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Early clinical outcomes of surgical myocardial revascularization in patients with preoperative platelet dysfunction

Neposredni ishodi hirurške revaskularizacije miokarda kod bolesnika sa preoperativnom disfunkcijom trombocita

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Abstract

Background/Aim. Coronary artery bypass grafting (CABG) is the treatment of choice for a significant number of patients with ischemic heart disease. Some of the postoperative complications are closely linked with the preoperative antiplatelet therapy (APT). The aim of this study was to compare the early clinical outcomes of CABG in patients with preserved platelet (PLT) function and patients with PLT function impaired by the residual therapeutic effect of APT. **Methods.** A total of 181 patients with isolated CABG were enrolled in this prospective, nonrandomized, observational study. Patients were divided into four groups: control group (arachidonic acid-dependent PLT aggregation group), with aspirin-induced platelet inhibition (ASPI) test ≥ 790 aggregation units (AU)/min; mild (M) acetylsalicylic acid (ASA) effect (MASAE) group, with ASPI test = 410–789 AU/min; pronounced (P) ASA effect (PASAE) group, with ASPI test ≤ 409 AU/min; dual (D) APT (DAPT) group, with ASPI test ≤ 789 AU/min and adenosine diphosphate (ADP) test ≤ 405 AU/min. Preoperative data, intraoperative characteristics, and postoperative outcomes were obtained and compared between the groups. **Results.** A significant difference was found regarding the average time of APT cessation between groups ($p < 0.001$). The DAPT group had a significantly higher frequency of drainage compared to the control ($p = 0.004$), MASAE ($p = 0.001$), and PASAE ($p = 0.006$) groups. The PASAE group had a significantly higher rate of chest reexploration compared to the MASAE group ($p = 0.032$). The DAPT group required significantly more packed red blood cells (PRBC) compared to the control ($p < 0.001$) and MASAE ($p = 0.009$) groups. The PASAE group received significantly more PRBC compared to the control ($p < 0.001$) and MASAE ($p = 0.019$) groups. The DAPT group required higher amounts of PLTs compared to the control ($p < 0.001$), MASAE ($p = 0.002$), and PASAE ($p < 0.001$) groups. The DAPT group received higher amounts of cryoprecipitate compared to the control ($p = 0.002$), MASAE ($p = 0.009$), and PASAE ($p = 0.016$) groups. **Conclusion.** Patients with a residual effect of DAPT, as well as patients with a pronounced residual effect of ASA, have a higher risk of postoperative bleeding and chest reexploration, as well as increased transfusion demands.

Key words:
coronary artery bypass; coronary disease; platelet aggregation; platelet aggregation inhibitors; treatment outcome.

Apstrakt

Uvod/Cilj. Hirurška revaskularizacija miokarda (*coronary artery bypass grafting* – CABG) kod značajnog broja bolesnika je osnovni vid lečenja ishemijske bolesti srca. Neke od postoperativnih komplikacija su blisko povezane sa preoperativnom antiagregacionom terapijom (AAT). Cilj rada bio je da se uporede neposredni ishodi CABG kod bolesnika sa očuvanom funkcijom trombocita i bolesnika kod kojih je funkcija trombocita bila narušena rezidualnim efektom AAT. **Metode.** Prospektivnom, opsrevacionom, nerandomizovanom studijom obuhvaćeno je 181 bolesnika sa izolovanim CABG. Bolesnici su bili podeljeni na četiri grupe: kontrolnu grupu (agregacija trombocita zavisna od arahidonske kiseline), sa *aspirin-induced platelet inhibition* (ASPI) testom ≥ 790 agregacionih jedinica (*aggregation units* – AU)/min; grupu bolesnika sa blagim efektom (BE) acetilsalicilne kiseline (ASK) (BEASK), sa ASPI testom = 410–789 AU/min; grupu bolesnika sa izraženim efektom (IE) ASK (IEASK), sa ASPI testom ≤ 409 AU/min; grupu bolesnika sa dvojnom (D) AAT (DAAT), sa ASPI testom ≤ 789 AU/min i adenozin difosfat (ADF) testom ≤ 405 AU/min. Preoperativni podaci, intraoperativne karakteristike i postoperativni ishodi upoređeni su među grupama. **Rezultati.** Ispitivane grupe su se značajno razlikovale u odnosu na prosečno vreme obustave AAT

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(p < 0,001). DAAT grupa imala je značajno češću drenažu u poređenju sa kontrolnom (p = 0,004), BEASK (p = 0,001) i IEASK (p = 0,006) grupom. Grupa IEASK imala je značajno veću učestalost reeksploracije grudnog koša u poređenju sa BEASK grupom (p = 0,032). Bolesnici iz DAAT grupe primili su značajno više koncentrovanih eritrocita u poređenju sa kontrolnom (p < 0,001) i BEASK (p = 0,009) grupom. Bolesnici iz IEASK grupe primili su značajno više koncentrovanih eritrocita u poređenju sa kontrolnom (p < 0,001) i BEASK (p = 0,019) grupom. DAAT grupa primila je značajno više trombocita u poređenju sa kontrolnom (p < 0,001), BEASK (p = 0,002) i IEASK (p < 0,001) grupom. Transfuzije krioprecipitata bile su značajno češće u DAAT grupi u poređenju sa kontrolnom (p = 0,002), BEASK (p = 0,009) i IEASK (p < 0,016) grupom. **Zaključak**. Bolesnici sa rezidualnim efektom DAAT, kao i bolesnici sa izraženim rezidualnim efektom ASK imaju povišen rizik od postoperativnog krvarenja i reeksploracije grudnog koša, kao i povećanu potrebu za transfuzijama.

Ključne reči:
aortokoronarno premošćavanje; koronarna bolest; trombociti, agregacija; antiagregaciona sredstva; lečenje, ishod.

Introduction

Surgical myocardial revascularization is the treatment of choice for patients with ischemic heart disease who are not candidates for percutaneous coronary interventions (PCI) [1]. Even though coronary artery bypass grafting (CABG) has been one of the most performed surgical procedures, operative mortality is still high, about 2.8%. The incidence of postoperative complications after CABG surgery ranges between 30% and 40%, depending on the study and type of complication [2, 3].

Perioperative coronary events and bleeding are common and important complications after CABG, and both of them are strongly influenced by the management of preoperative antiplatelet therapy (APT) [4].

The incidence of perioperative myocardial infarction (PMI) ranges from 2–12%, depending on the definition and methodology used in detection [5]. Studies conducted so far have shown that PMI is a significant predictor of increased mortality in the first 30 days and the first six months after surgery [6].

Bleeding is the most important cause of chest reexploration (2–5% of patients) after CABG. In patients with this complication, there is a significantly higher in-hospital mortality (3.3% vs. 9.5%), a twice as long stay in the intensive care unit, more frequent need for inotropic therapy, as well as frequent need for an expensive broad spectrum antibiotic as meropenem active against gram-positive and gram-negative bacteria [7]. Hemorrhagic events are associated with more transfusions of blood products and thus increase operative mortality and morbidity and compromise the long-term benefits of CABG [8, 9].

According to current guidelines, dual APT (DAPT) is recommended for all patients after acute coronary syndrome and after percutaneous myocardial revascularization. In patients with stable coronary disease, routine use of DAPT is not indicated [10]. The main problem with DAPT is establishing a balance between adverse ischemic events and hemorrhagic complications, which are frequent in patients on antiplatelet drugs. That is especially pronounced in patients in whom both CABG and DAPT are indicated, such as patients who require more urgent CABG in the early period after acute coronary syndrome, which is about 5–10% of all patients with acute coronary syndrome [11].

The results of the studies conducted so far, which refer to the preoperative use of acetylsalicylic acid (ASA), are largely contradictory, and the recommendations related to the use of ASA in cardiac surgery patients have often changed. Most recent studies indicate better short-term and long-term survival, lower incidence of adverse cardiovascular events, and better long-term patency of the vein graft in patients treated preoperatively with ASA without a significant increase in adverse hemorrhagic events [12, 13].

Therefore, according to current guidelines, stopping ASA before cardiac surgery is not recommended [14].

Based on our clinical experience [15] and what has been confirmed in a large number of studies, the preoperative administration of platelet (PLT) $P2Y_{12}$ receptor ($P2Y_{12}R$) antagonists is associated with excessive blood loss, a higher frequency of chest reexploration, and increased transfusion requirements in the postoperative period [16].

According to current guidelines, clopidogrel should be stopped at least five days before surgery and ticagrelor three days before surgery. In patients in whom urgent myocardial revascularization is indicated, $P2Y_{12}R$ antagonists should be stopped at least 24 hours before surgery [14].

The aim of this study was to compare the early clinical outcomes of surgical myocardial revascularization in patients with preserved PLT function and patients with PLT function impaired by the residual therapeutic effect of APT.

Methods

Study design

The study was conducted as a prospective, nonrandomized, observational study and included 181 patients. Patients were treated at the Department of Cardiac Surgery, University Clinical Center of Niš, Serbia from June 2021 to October 2022.

The research was approved by the Ethics Committee of the University Clinical Center of Niš (No. 3830/6, from February 4, 2020) and by the Ethics Committee of the Faculty of Medicine of Niš (No. 12-15637-2/9, from December 24, 2019) and was conducted following the ethical standards specified in the Declaration of Helsinki (1964) and subsequent amendments of the declaration.

All patients older than 18 years who underwent isolated, elective surgical myocardial revascularization with extracorporeal circulation and cardioplegic arrest were included in the study. Exclusion criteria were the following: patients with elevated preoperative values of cardiac enzymes [high sensitivity troponin I (hsTnI) and creatine kinase-MB fraction (CK-MB)]; myocardial revascularization with "off-pump" technique; patients who underwent combined myocardial revascularization and heart valve surgery or aortic surgery; emergency patients operated in a cardiogenic shock; patients whose biological material was inadequately sampled.

Clinical methodology

Upon admission to the hospital, all patients underwent a physical examination with anthropometric parameters measurement. The 12-channel electrocardiogram (ECG) and an echocardiographic examination, focusing on the ejection fraction (Teicholz) and the kinetics of the left ventricular walls, were performed.

The patients underwent standard surgical revascularization of the myocardium under general endotracheal anesthesia, with extracorporeal circulation (ECC) and cardioplegic arrest. Cold crystalloid cardioplegia was used, and surgical procedures were performed under conditions of mild hypothermia 32–35 °C. The left internal thoracic artery and the great saphenous vein were used as grafts. The Cell Saver model Xtra device (LivaNova, United Kingdom) was used for intraoperative blood saving.

All patients received a single bolus dose of 30 mg/kg of tranexamic acid after heparin administration before ECC. Heparin reversal was achieved with protamine in a 1:1 fixed dose ratio. Effective heparin reversal was defined as post-reversal activated coagulation time (ACT) within 10% of the baseline ACT value.

Every postoperative day, patients underwent a 12-channel ECG. Echocardiography was performed on the second postoperative day and more often if necessary.

Transfusions were administered according to the clinic's established protocol, based on the blood count, the results of impedance aggregometry, and rotational thrombelastometry (ROTEM, Delta Roche, Germany). For rotational thrombelastometry, 4 mL of whole blood was sampled in a test tube with sodium citrate.

The indication for intraoperative packed red blood cells (PRBC) transfusion was a hematocrit value < 22% during ECC. After surgery, the decision for transfusions was based on postoperative hemodynamics, laboratory parameters, and chest tube drainage.

The decision to perform chest reexploration was based on conventional guidelines, the amount of blood loss according to the Kirklin and Barratt-Boyes criteria: 1) drainage of more than 500 mL during the first hr, more than 400 mL during each of the first 2 hrs, more than 300 mL during each of the first 3 hrs, more than 1,000 mL in total during the first 4 hrs, and more than 1,200 mL in total during the first 5 hrs; 2) excessive bleeding that restarts; 3) sudden massive bleeding; 4) hemodynamic status of the patient and laboratory parameters.

Laboratory analysis

To assess PLT function, a whole blood impedance aggregometry (MULTIPLATE, Roch, Germany) was used. Blood for analysis was sampled upon admission and 2 hrs before the start of the operation in a 4 mL test tube with the anticoagulant lithium-heparin. All analyses were carried out within 30 min from the moment of sampling. The values of the parameters of the multiplate test that indicate a disorder of PLT function were defined based on the manufacturer's recommendations and guides: adenosine diphosphate (ADP) test reference range (RR) values 406–1,130 aggregation units per min (AU/min); arachidonic acid-dependent PLT aggregation (ASPI) test RR values 790–1,490 AU/min.

Cardiac enzymes (hsTnI and CK-MB) were measured: 24 hrs before surgery, blood sampling from a peripheral vein; perioperative – 10 min after releasing the aortic clamp, blood sampling from the arterial line; 24 hrs after surgery, blood sampling from the arterial line. For analysis, 4 mL of whole blood was sampled in a test tube with ethylenediaminetetraacetic acid (EDTA) anticoagulant. RR values for hsTnI were 0.00–0.04 ng/mL, and for CK-MB, 0–24 U/L.

According to the PLT function, all patients were classified into four groups. Patients with ADP and ASPI tests within the RR had preserved PLT function and were classified into the control group (n = 57). Patients with ASPI test < 790 AU/min had a residual effect of ASA and were divided into two groups: mild (M) ASA (MASA) effect (MASAE) group – ASPI test in the range 410–789 AU/min (n = 37) and pronounced (P) ASA (PASA) effect (PASAE) group – ASPI test ≤ 409 AU/min (n = 47). Patients with both the ASPI test ≤ 789 AU/min and the ADP test ≤ 405 AU/min were classified into the DAPT group (n = 40), given that they had a residual effect of both ASA and PLT $P2Y_{12}R$ antagonists.

Patients from the control group and MASAE group were considered to be at low risk for hemorrhagic complications, while subjects from the PASAE group and the DAPT group were at high risk for hemorrhagic adverse events.

The investigated variables were divided into three groups: preoperative, perioperative, and postoperative data.

Preoperative data: basic demographic data (gender, age); present comorbidities: diabetes mellitus, heart failure (defined as ejection fraction < 40%), and obesity (defined as body mass index > 30 kg/m^2); characteristics of coronary disease: left main stenosis > 50%, previous PCI; APT (type of drug, discontinuation of therapy).

Perioperative characteristics were the following: number of grafts, left internal thoracic artery (also known as left internal mammary artery – LIMA) usage, aortic cross-clamp (ACC) time, extracorporeal circulation (ECC) time, autotransfusion with cell saver, and perioperative values of hsTnI and CK-MB.

Postoperative outcomes were the following: hsTnI and CK-MB values (24 hrs after surgery), postoperative chest tube drainage, transfusion requirements, chest reexploration, PMI (defined according to the recommendations of the European Association of Cardiology [17]), postoperative inotropic therapy, heart rhythm disorders that required therapy, prolonged intubation (over 24 hrs), pneumonia, pneumothorax, pleural effusion requiring thoracentesis or drainage, cerebrovascular insult, transient ischemic attack, acute renal failure (requiring hemodialysis), chest wound infection, intensive care length of stay, total length of hospitalization (after surgery), and intrahospital mortality.

Statistical analysis

The data were described using the measures of central tendency in the form of the arithmetic mean and standard deviation or in the form of absolute and relative numbers. The normality of data distribution was tested with the Kolomogorov-Smirnov test. Comparisons of continuous variables, normally distributed between the four groups, were performed by analysis of variance (ANOVA) with the *post-hoc* Bonferroni test. If the data distribution was not normal, the comparison of values between the groups was performed using the Kruskal-Wallis test. A comparison of categorical features was performed using the Chi-squared test and Fisher's test. IBM SPSS version 16 (Chicago, Illinois) was used for the statistical analysis. The results were presented in the given Tables and Figures. Statistical significance was set at the *p*-value of less than 0.05.

Results

Data provided from 181 patients were evaluated. The patients were divided into four groups: patients with normal PLT function (n = 57); patients with MASA residual effect (n = 37); patients with PASA residual effect (n = 47); patients with ASA and $P2Y_{12}$ antagonist residual effect (n =40). The demographic and preoperative characteristics of patients are shown in Table 1.

There was no significant difference between groups regarding the demographic and preoperative clinical characteristics, except for the average time of APT cessation, which differed significantly between the studied groups. We found a statistically significant difference in the average time of ASA cessation between groups. Patients from the MASAE group had a significantly shorter average time of ASA withdrawal compared to the control group ($p < 0.001$). Patients from the PASAE group had a significantly shorter average time of ASA cessation compared to the control group ($p < 0.001$) and the MASAE group ($p < 0.001$). Patients from the DAPT group had a significantly shorter average time of ASA withdrawal compared to the control group ($p < 0.001$) and the MASAE group ($p = 0.011$). We did not find a statistically significant difference regarding ASA withdrawal average time between the PASAE and DAPT groups. Patients from the DAPT group had a significantly shorter average time of $P2Y_{12}$ antagonist withdrawal compared to the control, MASAE, and PASAE groups ($p < 0.001$ for all). There was no statistically significant difference in the average time of a $P2Y_{12}$ antagonist withdrawal between the control group and the MASAE and PASAE groups. Patients' perioperative characteristics are shown in Table 2, and the examined variables were not different between the groups. The lowest average chest tube drainage was recorded in the MASAE group (1,017.84 ± 520.11 mL), and the highest drainage was in the DAPT group (1,451.5 ± 700.5 mL). It was determined that there was a statistically significant difference in postoperative drainage among the examined groups ($p = 0.002$). Patients from the DAPT group had significantly higher drainage compared to the control ($p = 0.004$), MASAE ($p = 0.001$), and PASAE ($p = 0.006$) groups. There was no significant difference regarding postoperative drainage between the control group and the MASAE and PASAE groups.

The frequency of chest reexploration between the examined groups was significantly different ($p = 0.017$). Patients from the PASAE group had a significantly higher rate

Table 1

Demographic and preoperative characteristics of the patients

Characteristics	Groups				*p*-value
	Control	MASAE	PASAE	DAPT	
Age (years)	62.91 ± 7.98	63.19 ± 7.40	63.28 ± 7.95	63.78 ± 8.72	0.965[1]
Subjects	57 (31.5)	37 (20.4)	47 (26)	40 (22.1)	0.183[2]
female	14 (24.6)	6 (16.2)	14 (29.8)	5 (12.5)	0.179[2]
male	43 (75.4)	31 (83.8)	33 (70.2)	35 (87.5)	0.179[2]
Diabetes mellitus	22 (38.6)	16 (43.2)	19 (40.4)	10 (25.0)	0.318[2]
Obesity	14 (24.6)	10 (27.0)	17 (36.2)	7 (17.5)	0.257[2]
LM stenosis	13 (22.8)	11 (29.7)	18 (38.3)	18 (45.0)	0.107[2]
Previous PCI	7 (12.3)	4 (10.8)	7 (14.9)	4 (10.0)	0.905[2]
Ejection fraction	51.53 ± 8.88	49.32 ± 7.73	51.83 ± 7.91	51.30 ± 9.56	0.555[1]
Ejection fraction < 40%	9 (15.8)	7 (18.9)	6 (12.8)	8 (20.0)	0.797[2]
ASA withdrawal (days)	5.92 ± 1.8[a,b,c]	2.56 ± 1.7[a,b]	1.23 ± 0.7	1.88 ± 1.6	< 0.001[3]
$P2Y_{12}$ antagonist withdrawal (days)	6.06 ± 1.33[a]	6 ± 1.26[a]	5.63 ± 1.70[a]	3.58 ± 1.4	< 0.001[3]

MASAE – mild acetylsalicylic acid effect; PASAE – pronounced acetylsalicylic acid effect; DAPT – dual antiplatelet therapy; LM – left main coronary artery; PCI – percutaneous coronary intervention. All values are expressed as numbers (percentages) or mean ± standard deviation. [1]ANOVA – analysis of variance test; [2]Chi-squared test; [3]Kruskal-Wallis test.

[a]*p* < 0.05 vs. DAPT group; [b]*p* < 0.05 vs. PASAE group; [c]*p* < 0.05 vs. MASAE group.

Table 2

Surgery-related characteristics of the patients

Parameter	Groups				p-value
	Control	MASAE	PASAE	DAPT	
Average graft No	2.70 ± 0.57	2.70 ± 0.57	2.77 ± 0.67	2.68 ± 0.66	0.912[1]
LIMA	53 (93.0)	35 (94.6)	39 (83)	34 (85)	0.205[2]
ACC (min)	50.19 ± 16.34	50.81 ± 22.05	52.96 ± 21.51	51.18 ± 18.09	0.907[1]
ECC (min)	96.63 ± 22	98.76 ± 29.9	99.87 ± 26.01	105.73 ± 35.5	0.467[1]
Cell saver (mL),	926.32 ± 264.09	956.76 ± 315.6	1,025.53 ± 315.69	1,152.5 ± 483.57	0.123[3]
hsTnI (ng/mL)	0.82 ± 0.78	0.84 ± 0.89	0.9 ± 1.13	0.91 ± 1.38	0.964[3]
CK-MB (U/L)	33.48 ± 11.17	31.81 ± 8.73	35.59 ± 16.19	34.03 ± 9.52	0.548[1]

LIMA – left internal thoracic artery; ACC – aortic cross-clamp; ECC – extracorporeal circulation; hsTnI – high sensitivity troponin I; CK-MB – creatine kinase-MB fraction; min – minutes. For abbreviations of other terms, see Table 1.
All results are shown as mean ± standard deviation, except the LIMA parameter which is shown as number (percentage).
[1]ANOVA; [2]Chi-squared test; [3]Kruskal-Wallis test.

of chest reexploration compared to the MASAE group ($p = 0.032$). There was no statistically significant difference in the chest reexploration rate between the control group and MASAE, PASAE, and DAPT groups. Moreover, no significant difference was found regarding the chest reexploration rate between the MASAE and DAPT groups, as well as between the PASAE and DAPT groups (Table 3).

Using the Kruskal-Wallis test, we found a statistically significant difference regarding the intraoperative and postoperative PRBC transfusion requirements ($p < 0.001$). Subjects from the DAPT group required significantly more PRBC compared to the control group ($p < 0.001$) and the MASAE group ($p = 0.009$). Subjects from the PASAE group received significantly more PRBC compared to patients from the control group ($p < 0.001$) and the MASAE group ($p = 0.019$). There was no statistically significant difference regarding PRBC requirements between the control and MASAE groups, as well as between PASAE and DAPT groups. Intraoperative and postoperative PLT transfusion requirements differed significantly between the studied groups ($p < 0.001$). Patients from the DAPT group required higher amounts of PLT compared to the control ($p < 0.001$), MASAE ($p = 0.002$), and PASAE ($p < 0.001$) groups. There was no significant difference in PLT transfusion requirements between the control, MASAE, and PASAE groups. There was a statistically significant difference regarding the cryoprecipitate (Cryo) transfusion requirements ($p = 0.004$). Patients from the DAPT group received higher amounts of Cryo compared to the control group ($p < 0.002$), the MASAE group ($p = 0.009$), and the subjects from the PASAE group ($p < 0.016$). Cryo transfusion requirements did not differ significantly between the control, MASAE, and PASAE groups. No significant disparities were found regarding transfusion of fresh frozen plasma (FFP) requirements between groups ($p = 0.872$) (Table 4).

PMI was recorded in 12 subjects (6.6%). The highest rate was recorded in the control group with preserved PLT function and the lowest in the DAPT group (8.8% vs. 2.5%). Using the Chi-squared test, it was shown that there is no statistically significant difference in the frequency of PMI among the examined groups ($p = 0.541$). The hsTnI and CK-MB values 24 hrs after surgery did not differ significantly

Table 3

Adverse hemorrhagic events in the postoperative period

Parameter	Groups				p-value
	Control	MASAE	PASAE	DAPT	
Drainage (mL), mean ± SD	1,080.96 ± 387.02[a]	1,017.84 ± 520.11[a]	1,186.6 ± 669.54[a]	1,451.5 ± 700.5	0.002[1]
Chest reexploration, n (%)	2 (3.5)	0 (0)[b]	6 (12.8)	5 (12.5)	0.017[2]

For abbreviations, see Table 1. [1]ANOVA; [2]Chi-squared test; [a] $p < 0.05$ vs. DAPT group; [b]$p < 0.05$ vs. PASAE group (Fisher test).

Table 4

Transfusion requirements

Parameter	Groups				p-value
	Control	MASAE	PASAE	DAPT	
PRBC (mL)	417.54 ± 420.62[a,b]	510.81 ± 525.61[a,b]	872.34 ± 774.16	988.75 ± 834.63	< 0.001
PLT (U)	1.49 ± 3.53[a]	2.43 ± 4.95[a]	2.81 ± 7.02[a]	6.05 ± 5.34	< 0.001
Cryo (U)	1.40 ± 3.50[a]	1.57 ± 3.62[a]	1.91 ± 3.98[a]	4.50 ± 5.52	0.004
FFP (mL)	505.61 ± 284.92	508.65 ± 293.47	580.43 ± 433.80	599.50 ± 395.40	0.872

PRBC – packed red blood cells; PLT – platelets; Cryo – cryoprecipitate; FFP– fresh frozen plasma; U – unit. For abbreviations of other terms, see Table 1. [a]$p < 0.05$ vs. DAPT group; [b]$p < 0.05$ vs. PASAE group (Kruskal-Wallis test). All results are shown as mean ± standard deviation.

Table 5

Perioperative and postoperative myocardial infarction (PMI) incidence and cardiac enzyme values (24 hrs)

Parameter	Groups				*p*-value
	Control	MASAE	PASAE	DAPT	
PMI	5 (8.8)	2 (5.4)	4 (8.5)	1 (2.5)	0.541[1]
hs-TnI (ng/mL)	5.89 ± 8.87	4.1 ± 3.4	5.71 ± 9.03	4.44 ± 4.07	0.653[2]
CK-MB (U/L)	53.25 ± 31.95	54.43 ± 39.44	48.72 ± 39.4	43.48 ± 25	0.653[2]

For abbreviations, see Tables 1 and 2. All results are shown as mean ± standard deviation, except the PMI parameter which is shown as number (percentage). [1]Chi-squared test; [2]ANOVA.

Table 6

In-hospital outcomes

Parameter	Groups				*p*-value
	Control	MASAE	PASAE	DAPT	
Inotropic support	16 (28.1)	11 (29.7)	20 (42.6)	10 (25.0)	0.294[1]
Arrhythmias	16 (28.1)	9 (24.3)	16 (34.0)	13 (32.5)	0.761[1]
Intubation > 24 hrs	4 (7.0)	1 (2.7)	6 (12.8)	3 (7.5)	0.365[1]
Pneumonia	1 (1.8)	1 (2.7)	1 (2.1)	0 (0.0)	0.658[1]
Pneumothorax	0 (0.0)	2 (5.4)	3 (6.4)	4 (10.0)	0.053[1]
Pleural effusion	2 (3.5)	1 (2.7)	5 (10.6)	1 (2.5)	0.280[1]
Hospitalization (days)	7.12 ± 2.10	6.97 ± 1.17	8.66 ± 6.22	7.43 ± 1.65	0.165[2]
ICU (days)	3.00 ± 1.87	2.78 ± 1.25	4.64 ± 6.39	3.45 ± 1.81	0.268[2]

ICU – intensive care unit. For abbreviations of other terms, see Table 1. All results are shown as numbers (percentages) except hospitalization and ICU, which are shown as mean ± standard deviation. [1]Chi-squared test; [2]ANOVA.

between the examined groups ($p = 0.653$) (Table 5). Postoperative outcomes and complications are shown in Table 6. There was no significant difference between groups regarding the postoperative outcomes.

In our study, there was no intrahospital mortality, no adverse cerebrovascular events, no acute renal failure requiring hemodialysis, and no chest wound infections manifested during the early postoperative period.

Discussion

A significant number of patients who had to undergo CABG are exposed to DAPT. According to the current guidelines, preoperative withdrawal of ASA is not recommended, given that a number of studies confirm lower operative mortality and a lower rate of adverse cardiovascular events in patients who did not discontinue ASA. On the other hand, due to the increased risk of adverse hemorrhagic events, current guidelines recommend preoperative cessation of clopidogrel for at least five days and ticagrelor for three days before surgery.

However, it is not always possible to wait three to five days after cessation of DAPT to perform CABG because many patients require urgent myocardial revascularization or are at increased risk of stent thrombosis [18]. In these patients, we expect an increased rate of hemorrhagic complications in the postoperative period, as well as an increased transfusion requirement. In the majority of studies conducted so far, the risk of hemorrhagic events was assessed based on the time of APT cessation. In our opinion, the only reliable way to assess the risk of hemorrhagic complications related to the application of APT is the preoperative analysis of PLT function using impedance aggregometry. The time of discontinuing APT preoperatively is not an accurate indicator of PLT function due to individual differences in drug reactivity, as well as possible resistance to therapy.

Data related to the importance of routine application of PLT function tests in CABG patients are available in the literature [15, 19]. Furthermore, in the majority of conducted studies, all patients treated with ASA are classified in the same group. In our study, patients were divided into two groups according to the residual effect of ASA intensity. Data from the literature indicate a lower rate of PMI in patients who preoperatively received APT. In this research, we tried to determine how APT affects intraoperative and postoperative values of cardiac enzymes. There was no significant difference between the investigated variables among the examined groups, except for the average time of APT cessation, which was expected.

Although there is no significant difference, it is evident that the lower utilization of LIMA is a characteristic of the groups with an increased risk of intraoperative and postoperative bleeding (PASAE group 83.0%, DAPT group 85.0%). In the control and MASAE groups, LIMA usage corresponds to the data from the available literature (93.0%, 94.6%). A lower utilization of LIMA, without a statistically significant difference, in patients on DAPT compared to patients on ASA monotherapy was also noted in the study conducted by Qu et al. [20] (94.9% vs. 92.7%). Based on these results, it can be concluded that in patients with significantly impaired PLT function, there is a more demanding LIMA harvesting, with an increased risk of iatrogenic trauma, which is probably a consequence of difficult hemostasis during the preparation. In all subjects, we used the pedicled LIMA harvesting technique, which can affect obtained results, as well as surgeon experience. Of particular importance is the fact that in patients with a stronger residual effect of ASA, LIMA usage is 11.4% lower compared to subjects with a mild residual effect of ASA.

We did not find a statistically significant difference in the duration of ECC and ACC between the examined groups. Therefore, we can rule out the negative effect of prolonged ECC on postoperative hemostasis. The obtained results are in correlation with the study conducted by Charif et al. [21]. There was no statistically significant difference in the amount of intraoperatively saved blood among the examined groups. That correlates with the results of the study by Kapetanakis et al. [22] and Cao et al. [23]. In addition, about 200 ml more blood was saved intraoperatively in the DAPT group compared to the control group.

There was no significant difference in the intraoperative and postoperative values of myocardial necrosis markers (hsTnI/CK-MB) between the studied groups. In the available literature, there is no data regarding the influence of preoperative PLT function on intraoperative and postoperative values of myocardial necrosis markers. Based on these results, it cannot be determined with certainty whether APT has a protective effect on the myocardium in cardiac surgery patients, so additional research in this field is necessary.

Patients with a residual therapeutic effect of DAPT had the highest postoperative chest tube drainage. In this group, drainage was significantly higher compared to the group with normal PLT function and compared to both groups where the PLT function was impaired due to the residual effect of ASA. The study by Petricevic et al. [15] also confirmed a higher risk of postoperative bleeding in patients with a residual effect of PLT $P2Y_{12}$ antagonist. The difference in the amount of drained blood between patients with normal PLT function and patients from the groups with residual effect of ASA was not significant. That correlates with the study by Myles et al. [24]. On the other hand, most of the older studies conducted before the year 2000 showed significantly higher drainage in patients on ASA compared to the control group. Patients from the PASAE group had a significantly higher frequency of hemorrhage-induced chest reexploration compared to the MASAE group. The majority of the studies conducted so far did not divide patients with residual ASA effect and compare chest reexploration rate according to the residual ASA effect intensity. In our study, there was no statistically significant difference in the chest reexploration rate between the control and MASAE group, between the control and PASAE group, and between the control and DAPT group. Likewise, we did not find significant differences regarding the chest reexploration rate between the MASAE and DAPT groups, as well as between the PASAE and DAPT groups. Results from studies available in the literature are conflicting. A study by Morawski et al. [25] indicates an increased frequency of chest reexploration in patients treated with ASA preoperatively, compared to the control group, while in the study of Myles et al. [24], no such difference was found. The results of Kapetanakis et al. [22] indicate a significantly higher risk of chest reexploration in the group of patients with the preoperative effect of clopidogrel. Similar results were obtained in the meta-analysis conducted by Cao et al. [23]. Significantly greater drainage in the DAPT group compared to the other groups, without a significant difference in the frequency of chest reexploration, can be explained by the fact that during the postoperative period, in patients from the DAPT group, greater drainage was expected and tolerated, and the priority was given to pharmacological treatment, while the indication for chest reexploration was delayed.

The amount of FFP transfusions did not differ significantly among the studied groups. Patients with the DAPT effect received a significantly higher amount of PRBC compared to patients from the control and MASAE groups. PRBC transfusion requirements in subjects from the PASAE group were significantly higher compared to the subjects from the control and MASAE groups. Subjects with the DAPT effect received significantly more PLT and Cryo transfusions compared to the other three groups. Most of the studies conducted so far indicate a higher rate of transfusion requirements in patients who preoperatively received PLT $P2Y_{12}R$ inhibitors, while the results related to the influence of ASA are conflicting [16, 18, 20]. That is very important because a recent study has demonstrated that postoperative bleeding and blood transfusion are independent predictors of increased long-term mortality after CABG and have a direct negative impact on patient prognosis.

PMI was recorded in 6.6% of subjects. That correlates with the results of previous studies, where the incidence ranges from 2–12%. Although PMI occurred 3.5 times more often in patients with normal PLT function compared to the DAPT group (8.8% vs. 2.5%), no statistically significant difference was found. Furthermore, there was no significant difference between other groups. The obtained results correlated with the study by Myles et al. [24]. The results of the study by Hastings et al. [26] showed that there was a significantly lower rate of PMI in patients treated with ASA until surgery. Cao et al. [23] showed that there is a significantly lower rate of PMI in patients treated with PLT $P2Y_{12}R$ inhibitors before surgery compared to patients who did not receive this therapy. Interestingly, the frequency of this complication is almost identical in patients with normal PLT function and patients with pronounced residual effects of ASA. The unexpectedly high frequency of PIM in the PASAE group could be explained by the highest average number of grafts in this group but with very low LIMA utilization. PMI due to early venous graft occlusion is well established. Higher postoperative troponin values correlate with groups with a higher incidence of myocardial infarction. That proves the claim that postoperative troponin values are a good indicator of PMI. The frequency of postoperative arrhythmias and inotropic support did not differ significantly between the studied groups. The obtained results correlated with the study by Sadgehi et al. [27] and with the results of the study conducted by Qu et al. [20].

Prolonged intubation, pneumonia, pleural effusion, and pneumothorax are respiratory complications monitored in the postoperative period. No significant difference was found in the frequency of respiratory complications among the studied groups. That correlates with the study by Kapetanakis et al. [22], but the results differ from the study by Cao et al. [23], where patients with residual clopidogrel effects spent more time on mechanical ventilation. The results of our study show an almost four times higher frequency of prolonged intubation and pleural effusion that required thoracentesis or drainage in the PASAE group compared to the MASAE group. The high frequency of prolonged intubation in the PASAE group could be explained by the higher incidence of hemorrhage-induced chest reexploration and peri/postoperative infarction in these patients. A large number of postoperatively detected pneumothoraces in the DAPT group could be a consequence of more frequent iatrogenic injuries of the lung parenchyma due to difficult hemostasis of the operative field.

Intensive care length of stay and total length of hospitalization did not differ significantly among the studied groups. The results of the research conducted so far are conflicting. The study by Cao et al. [23], as well as the study by Sadeghi et al. [27], show a significantly longer stay in the intensive care unit among patients with continuous administration of clopidogrel compared to subjects who were on monotherapy with ASA. The results of Kapetanakis et al. [22] correlate with the results obtained in our research. The results of the meta-analysis by Hastings et al. [26] on 2,399 patients showed no significant difference in the length of hospitalization and the length of stay in the intensive care unit between subjects who were on ASA preoperatively compared to the control group.

Conclusion

The results obtained in this study demonstrate the importance of preoperative PLT function assessment in CABG patients. Patients with a residual effect of DAPT, as well as patients with a pronounced residual effect of ASA, have a higher risk of postoperative bleeding and chest reexploration, as well as increased transfusion demands.

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