics software (version 3.1.9.6). The sample size was difficult to calculate because no similar research could be found. The results showed that the required minimum sample size for each group was 45 to achieve 0.80 power for detecting a medium effect size (0.6) at a significance criterion of $\alpha = .05$. Thus, the sample size of 109 in this study seems adequate to obtain correct results. The Shapiro-Wilk test and the Q–Q plot test were used to determine whether the data followed a normal distribution. Data without normal distribution were compared with the Mann-Whitney *U* test and presented as median (minimum-maximum). A t test for continuous variables with normal distribution was used and presented as mean (SD). A χ^2 or Fisher exact test was used for categorical variables. Two-sided $P < .05$ was considered statistically significant. All statistics were calculated using the SPSS Statistics for Macintosh (version 27.0; IBM Corp).

Results

There was no statistically significant difference in clinical characteristics between the 2 groups (Table I). When the intraoperative data, such as the number of grafts and

TABLE I. Preoperative Patient Characteristics

Parameter	Group 1 (PPC) (n = 63)	Group 2 (non-PPC) (n = 46)	*P* value[a]
Age, mean (SD), y	61.65 (9.86)	61.00 (10.96)	.74
Female, No. (%)	25 (39.7)	20 (43.5)	.69
BMI, median (range)	30.12 (22.04-43.26)	30.45 (25.43-36.58)	.18
LVEF, median (range), %	45.00 (35.00-60.00)	45.00 (35.00-55.00)	.32
Diabetes mellitus, No. (%)	16 (25.4)	12 (26.1)	.93
Peripheral arterial disease, No. (%)	3 (4.76)	2 (4.34)	.91
Cerebrovascular disease, No. (%)	4 (6.34)	3 (6.52)	.97
Unstable angina, No. (%)	22 (34.92)	20 (43.47)	.36
LMCA >50% stenosis, No. (%)	10 (15.87)	8 (17.39)	.83
Hypertension, No. (%)	26 (41.3)	17 (37.0)	.64
Smoking, No. (%)	20 (31.7)	16 (34.8)	.73
PT, median (range), s	12.50 (11.00-15.00)	12.75 (11.00-15.00)	.87
INR, median (range)	1.10 (1.00-1.40)	1.10 (1.00-1.40)	.78
Creatinine levels, median (range), mg/dL	1.00 (0.80-2.10)	1.10 (0.80-1.80)	.32
GFR, median (range), mL/min	82.00 (67.00-95.00)	80.00 (64.00-95.00)	.21
Preoperative vasopressor support, No. (%)	5 (7.93)	6 (13.04)	.38
Preoperative IABP	None	None	-

BMI, body mass index; GFR, glomerular filtration rate; IABP, intra-aortic balloon pump; INR, international normalized ratio; LMCA, left main coronary artery; LVEF, left ventricle ejection fraction; PPC, pooled platelet concentrate; PT, prothrombin time.

[a] $P < .05$ is considered significant.

operation time, were compared, there was no difference between the 2 groups (Table II). However, the mean (SD) drainage amount was significantly higher in group 2 (475.39 [101.94] mL in group 1 and 679.34 [232.03] mL in group 2, $P = .001$), and as a result of this problem, the surgical revision rate was higher in group 2 (0% in group 1 and 15.2% in group 2, $P = .002$). During postoperative follow-up, although the length of stay in the intensive care unit was similar in the 2 groups, the time to discharge from the hospital was significantly longer for group 2 patients than for group 1 patients (Table II). Postoperative hospital mortality rates were similar in both groups (0% in group 1 and 2.2% in group 2, $P = .24$).

Preoperative Hb levels and platelet counts were similar between the groups (Table III); in addition, Hb levels and platelet counts decreased in the postoperative period. However, when the reduction rates in these values were compared, it was observed that the decrease of Hb in group 2 patients was much higher than that in group 1 patients (rate of decline in Hb: 23.7% in group 1 and 31.4% in group 2, $P = .001$; rate of decrease in platelet count; 17.9% in group 1 and 28.0% in group 2, $P = .001$).

The type and number of blood products used in patients are provided in Table IV. The PPC used for group 1 patients was also considered when calculating the number of blood products because PPC is also a blood product. In group 1, only 13 of 63 patients required erythrocyte suspension, and only 1 unit of erythrocyte was given to each of these 13 patients. In group 2, all 46 patients received red blood cell transfusions, and some patients were given a total of 95 units of red blood cell suspension because more than 1 unit of erythrocytes was transfused ($P = .001$). Similar results are obtained for FFP between the 2 groups: only 6 of 63 patients in group 1 required FFP transfusion, whereas in group 2, 45 of 46 patients underwent FFP transfusion. Moreover, many patients in group 2 required more than 1 unit of FFP ($P = .001$). As shown in Table IV, 63 patients in group 1 required 82 units of blood product in total (1.30 blood products/patient), whereas in the second group, this rate was calculated as 165 units of blood products for 46 patients (3.58 units of blood products/patient; $P = .001$). Although we added the number of PPC as blood products in group 1, the total number of blood products that were used was almost 3 times higher in group 2 than in group 1.

TABLE II. Operative and Postoperative Patient Data

Parameter	Group 1 (PPC) (n = 63)	Group 2 (non-PPC) (n = 46)	*P* value[a]
Time from administration of DAPT to surgery, median (range), h	10.00 (3.00-18.00)	12.0 (4.00-22.00)	.32
Graft count, median (range)	3.00 (1.00-5.00)	3.00 (1.00-5.00)	.69
Operation time, median (range), min	130 (65-185)	140 (55-185)	.14
Preoperative ACT, median (range), s	160 (110-220)	146 (100-220)	.42
Peak ACT during surgery, median (range), s	270 (200-400)	270 (200-400)	.91
Lowest intraoperative Hct, median (range), %	32 (28-42)	334 (26-42)	.53
Drainage amount, mean (SD), mL	475.39 (101.94)	679.34 (232.03)	.001
Surgical revision, No. (%)	0 (0)	7 (15.2)	.002
Postoperative inotropic support, No. (%)	5 (7.93)	6 (13.04)	.38
Postoperative mechanical support (IABP)	None	None	-
Stay at ICU, median (range), d	2 (2-3)	2 (2-4)	.36
Discharge after surgery, median (range), d	4 (4-6)	6 (4-9)	.001
Stroke, No. (%)	0 (0)	1 (2.17)	.24
Mortality, No. (%)	0 (0)	1 (2.17)	.24

ACT, activated clotting time; DAPT, dual antiplatelet therapy; Hct, hematocrit; IABP, intra-aortic balloon pump; ICU, intensive care unit; PPC, pooled platelet concentrate.

[a] $P < .05$ is considered significant.

TABLE III. Patient Hemoglobin and Platelet Counts

Factor	Group 1 (PPC) (n = 63)	Group 2 (non-PPC) (n = 46)	*P* value[a]
Preoperative Hb, mean (SD), g/dL	13.8 (1.35)	13.7 (0.83)	.67
Postoperative Hb, median (range), g/dL	11.0 (8.0-12.4)	10.0 (7.8-10.6)	.001
Rate of decrease in Hb, mean (SD), %	23.7 (6.74)	31.4 (6.13)	.001
Preoperative platelet count, median (range), × 10^9/L	185 (140-330)	185 (140-300)	.66
Postoperative platelet count, median (range), × 10^9/L	150 (108-270)	136 (100-208)	.001
Rate of decrease in platelet count, median (range), %	17.9 (6.8-33.0)	28.0 (12.5-35.0)	.001

Hb, hemoglobin; PPC, pooled platelet concentrate.

[a] $P < .05$ is considered significant.

TABLE IV. Use of Blood Products

	Group 1 (PPC) (n = 63)			Group 2 (non-PPC) (n = 46)			
	No. (%) of patients	Total No. of units	Median (range)	No. (%) of patients	Total No. of units	Median (range)	*P* value[a]
Used ES	13 (20.6)	13	0 (0-1)	46 (100)	95	2 (1-4)	.001
Used FFP	6 (9.5)	6	0 (0-1)	45 (97.8)	70	2 (0-3)	.001
Used PPC	63 (100)	63	-	-	-	-	-
No. of total transfused blood products (including PPC in group 1)	63	82	1 (1-4)	46	165	3 (2-7)	.001
Total transfused blood products, units/patient	1.30			3.58			.001

ES, erythrocyte suspension; FFP, fresh frozen plasma; PPC, pooled platelet concentrate.

[a] $P < .05$ is considered significant.

Discussion

Today, the use of DAPT is vital in treating coronary artery disease. It has become the cornerstone of therapy, especially in patients with ACS, by being administered as soon as possible and providing significant benefits to patient outcomes.[4] Recent guidelines recommend specific loading doses for DAPT for patients with ACS, along with specific doses for maintenance therapy.[1] Unfortunately, despite the excellent antiplatelet effects of DAPT, there are also risks of spontaneous or surgical bleeding.[5] Patients undergoing emergent coronary artery bypass surgery under the influence of DAPT loading have more frequent surgical bleeding complications and worse outcomes due to bleeding.[6] Therefore, current revascularization guidelines recommend stopping these drugs at least 5 days before elective surgery.[1] However, the cardiac conditions may necessitate immediate surgery.

Dual antiplatelet therapies have long half-lives; therefore, a new drug that either has a much shorter half-life or that can be easily neutralized must be developed. As another option, new treatment strategies, such as off-pump surgery, should be emphasized to increase surgical safety.

On the other hand, research continues for new drug therapies to provide safer treatment. Therefore, in this study, it was hypothesized that new platelets taken from healthy donors not affected by DAPT might decrease bleeding complications.

Recently, Charif et al[7] published an article investigating the same problem; however, the amount of chest tube drainage was similar in both groups. On the other

hand, the amount of blood products used in both patient groups was relatively low compared with this case series. Despite not using PPC in patients given DAPT, 24-hour drainage amounts were approximately 240 mL in this investigation. Moreover, Charif et al[7] performed all surgeries as on-pump. However, in the current study, a statistically significant difference in the amount of drainage between the 2 groups was observed (Table II). In another investigation, van Hout et al[8] reported that platelet suspension decreased the amount of postoperative bleeding but increased the need for transfusion of other blood products. This study arouses curiosity about why the need for blood product transfusion is higher, although the amount of bleeding is more minor.

Patients with ACS are candidates for percutaneous coronary interventions and coronary artery bypass surgery. DAPT drugs reduce the risk of ischemia but, on the other hand, increase the risk of bleeding.[9,10] In this investigation, the amount of bleeding in the PPC group was statistically lower than that in the non-PPC group (P = .001). This result shows that the administration of PPC significantly reduces the amount of drainage; as a result, when the number of surgical revisions was compared, patients who received PPC had a statistically significant lower need for surgical revision (0% vs 15.2%, P = .002).

The use of blood products increases the risks of blood transfusions (infection, inflammatory response, renal impairment, etc) and costs. The cost-effectiveness of blood products was not calculated in this study. Lower use of blood products has benefits such as reducing infection[11] and kidney problems.[12] There is morbidity associated with homologous blood products, such as transfusion reactions, wound infections, sepsis, increased hospital mortality, and decreased postdischarge survival.[9] In this study, the need for FFP and erythrocyte suspension was significantly lower in the PPC group (Table IV). Whereas only 20.63% of the patients in the PPC group required erythrocyte suspension, 100% of the patients in the non-PPC group required erythrocyte suspension (P = .001). As a reflection that the amount of bleeding in the patients who received PPC was lower, the surgical revision rate was significantly lower, and surgical drains could be removed earlier in patients with minor bleeding. Thus, patients were mobilized earlier with increased comfort.

Despite the risk for emergent coronary artery bypass surgery for all patients with ACS, the use of DAPT has now become an accepted treatment option.[13] Many researchers report that the application of off-pump surgery causes significantly less postoperative bleeding and a lower need for blood transfusion.[14,15] The CORONARY study (The CABG Off or On Pump Revascularization Study), a multicenter worldwide survey with many patients, revealed that off-pump surgery causes less bleeding than on-pump surgery.[16] It is well known that cardiopulmonary bypass has many adverse effects on hemolysis, fibrinolysis, fibrinogen, plasminogen, and coagulation factors. It also negatively affects platelet count and functions. Therefore, the use of PPC during on-pump surgery will benefit patients who have received DAPT. However, new research, including on-pump patients, should be planned for more precise results.

Limitations of the Study

First, all the patients in this study underwent off-pump surgery; therefore, the consequences when performing on-pump surgery are unknown. Many factors that are difficult to control during on-pump surgery will influence bleeding because cardiopulmonary bypass has many adverse effects on many systems, causing inflammatory responses. During on-pump surgery, the necessary administration of higher doses of heparin than in off-pump surgery may increase bleeding and, therefore, increase the need for blood product transfusion.

Second, within the scope of DAPT, there are many new-generation antiplatelet drugs other than clopidogrel. In this study, only patients who were given acetylsalicylic acid combined with clopidogrel as DAPT were examined to avoid confusion. A comparative study with patients using other antiplatelet agents may be needed.

Last, this was a single-center study that included a small number of patients. According to the experience and surgical strategy of the centers, the average amount of postoperative bleeding may differ in many centers. Although an imposing result regarding the total number of transfusions was reported, a more comprehensive study involving many surgical teams is required to attain more objective results.

Conclusion

Because DAPT given in treating ACS has irreversible effects on platelet functions, it is impossible to neutralize the effects of these drugs. Instead, it is safe to administer unaffected platelets to the patient. Using perioperative PPC in patients with DAPT loading reduces the amount of postoperative bleeding, reduces the need for

blood products, and shortens hospital stay. As a result, it has beneficial effects for early mobilization and improves patient comfort.

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