Original article

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DISORDERS OF COAGULATION STATUS AND HAEMOSTASIS AS PROGNOSTIC PARAMETERS OF IMMEDIATE AND EARLY RESULTS AFTER SURGICAL MYOCARDIAL REVASCULARISATION

Dragan Milić[1,2], Milan Lazarević[1], Dragan Bogdanović[3], Zoran Damnjanović[4], Saša Živić[1], Dejan Perić[1], Aleksandar Kamenov[1], Vladimir Stojiljković[1], Mladjan Golubović[5]

Surgical myocardial revascularization is one of the most commonly performed surgical procedures in the world. Over time, with the development of technology and modern diagnostic procedures, as well as the advancement of surgical techniques, the mortality rate for elective uncomplicated cases has fallen to below 2%. Nevertheless, despite the exceptional development of the surgical techiniques, the rate of postoperative complications, that can compromise the patients, is over 10%. The aim of this study was to define a group of patients with an increased risk of postoperative complications depending on the disorders of coagulation status and haemostasis.

Twenty eight patients who underwent surgical revascularization of the myocardium were included in this prospective, non-randomized study. The study was conducted at the Clinic for Cardiac Surgery, Clinical Center Nis, from January to April 2017. Preoperatively as well as 3 hours, 24 hours, 48 hours, 3 days, and 5 days postoperatively, the following parameters were determined: blood count, inflammation parameters (C reactive protein, presepsin); coagulation status (prothrombin time (PT), International Normalized Ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, anti-thrombin III, D dimer).

The only preoperative independent prognostic parameter for increased postoperative drainage was INR. Activated clothing time (ACT) was an independent postoperative prognostic parameter of increased postoperative drainage, probably due to delayed or prolonged heparin activity. Inflammation parameters showed no association with the onset of postoperative complications. In relation to patients without bleeding, in patients with bleeding, significantly higher values of urea and the difference in APTT values, preoperatively and at the end of the monitoring period, were detected. Multivariate logistic regression analysis, confirmed the difference in APTT values preoperatively and at the end of the monitoring period, as the only factor, significantly associated with the risk of bleeding. Multivariate linear regression analysis, confirmed the value of the urea, as the only factor significantly associated with the change in total allogeneic transfusion value. Increase in urea levels is associated with an increase in the total amount of allogeneic transfusion. Correlation analysis showed that the increased number of days in the intensive care was significantly associated with female gender, number of grafts, prolonged ECC, clamping time, hematocrit (HCT), PT, INR preoperatively and at the end of the follow-up period.

Surgical myocardial revascularization is a safe method with a minimal morbidity rate. Using of modern methods for the preoperative monitoring of haemostasis may significantly reduce the risk of postoperative bleeding and the need for transfusion of red blood cells and other blood derivatives.

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Key words: *cardiosurgery, coagulation status, inflammation parameters, risk factors*

[1]Department of Cardiac Surgery, Clinical Centre of Niš, Niš, Serbia
[2]University of Nis, Faculty of Medicine, Niš, Serbia
[3]Institute for Public Health Niš, Niš, Serbia
[4]Department of Vascular surgery, Clinical Centre of Niš, Niš, Serbia
[5]Department of Anesthesiology, Clinical Centre of Niš, Niš, Serbia

Contact: Dragan Milić
Boulevard dr Zorana Djindjića 81, 18000 Niš, Serbia
E-mail: drdraganmilic@gmail.com

Introduction

Cardiovascular (CV) diseases are leading cause of death in most developed countries and in many undeveloped countries. Epidemiological data indicate that CV diseases cause almost half of total mortality, while malignant tumors and lung diseases are represented by 22% and 10%, respectively. Every year, over 17 million people die from cardiovascular dise-

ases in the world, which is a third of the population dying (1, 2).

Cardiovascular diseases include: ischemic heart disease (stable angina pectoris, acute coronary syndrome, sudden cardiac death, cardiac insufficiency), acute stroke (ischemic stroke and haemorrhagic stroke), and peripheral arterial occlusive disease.

According to World Health Organization (WHO) estimation, the dying structure from cardiovascular diseases is as follows: ischemic heart disease is on average 41%, stroke with 32% and other heart disease with 27% (3). In our country the situation is significantly different: slightly more than half of those who died of CV disease had a diagnosis of one of the heart diseases, while the participation of the stroke was 29% (4).

Coronary artery disease (coronary or ischemic heart disease) is the most common cause of death, leading to death, disability and economic losses more than any other illness, despite a significant reduction in mortality over the past three decades. The frequency of may be been seen from the results of large studies, according to which, the risk of the onset of coronary artery disease during life, for a man at the age of 40, is almost 40% (3).

The role of the surgeon in the process of CV disease treatment, finds its significant place from the moment when it came to the knowledge that obstructive atherosclerotic lesions on the coronary arteries are directly responsible for the onset of coronary disease. Aortocoronary bypass is a procedure that is carried out at the heart in order to overcome narrowing of blood vessels that nourish the heart. The results of the conducted research show that in the United States alone, 1 500 000 patients suffer from coronary heart disease annually, while surgical myocardial revascularization is performed in almost every fourth patient. A similar trend was observed in the countries of Western Europe (1,000 revascularization per million inhabitants), while in our country this number is significantly lower (600 revascularization per million inhabitants) (5).

Although surgical revascularization of the myocardium is now the most commonly performed surgical procedure in general, with mortality of about 1% in elective cases, there is still a high risk of emergency surgery in patients with acute coronary syndrome (6). Previous studies suggest that surgical revascularization of the myocardium has been a method of choice for the treatment of most patients with coronary heart disease for more than 50 years. The results of surgical treatment are superior in comparison with empirical medication therapy, in almost all investigated subgroups of patients. After performing this surgical procedure, a longer survival, longer period without new myocardial infarction, and significant improvement in the quality of life is achieved, while the incidence of the new chest pain onset is lower and the working capacity of the majority of operatives is excellent. It is therefore important to note that there are many benefits of early surgical revascularization, including limiting of infarction expansion, avoiding left ventricular dysfunction and cardiac insufficiency. The underlying risk lies in the ischemic-reperfusion myocardial damage, which can lead to the appearance of a hemorrhagic infarction, with all of its complications (5, 7, 8).

Material and methods

The aim of this study was to examine the correlation between mortality, bleeding and the need for transfusion, the length of hospitalization and the presence of postoperative complications (respiratory, renal and hepatic) in relation to parameters of coagulation and fibrinolysis activation, platelet function disorders and inflammatory parameters, in patients who underwent surgical myocardial revascularization.

According to the statistical tests and calculations in the G-Power software package, this study included 28 patients who underwent surgical myocardial revascularization at the Clinic for Cardiovascular with Transplantation Surgery KC Niš, in the period from January to April 2017, which is reduced the probability of α error to a level of significance $r < 0.05$ with a defined power of study of 80%.

Preoperatively as well as 3 hours, 24 hours, 48 hours, 3 days, and 5 days postoperatively, the following parameters were determined:

1. blood count (erythrocyte count, hemoglobin, hematocrit, leukocyte count, platelet count);
2. Inflammation parameters (C reactive protein, presepsin);
3. coagulation status (prothrombin time, International Normalized Ratio, activated partial thromboplastin time, fibrinogen, anti-thrombin III, D dimer);
4. parameters of thrombocyte function (platelet activation adenosine di-phosphate (ADP HS), platelet activation with arachidonic acid (ASPI));
5. Rotational thrombelastometry parameters (direct activation of the thrombin peptide receptor (TRAP), internal and external coagulation pathway (clotting time, maximal clotting firmness, clot amplitude after 10 minutes, alpha angle, maximum lysis, functional fibrinogen).

The correlation of the above parameters with comparison to the duration of the extracorporeal circulation and the duration of the aortic cross clamp is determined.

Statistical analysis

Quantitative statistical analysis was carried out on a computer. Excel program from the Microsoft Office 2010 software package was used for typing, ranking, grouping, table and graphical data presentation. The calculations were made using the SPSS program in version 18.0.

The following statistical parameters were displayed: arithmetic mean (AS), standard deviation (SD) and structure index (%).

Comparison of mean values of numerical features between groups of patients with and without bleeding was performed by Student's T test or Man-Whitney U test, in cases where the distribution of values did not meet the requirements of normal

schedule. Comparison of mean values of numerical features in the same patients between two measurements was done by the Paired-samples t test.

A comparison of the frequency of attributes between groups was performed by Mantel-Hensel's Quadratic Test (Mantel-Haenszel Chi square test) or Fisher exact test of the exact probability of a zero hypothesis (Fisher exact test) when one of the expected frequency of the mark was less than five. Changes in the value of the mark during the follow-up period were examined by Repeated measures ANOVA.

The study of the relationship between the amount of allogeneic transfusion, the number of days of total hospitalization, the number of days of hospitalization in intensive care, total drainage and all other investigated features was carried out by Spearman's rank correlation.

Determination of significant bleeding predictors was performed by multivariate logistic regression analysis. The odds ratio (OR) and the 95% confidence interval (CI) were calculated. By using the Wald method step-by-step (Backward: Wald) from a multivariate model, all factors, the statistical significance of which, was not confirmed were excluded.

Multivariate linear regression analysis was used to determine factors significantly related to the values of allogeneic transfusion, the number of days of hospitalization overall, the number of days in intensive care and total drainage. The values of regression coefficients (B) and the limits of their 95% confidence interval were calculated. Using stepwise methods in final models, only those factors that are significantly related to dependent variables are retained. As a threshold of statistical significance in the conclusion, the estimation error was less than 5% ($p < 0.05$). The statistical analysis results were showed as tables and graphically.

Results

The study included 28 patients, 22 men (79%) and 6 women (21%), the average age of 64 years. The basic characteristics of the respondents are shown in Table 1.

Table 1. The basic characteristics of the respondents

Characteristic	Value
Age	64.14 ± 6.85
Gender	
Male	22 (78.6)
Female	6 (21.4)
Smoking	6 (21.4)
Diabetes	13 (46.4)
Regulation of diabetes	
Without regulation	1 (3.6)
Oral	6 (21.4)
Insulin	6 (21.4)
BMI	29.94 ± 4.4
Triglycerides	1.86 ± 0.85
Cholesterol	4.36 ± 2.12
Urea	6.38 ± 1.46
Kreatinin	95.67 ± 18.34
EF percentage	53.86 ± 10.7
Surgery type (number of grafts)	2.57 ± 0.79
Duration extra corporal ECC	102.36 ± 22.22
Time of clamping	45.79 ± 11.63
The amount of given	1158.93 ± 278.57
Surgery type (number of grafts)	
CABG I	1 (3.6)
CABG II	13 (46.4)
CABG III	12 (42.9)
CABG IV	1 (3.6)
CABG V	1 (3.6)
Defibrilation	26 (92.9)
Diuresis	1346.43 ± 569.26
ACT at admittance	138.96 ± 13.33
ACT afterAH	584.46 ± 104.5
ACT after AP	125.79 ± 12.19
Autotransfusion	569.11 ± 124.27
Hospitalization in intensive care unit	4.54 ± 1.29
Hospitalization in semi-intensive care unit	2.43 ± 1.4
Total hospitalization	6.96 ± 0.51
Allogenic transfusion total	583.33 ± 224.11
Drainage total	975.75 ± 387.97
Diuresis total	11577.14 ± 3638.94

NOTE: values are displayed as arithmetic mean ± SD or as number (percentage)

Table 2. Application of allogeneic transfusion, blood derivatives, voluven and crystalloids, drainage and diuresis per follow-up days

	I day	II day	III day	IV day	V day	VI day	VII day	Total
Allogenic Transfusion	**3** (933 ± 728.6)	**2** (350.0 ± 0.0)	**1** (700.0 ± 0.0)	**4** (350.0 ± 0.0)	-	**2** (350.0 ± 0.0)	**2** (350.0 ± 0.0)	**2** (583 ± 224)
Application of plasma	-	-	-	-	-	-	-	-
Application of cryo	-	-	-	-	-	-	-	-
Application of thrombocytes	**4** (6.25 ± 2.87)	-	-	-	-	-	-	**4** (6.25 ± 2.87)
Crystaloids	-	-	-	-	-	-	-	-
Drainage	**28** (414.3 ± 207)	**28** (416.9 ± 141.9)	**18** (190.8 ± 140.6)	**3** (203.3 ± 131.3)	-	-	-	**28** (976 ± 388)
Diuresis	**28** (2779 ± 764)	**28** (3004 ± 1406)	**28** (2795 ± 1263)	**17** (2852 ± 1205)	**9** (3105 ± 686)	**2** (2850 ± 0.0)	**1** (1800 ± 0.0)	**28** (11577 ± 3639)

NOTE: values are displayed as number of patients (arithmetic mean ± SD)

Allogeneic transfusion was administered in 3 patients on the first postoperative day, and the average blood amount was 933.3 ml (Table 2). On the second day it was applied in two patients, 350 ml each, the third day in one patient, 700 ml, the fourth day in 4 patients, 350 ml each.

On the fifth postoperative day allogeneic transfusion was not applied to any patient. On the sixth and seventh day, allogeneic transfusion was administered in 2 patients, in 350 ml each. In total, allogeneic transfusion was received by 12 patients, and the approximate amount of blood was 583 ml.

The drainage was measured for the first two days in all 28 patients, and the average value was 414.3 ml during the first day and 416.9 ml during the second day. On the third day, the drainage was measured in 18 patients, on average 190.8 ml, and on the fourth day in 3 patients on average 203.3 ml. After the fourth day, the drainage was not measured in any patient.

The diuresis was measured for the first three days in all 28 patients, and the average value was 2779 ml, 3004 ml and 2795 ml, by day. On the fourth day, the diuresis was measured in 17 patients, on average 2852 ml, on the fifth day in 9 patients on average 3105 ml, the six in 2 patients at 2850 ml, and on the seventh day in one patient, 1800 ml.

Platelets were administered only on the first day, in 4 patients with an average of 6.25 units, plasma, cryoprecipitate, volume and crystalloids were not applied.

The analysis of variance for repeated measurements showed that changes in the values of most of the features during monitoring were statistically significant (Table 3).

In almost all features, difference between preoperative values, values 2 hours after surgery and at the end of the follow-up period, was significant. In the period between 2 hours after the operation and at the end of the follow up period, the values of WBC, RBC, HGB and ACT decreased significantly, while the HCT and PLT values increased significantly. Compared to preoperative values, the values of MPV and INTEM CT were significantly lower than the preoperative values, until the values of CRP, P SEP, INR, fibrinogen, D dimer, ADP HS, ASPI, TRAP, EXTEM CT, EXTEM MCF , EXTEM A10, EXTEM ALPHA ANGLE, INTEM MCF, INTEM A10, INTEM ALPHA ANGLE, FIBTEM CT, FIBTEM MCF, FIBTEM A10, FIBTEM ALPHA ANGLE and troponin, were singnificantly higher.

Comparison of values in patients with and without bleeding, within the examined groups is shown in Table 4.

Diabetes was significantly more commonly reported in patients without bleeding (Table 4). In patients without bleeding., significantly higher BMI, triglycerides, cholesterol, ACT before surgery, PLT count preoperatively and INTEM ALPHA ANGLE were seen preoperativly, compare to patients with bleeding. In patients with bleeding, significantly higher values of the urea and difference in APTT preoperatively and at the end of the follow-up period, were detected compared to patients without bleeding. The values of all other features did not differ significantly in patients with and without bleeding.

Table 3. Values of the blood count, inflammation parameters, coagulation status, platlets, rotational thrombelastometry, internal and external coagulation pathway

Parameter	Preoperatively	2 hours after Surgery	24 hours after surgery	48 hours after surgery	72 hours after surgery	5 days after surgery	7 days after surgery	Effect time
WBC	7.2 ± 1.6	9.6 ± 4.1	9.2 ± 3.0	8.8 ± 2.6	7.6 ± 1.9	6.5 ± 2.9	7.1 ± 2.7	**<0.001**
RBC	4.6 ± 0.4	4.2 ± 0.5	4.1 ± 0.5	3.6 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	3.8 ± 0.6	**<0.001**
HGB	140.3 ± 10.1	121.0 ± 10.7	115.7 ± 10.0	103.5 ± 10.5	103.9 ± 10.6	105.1 ± 11.0	103.5 ± 22.4	**<0.001**
HCT	39.4 ± 8.2	34.7 ± 6.9	34.1 ± 3.6	30.6 ± 3.5	30.9 ± 3.1	41.0 ± 50.5	35.3 ± 14.0	0.272
PLT	241.6 ± 70.2	175.0 ± 50.0	191.9 ± 42.1	160.7 ± 50.5	172.2 ± 45.6	236.6 ± 59.1	271.1 ± 97.1	**<0.001**
MPV	8.7 ± 0.8	7.8 ± 0.7	8.2 ± 0.6	11.2 ± 15.1	8.3 ± 0.7	7.7 ± 0.7	7.7 ± 0.7	0.209
CRP	3.7 ± 3.9	4.6 ± 4.2	79.6 ± 39.8	188.9 ± 61.9	192.9 ± 79.3	125.6 ± 73.4	106.1 ± 134.2	**<0.001**
P SEP	177.6 ± 59	413.4 ± 196.2	461.6 ± 207.6	443.9 ± 254.7	496.1 ± 353.3	469.4 ± 284.2	504.1 ± 296.9	**<0.001**
PT	11.4 ± 1.3	18.8 ± 30.8	12.6 ± 1.6	12.2 ± 1.4	11.3 ± 1.5	16.3 ± 23.3	12.8 ± 4.1	0.444
INR	1.1 ± 0.1	1.8 ± 2.4	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.4	0.228
APTT	26.4 ± 3.3	30.1 ± 3.3	38.1 ± 52.0	30.4 ± 3.2	30.9 ± 5.9	27.2 ± 3.9	27.5 ± 4.0	0.364
Fibrinogen	4.1 ± 2.0	3.7 ± 1.5	5.1 ± 0.9	7.7 ± 1.8	18.9 ± 24.0	11.2 ± 10.8	9.2 ± 2.2	**0.005**
AT III	100.6 ± 14.1	77.4 ± 14.2	75.0± 13.6	75.5 ± 7.4	77.5 ± 11.6	89.3 ± 15.7	96.2 ± 17.0	**<0.001**
D dimer	282 ± 166.9	431.2 ± 852.6	279.9 ± 241.6	426.5 ± 856.7	447.3 ± 676.3	788.8 ± 982.3	1450.9 ± 1376.9	**<0.001**
ADP HS	435.4 ± 179.5	424.0 ± 199.0	629.3 ± 148.4	582.7 ± 125.2	605.1 ± 168.6	645.4 ± 169.3	804.1 ± 308.2	**<0.001**
ASPI	579.5 ± 238.6	958.4 ± 351.0	1055.9 ± 334.3	793.8 ± 209.2	775.1 ± 239.2	667.8 ± 287.1	918.2 ± 383.3	**<0.001**
TRAP	1021.7 ± 211.9	1142.8 ± 201.7	1123.6 ± 192.5	1033.1 ± 201.4	1074.6 ± 254.2	1131.3 ± 288.5	1230.5 ± 358.9	**0.022**
EXTEM CT	62.4 ± 6.1	70.5 ± 15.2	61.1 ± 18.7	61.4 ± 7.0	67.2 ± 16.0	66.6 ± 9.6	65.6 ± 11.1	0.074
EXTEM MCF	63.7 ± 4.5	57.2 ± 5.2	60.3 ± 5.8	65.3 ± 4.3	66.5 ± 3.7	70.5 ± 4.3	70.6 ± 3.5	**<0.001**
EXTEM A10	60.0 ± 4.6	51.4 ± 5.1	58.9 ± 4.8	60.7 ± 4.8	61.8 ± 3.7	66.4 ± 4.1	67.1 ± 4.2	**<0.001**
EXTEM ALPHA ANGLE	77.7 ± 2.2	72.3 ± 3.7	76.8 ± 2.3	78.3 ± 2.1	73.0 ± 18.5	79.0 ± 4.4	80.1 ± 2.3	**0.048**
INTEM CT	200.3 ± 44.7	216.1 ± 57.1	172.7 ± 38.0	191.7 ± 43.9	197.4 ± 68.1	176.6 ± 33.4	162.3 ± 33.6	**0.001**
INTEM MCF	59.0 ± 4.5	54.4 ± 5.4	58.9 ± 4.3	61.3 ± 5.2	63.2 ± 5.7	68.2 ± 4.5	68.9 ± 4.2	**<0.001**
INTEM A10	57.8 ± 4.6	50.5 ± 5.2	57.9 ± 3.8	59.5 ± 4.2	59.5 ± 10.2	65.8 ± 4.0	66.4 ± 4.7	**<0.001**
INTEM ALPHA ANGLE	74.5 ± 5.2	71.4 ±5.1	76.0 ± 4.5	76.8 ± 3.5	76.6 ± 5.3	79.3 ± 1.8	79.5 ± 3.1	**<0.001**
FIBTEM CT	54.3 ± 12.2	60.0 ± 6.0	53.6 ± 6.0	55.8 ± 18.7	57.8 ± 7.1	71.0 ± 38.2	61.7 ± 9.4	**0.049**
FIBTEM MCF	21.0 ± 5.1	14.6 ± 3.8	22.2 ± 4.4	29.4 ± 4.5	30.1 ± 3.7	31.3 ± 6.8	32.5 ± 6.1	**<0.001**
FIBTEM A10	20.8 ± 5.0	14.0 ± 3.8	21.6 ± 4.3	28.8 ± 4.6	28.9 ± 3.4	30.3 ± 6.4	31.4 ± 5.9	**<0.001**
FIBTEM ALPHA ANGLE	76.0 ± 5.6	69.8 ± 11.9	77.2 ± 3.4	76.9 ± 5.1	78.6 ± 3.4	79.6 ± 2.9	80.4 ± 2.0	**<0.001**
Troponini	0.1 ± 0.2	3.4 ± 2.4	5.8 ± 6.1	3.9 ± 4.8	2.3 ± 2.8	1.2 ± 1.7	0.7 ± 1.0	**<0.001**
CK MB	21.7 ± 9.4	54.0 ± 19.9	54.5 ± 37.8	43.4 ± 40.1	34.4 ± 28.6	26.2 ± 27.9	22.7 ± 24.6	**<0.001**
ACT	-	130.0 ± 15.0	128.0 ±9.2	127.7 ± 7.3	127.1 ± 8.1	125.2 ± 8.3	125.9 ± 7.8	**0.044**

NOTE: values are displayed as arithmetic mean ± SD

Table 4. Comparison of values in patients with and without bleeding

Parameter	Without bleeding (n=16)	With bleeding (n=12)	p
Age	63.25 ± 6.71	65.33 ± 7.14	0.441
Gender			
Male	13 (81.3%)	9 (75%)	0.690
Female	3 (18.8%)	3 (25%)	
Smoking	3 (18.8%)	3 (25%)	0.690
Diabetes	10 (62.5%)	3 (25%)	**0.049**
Regulation of DM			
Without regulation	0 (0%)	1 (8.3%)	0.053
Oral	5 (31.3%)	1 (8.3%)	
Insulin	5 (31.3%)	1 (8.3%)	
BMI	31.43 ± 4.44	27.97 ± 3.64	**0.032**
Trigliceridi	2.18 ± 0.89	1.44 ± 0.57	**0.012**
Cholesterol	5.16 ± 1.91	3.29 ± 1.96	**0.019**
Urea	5.75 ± 1.14	7.21 ± 1.45	**0.009**
Creatinine	91.85 ± 15.64	100.76 ± 21.05	0.232
EF percents	54.56 ± 12.91	52.92 ± 7.22	0.672
Type of surgery (number of grafts)	2.56 ± 0.51	2.58 ± 1.08	0.952
Duration of EKK	100.75 ± 15.62	104.5 ± 29.51	0.694
Clamping time	43.56 ± 8.66	48.75 ± 14.59	0.289
The amount of given cardioplegia	1196.88 ± 315.95	1108.33 ± 222.42	0.392
Defibrilation	14 (87.5%)	12 (100%)	0.204
Diuresis	1400 ± 476.1	1275 ±690.36	0.597
ACT at admittance	144.44 ± 11.84	131.67 ± 11.97	**0.010**

ACT after AH	599.56 ± 95.68	564.33 ± 116.39	0.403
ACT after AP	125.63 ± 14.8	126 ± 8.14	0.933
Autotransfusion	578.44 ± 121.2	556.67 ± 132.59	0.660
Hospitalization in intensive unit	4.5 ± 1.32	4.58 ± 1.31	0.869
Hospitalization in semi- intensive unit	2.44 ± 1.46	2.42 ± 1.38	0.970
Hospitalization total	6.94 ± 0.57	7 ± 0.43	0.744
WBC preoperatively	7.3 ± 1.39	7.11 ± 1.94	0.775
RBC preoperatively	4.58 ± 0.39	4.61 ± 0.36	0.841
HGB preoperatively	141.75 ± 8.92	138.42 ± 11.62	0.418
HCT preoperatively	38.59 ± 10.49	40.48 ± 3.62	0.512
PLT preoperatively	269.31 ± 74.43	204.67 ± 43.9	**0.008**
MPV preoperatively	8.61 ± 0.71	8.89 ± 0.82	0.357
CRP preoperatively	4.38 ± 3.51	2.87 ± 4.34	0.334
P SEP preoperatively	172.07 ± 65.86	184.92 ± 50.38	0.564
PT preoperatively	11.46 ± 1.22	11.38 ± 1.49	0.892
INR preoperatively	1.07 ± 0.1	1.07 ± 0.13	0.903
APTT preoperatively	27.23 ± 3.06	25.25 ± 3.31	0.120
Fibrinogen preoperatively	3.99 ± 2.35	4.23 ± 1.32	0.739
AT III preoperatively	99.18 ± 11.49	102.41 ± 17.36	0.583
D dimer preoperatively	244.38 ± 122.48	332.17 ± 207.52	0.210
ADP HS preoperatively	449.75 ± 199.9	416.33 ± 154.6	0.622
ASPI preoperatively	587.19 ± 220.69	569.25 ± 270.47	0.853
TRAP preoperatively	962.38 ± 216.98	1100.83 ± 184.52	0.080
EXTEM CT preoperatively	62.81 ± 5.55	61.83 ± 6.95	0.692
EXTEM MCF preoperatively	64.25 ± 5.27	63 ± 3.22	0.446
EXTEM A10 preoperatively	60.94 ± 5.35	58.83 ± 3.16	0.205
EXTEM ALPHA ANGLE preoperatively	78.25 ± 2.02	76.92 ± 2.28	0.121
INTEM CT preoperatively	187.25 ± 39.77	217.75 ± 46.45	0.081
INTEM MCF preoperatively	59.88 ± 4.52	57.75 ± 4.31	0.218
INTEM A10 preoperatively	58.75 ± 4.7	56.42 ± 4.19	0.178
INTEM ALPHA ANGLE preoperatively	76.44 ± 2.78	71.92 ± 6.59	**0.042**
FIBTEM CT preoperatively	57.56 ± 5.53	50 ± 16.94	0.161
FIBTEM MCF preoperatively	22.38 ± 5.57	19.25 ± 3.77	0.089
FIBTEM A10 preoperatively	21.81 ± 5.62	19.33 ± 3.7	0.172
FIBTEM ALPHA ANGLE preoperatively	77.31 ± 5.4	74.33 ± 5.69	0.175
Troponines preoperatively	0.01 ± 0.03	0.11 ± 0.33	0.350
CK MB preoperatively	20.06 ± 5.23	23.87 ± 13.14	0.359
Drainage total	875.06 ± 313.4	1110 ± 448.46	0.137
Diuresis total	11718.13 ± 4002.87	11389.17 ± 3253.59	0.812
WBC diffrence preoperatively and 2 h after surgery	2.07 ± 3.31	2.9 ± 4.36	0.587
RBC difference preoperatively and 2 h after surgery	-0.35 ± 0.47	-0.39 ± 0.39	0.819
HGB difference preoperatively and 2 h after surgery	-19.69 ± 13.39	-18.75 ± 10.64	0.838
HCT difference preoperatively and 2h after surgery	-2.41 ± 10.84	-7.65 ± 8.99	0.175
PLT difference preoperatively and 2h after surgery	-75.25 ± 44.28	-55.08 ± 42.29	0.233
WBC difference 2h after surgery and at the end of follow-up	-2.93 ± 3.84	-2.02 ± 5.36	0.624
RBC difference 2h after surgery and at the end of follow-up	-0.33 ± 0.92	-0.58 ± 0.52	0.371
HGB difference 2h after surgery and at the end of a follow-up	-13.44 ± 16.65	-14.67 ± 15.16	0.840

HCT difference 2h after surgery and at the end of follow-up	2.14 ± 18.35	-1.47 ± 10.49	0.518
PLT difference 2h after surgery and at the end of follow-up	105.26 ± 119.96	83.83 ± 32.21	0.504
MPV difference preoperatively and at the end of follow-up	-1.14 ± 0.71	-0.93 ± 0.95	0.511
CRP difference preoperatively and at the end of follow up	113.78 ± 168.61	87.08 ± 68.8	0.573
P SEP difference preoperatively and at the end of follow-up	299.62 ± 289.07	362.42 ± 307.98	0.589
PT difference preoperatively and at the end of follow-up	0.51 ± 1.87	2.54 ± 5.31	0.226
INR difference preoperatively and at the end of follow-up	0.1 ±0 .14	0.26 ± 0.51	0.321
APTT difference preoperatively and at the end of follow-up	-0.56 ± 3.22	3.3 ±4.35	**0.018**
Fibrinogen difference preoperatively and at the end of follow-up	4.94 ± 3.26	5.27 ± 2.57	0.762
AT III difference preoperatively and at the end of follow-up	-1.01 ± 23.4	-8.83 ± 22.11	0.375
D dimer difference preoperatively and at the end of follow-up	843.38 ± 1076.16	1602.92 ± 1658.62	0.184
ADP HS difference preoperatively and at the end of follow-up	403.88 ± 349.86	321.67 ± 356.48	0.549
ASPI difference preoperatively and at the end of follow-up	378.94 ± 394.24	285 ± 496.68	0.595
TRAP difference preoperatively and at the end of follow-up	256.31 ± 497.59	145.42 ± 338.83	0.490
EXTEM CT difference preoperatively and at the end of follow-up	1.63 ± 12.96	5.33 ± 15.65	0.512
EXTEM MCF difference preoperatively and at the end of follow-up	6.5 ± 4.82	7.5 ± 5.16	0.607
EXTEM A10 difference preoperatively and at the end of follow-up	6.31 ± 5.1	8.08 ± 5.65	0.401
EXTEM ALPHA ANGLE difference preoperatively and at the end of follow-up	2.31 ± 2.75	2.67 ± 3.7	0.783
INTEM CT difference preoperativelyand at the end of follow-up	-20.69 ± 46.07	-61.08 ± 63.53	0.078
INTEM MCF difference preoperatively and at the end of follow-up	8.75 ± 4.93	11.42 ± 7.37	0.292
INTEM A10 difference preoperatively and at the end of follow-up	7.38 ± 5.2	10.25 ± 7.47	0.268
INTEM ALPHA ANGLE difference preoperatively and at the end of follow-up	3.06 ± 2.59	7.67 ± 8.42	0.091
FIBTEM CT difference preoperatively and at the end of follow-up	3.19 ± 9.93	12.92 ± 24.93	0.223
FIBTEM MCF difference preoperatively and at the end of follow-up	9.63 ± 6.63	13.83 ± 6.9	0.118
FIBTEM A10 difference preoperatively and at the end of follow up	9.19 ± 6.12	12.67 ± 7.02	0.185
FIBTEM ALPHA ANGLE difference preoperatively and at the end of follow-up	3.19 ± 5.96	6 ± 5.56	0.211
Troponines- difference preoperatively and at the end of follow-up	0.64 ± 0.87	0.68 ± 1.2	0.910
CK MB difference preoperatively and at the end of follow-up	-4.38 ± 12.89	8.06 ± 22.02	0.100
ACT difference 2h after surgery and at the end of follow up	-6 ± 12.12	-1.67 ± 4.7	0.206

Multivariate logistic regression analysis, confirmed that the only factor significantly associated with the risk of bleeding, is a difference in APTT values preoperatively and at the end of the follow-up period (Table 5). An increase in this difference is associated with an increased risk of bleeding.

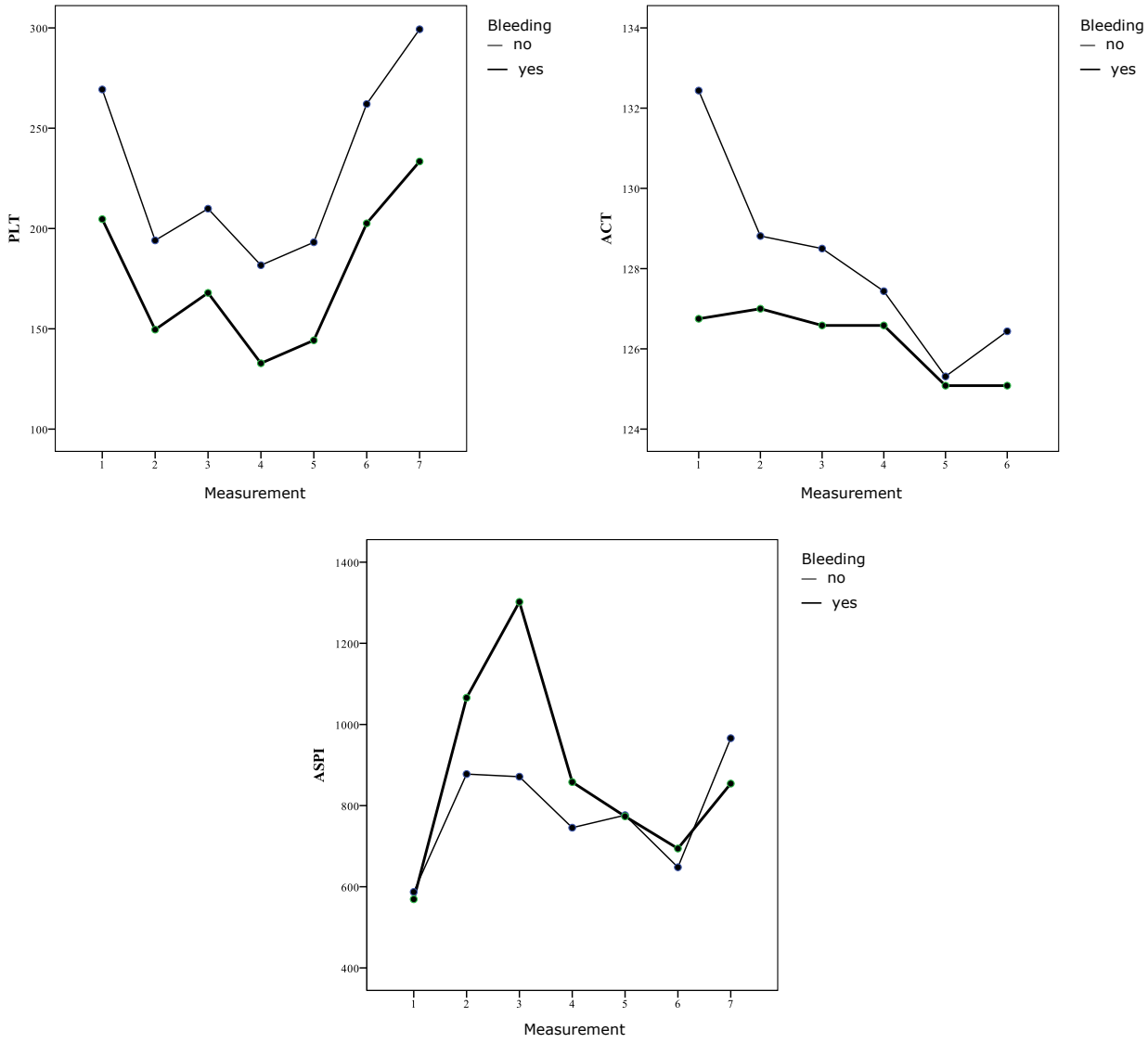
Variance analysis for repeated measurements showed that significant differences between the group of patients with and without bleeding existed at the PLT and ACT values over the entire period of follow-up (Table 6, Graph 1).

Table 5. Association of the investigated parametres and risk for bleeding, results of multivariate logistic regression analysis

Parameter	OR	95% confidence interval		P
		Lower	Upper	
APTT difference preoperatively and at he end of follow-up	2.87	1.141	7.22	0.025
Constant	1421.1			0.023

Table 6. Evaluation of the effects of the group (bleeding) and interaction between time and group on the values of individual parameters during the entire monitoring period, results of variance analysis for repeated measurements (RM ANOVA)

Parameter	Bleeding	Time*bleeding
WBC	0.345	0.225
RBC	0.381	0.540
HGB	0.299	0.771
HCT	0.746	0.263
PLT	**0.001**	0.780
MPV	0.117	0.270
CRP	0.435	0.705
PSEP	0.332	0.227
PT	0.341	0.552
INR	0.514	0.404
APTT	0.479	0.439
Fibrinogen	0.210	0.051
ATIII	0.603	0.616
Ddimer	0.118	0.288
ADPHS	0.898	0.301
ASPI	0.152	0.112
TRAP	0.293	0.478
EXTEMCT	0.240	0.181
EXTEMMCF	0.170	0.160
EXTEMA10	0.080	0.682
EXTEMALPHAANGLE	0.567	0.234
INTEMCT	0.439	0.218
INTEMMCF	0.120	0.299
INTEMA10	0.118	0.153
INTEMALPHAANGLE	0.143	0.212
FIBTEMCT	0.269	0.519
FIBTEMMCF	0.834	0.227
FIBTEMA10	0.838	0.315
FIBTEMALPHAANGLE	0.975	0.540
Troponines	0.774	0.652
CKMB	0.136	0.139
ACT	**<0.001**	0.296



Graph 1. PLT, ACT, and ASPI values in patients with and without bleeding

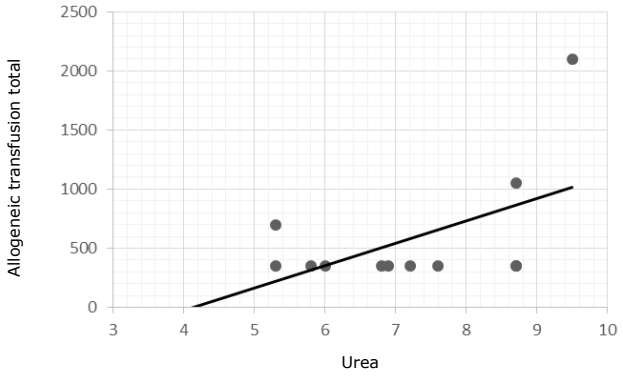
Changes in ASPI values occurred in a significantly different way throughout the entire monitoring period in patients with and without bleeding.

There were no significant effects of the group (bleeding) and the interaction between time and group in the overall monitoring period regarding the value of other parameters.

Multivariate linear regression analysis showed that the only factor significantly associated with the change in the total allogeneic transfusion value was the value of urea (Table 7). Increase in urea levels is associated with an increase in total allogeneic blood transfusion values (Graph 2).

Table 7. Connection betweenl total allogeneic transfusion and values of other investigated features, results of multivariate linear regression analysis

Parameter	B	95% confidence interval		
		Lower	Upper	P
(Constant)	-887.191	-1541.135	-233.246	0.010
Urea	178.383	78.292	278.474	0.001



Graph 2. The relationship between the value of total allogeneic transfusion amount and urea values

Multivariate linear regression analysis confirmed: the type of surgery (number of grafts), diuresis, ACT after AP, and an increase in HCT from preoperative period to period 2h after surgery, as factors significantly associated with changes in the number of days in intensive care (Table 8).

An increase in the number of grafts and diuresis is associated with an increase in the number of days in intensive care, while the rise in ACT after AP and HCT difference preoperatively and 2h after surgery, are associated with a decrease in the number of days in intensive care (Graph 3).

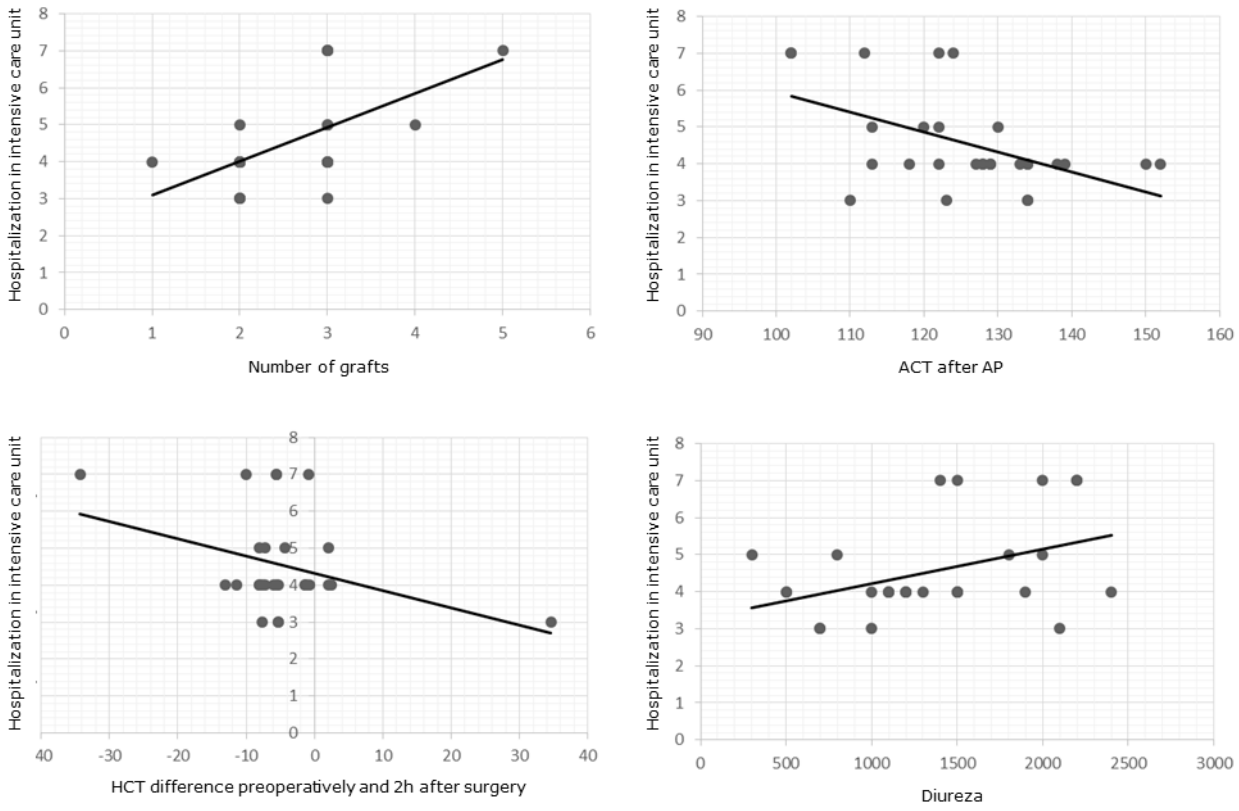
Multivariate linear regression analysis, confirmed the amount of cardioplegia, the difference in RBC values in the period of 2 hours after the operation to the end of the monitoring period, and the difference in values of PT and EXTEM CT in the period before surgery to the end monitoring period as factors significantly associated with changes in the number of days of total hospitalization (Table 9).

An increase in the amount of cardioplegia has been associated with a reduction in the number of days of total hospitalization, while an increase in RBC values in the period from 2 hours after operation to the end of the follow-up period, as well as an increase in the values of PT and EXTEM CT from the period before surgery to the end of the monitoring period, has been associated to increased number of days of total hospitalization.

Multivariate linear regression analysis, confirmed the preoperative value of INR as the only factor significantly associated with changes in total drainage value (Table 10). The increase in preoperative INR value is associated with an increase in the total drainage value (Graph 4).

Table 8. The relationship between the number of days in intensive care and the value of all other investigated features, the results of the multivariate linear regression analysis

Parameters	B	95% confidence interval		
		Lower	Upper	p
(Constant)	6.722	3.410	10.034	<0.001
Type of surgery (number of grafts)	0.674	0.310	1.038	0.001
ACT after AP	-0.042	-0.065	-0.019	0.001
HCT difference preoperatively and 2h after surgery	-0.059	-0.087	-0.031	<0.001
Diuresis	0.001	<0.001	0.001	0.004



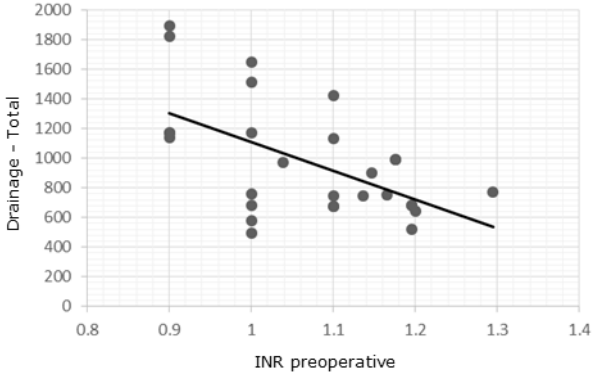
Graph 3. The relationship between the number of days in intensive care and the number of grafts, ACT after AP, HCT difference preoperatively and 2h after surgery and diuresis

Table 9. The relationship between the number of days of total hospitalization and the value of all other investigated features, the results of multivariate linear regression analysis

Parameter	B	95% confidence interval		
		Lower	Upper	p
(Constant)	7.786	7.302	8.270	<0.001
The amount of given cardioplegia	-0.001	-0.0012	-0.0008	0.002
RBC diffrence 2h after surgery and at the end of follow-up	0.260	0.106	0.413	0.002
EXTEM CT difference preoperatively and at the end of follow-up	0.016	0.008	0.024	0.001
PT difference preoperatively and at the end of follow-up	0.035	0.004	0.067	0.030

Table 10. The relationship between the total drainage value and the value of all other investigated features, the results of the multivariate linear regression analysis

Parameter	B	95% confidence interval		
		Lower	Upper	p
(Constant)	3052.12	1817.42	4286.82	<0.001
INR preoperatively	-1942.87	-3092.06	-793.67	0.002



Graph 4. The relationship between total drainage and preoperative value of INR

Discussion

Cardiosurgical interventions carry a certain risk with them. This risk depends on age, gender, heart function, condition of the whole organism, urgency of the intervention, etc. Statistical analysis of a large number of cardio-surgical patients has determined the factors that influence the operational risk.

According to the National Blood Collection & Utilization Survey (NBCUS), blood transfusions and blood derivatives, with the exception of platelet transfusions, declined between 2008. and 2011. in the United States (9). In this period, a reduction rate of 8.2% of red blood cell transfusions (RBC) was recorded, as well as a reduction in plasma transfusion by 13.4%. In the United States, contrary to the general trend, there has been an increase in blood transfusions and blood derivatives during cardiovascular surgery during 2010, when a total of 34% of patients undergoing transfusion received red blood cells or other blood derivatives (10). Moreover, cardiac surgery was a branch of surgery that consumed the largest amounts of blood, just before orthopedic surgery (11, 12). Transfusion is often necessary during cardiovascular surgery to cure coagulopathy, blood loss, and hemodilution due to priming (13). Very often, patients who undergo cardiac surgery have numerous comorbidities such as anemia or myocardial infarction, which increase the risk of complications, and therefore the need for blood transfusion is higher (10, 11, 14).

This study included a total of 28 patients who underwent surgical revascularization of the myocardium at the Clinic for Cardiovascular with Transplantation Surgery, Clinical Centre of Niš, 22 men (79%) and 6 women (21%), with average age of 64. The most common risk factor for these patients was diabetes mellitus, which was present in 46.4% of patients. In our study, there was 21.4% smokers fewer than in other published studies (13-14). This study also showed that BMI was a significant indicator of the incidence of coronary disease, so the average BMI for examiners in our study was 29.94.

The most commonly performed procedure for these patients was double and triple aorto-coronary bypass, with 46.4% of patients having a double aorto-coronary bypass, and 42.9% of patients with triple aorto-coronary bypass. The average number of grafts that patients received was 2.57.

The average ECC time was 102 minutes and the time for the aortic cross clamp was 45 minutes, on average, 1158 ml of cardioplegia was given.

Allogeneic transfusion was administered in 3 patients on the first postoperative day, and the average blood amount was 933.3 ml. On the second day it was applied in two patients, 350 ml each, the third day in one patient, 700 ml, the fourth day in 4 patients, 350 ml each.

On the fifth postoperative day allogeneic transfusion was not applied to all patients. On the sixth and seventh day, allogeneic transfusion was administered in 2 patients, in 350 ml each. In total, allogeneic transfusion was received by 12 patients, and the approximate amount of blood delivered to them was 583 ml.

The diuresis was measured for the first three days in all 28 patients, and the average value was 2779 ml, 3004 ml and 2795 ml, by day. On the fourth day the diuresis was measured in 17 patients, on average 2852 ml, on the fifth day in 9 patients on average 3105 ml, the six in 2 patients at 2850 ml, and on the seventh day in one patient 1800 ml.

Platelets were administered only on the first day, in 4 patients with an average of 6.25 units, plasma, cryoprecipitate, volume, and crystalloids were not applied.

Several studies published the results and effects of blood transfusion in anemic and non-anemic, haemodynamically stable patients. (15-26). A retrospective study carried out in Cleveland Clinic showed that patients undergoing cardio-pulmonary bypass and who did not have anemia during the ECC procedure (hematocrit > 25%), but who received an intraoperative blood, had a need for longer use of mechanical ventilation and they had reduced long-term survival compared to a non-anemic group of patients or with patients who had anemia but did not receive blood (27). Blood transfusions in patients un-

dergoing surgical myocardial revascularization, who were preoperatively classified in a group with a low or moderate risk according to EuroSCORE (< 8) and who had a postoperative hemoglobin greater than 10 g / dL and a minimum postoperative blood loss and without postoperative complications in the first 24 hours of surgery, caused an increased risk of postoperative events and infections in relation to those patients who did not receive blood replacement (17, 21-23, 28).

Shaw et al. compared the effects of blood transfusion in a group of patients who were stratified by the value of hematocrit. Preoperative hematocrit values were compared in patients undergoing cardiac surgery depending on whether they received blood transfusion or not (29). This study showed a statistically significantly higher rate of mortality after 30 days, for that group of patients who received blood transfusion compared to a group of patients who did not receive blood. These results are in agreement with previously published studies that confirm that there is a higher mortality rate in patients receiving blood transfusion (28, 30–33).

A retrospective study published by Schwann et al. investigated the correlation between blood transfusion and mortality in 6,947 patients who underwent surgical myocardial revascularization (34). The overall rate of the red blood cells transfusions was 33.9%. Postoperative complications were present in 35.2% of patients, and this was statistically significantly higher in comparison to a group of patients who did not receive blood transfusion. The most common complications of this type were present in older women with comorbidities. Early mortality (30 days after surgery) and five-year survival were higher among the group of patients receiving blood transfusion, compared to those who did not receive red blood cells. The authors concluded that red blood cell transfusion increased the risk of cardiac and non-cardiac mortality in patients who underwent surgical myocardial revascularization (34-36).

The initial decline after the operation, with a subsequent increase at the end of the monitoring period, was recorded for values of RBC, HGB, PLT, AT III, EXTEM MCF, EXTEM A10, EXTEM ALPHA ANGLE, INTEM MCF, INTEM A10, INTEM ALPHA ANGLE, FIBTEM MCF, FIBTEM A10 , FIBTEM ALPHA ANGLE and ACT.

The initial increase after surgery, with subsequent decline at the end of the monitoring period, was recorded for the values of WBC, CRP, fibrinogen, INTEM CT, troponins and CK MB.

The increasing trend during the entire monitoring period was recorded for values of P SEP, D dimer, ADP HS, ASPI, TRAP and FIBTEM CT.

In relation to preoperative values, the number of WBC significantly increased 2 hours after surgery, while the values of RBC, HGB, HCT, and PLT significantly dropped in the same period.

Diabetes was significantly more common in patients without bleeding. In patients without bleeding, significantly more BMI, triglyceride, cholesterol, preoperative ACT, PLT and INTEM ALPHA ANGLE were preoperatively detected, compare to patients with bleeding.

In patients with bleeding, significantly higher values of the urea and APTT difference preoperatively and at the end of the follow-up period were detected compared to patients without bleeding. The values of all other parameters did not differ significantly in patients with and without bleeding.

The multivariate logistic regression analysis, confirmed that the only factor significantly associated with the risk of bleeding, is a difference in APTT values preoperatively and at the end of the follow-up period. An increase in this difference is associated with an increased risk of bleeding.

The variance analysis for repeated measurements showed that significant differences between the group of patients with and without bleeding existed at the PLT and ACT values.

The changes in ASPI values occurred in a significantly different way throughout the entire monitoring period in patients with and without bleeding.

There were no significant effects of the group (bleeding) and the interaction between time and group in the overall monitoring period, in the value of other features.

The correlation analysis showed that the increased values of total allogeneic transfusion were significantly associated with elevated urea values and increased differences in APTT and CK MB values preoperatively and at the end of the follow-up period.

The multivariate linear regression analysis confirmed the value of urea as the only factor significantly associated with the change in the total allogeneic transfusion value. The increase in urea levels is associated with an increase in the total amount of allogeneic transfusion.

The correlation analysis showed that the increased number of days in intensive care was significantly associated with female gender, higher number of grafts, prolonged ECC time, aortic cross clamp time, diuresis, AT III preoperative, EXTEM CT preoperatively, increased differences in HCT, PT, INR preoperatively and at the end of the monitoring period.

An increased number of total hospitalization days was significantly associated with lowered values of given cardioplegia and PLT preoperative values with declines in WBC and HGB values in the period before surgery to 2 hours after surgery, as well as with the decline in troponine levels in the period before surgery to the end of the follow-up period.

The multivariate linear regression analysis confirmed the amount of cardioplegia, the difference in RBC values in the period of 2 hours after the operation to the end of the monitoring period, and the difference in values of PT and EXTEM CT in the period before surgery to the end of monitoring period as factors significantly associated with changes in the number of days of total hospitalization.

An increase in the amount of cardioplegia has been associated with a reduction in the number of days of the hospitalization, while an increase in RBC values in the period of 2 hours after operation to the end of the follow-up period, as well as an increase in the values of PT and EXTEM CT in the period before surgery to the end of the monitoring period, has been associated with increased number of hospitalization days overall.

The correlation analysis showed that an increase in the total drainage value was significantly associated with an increase in triglyceride and preoperative HCT values, while the increase in total drainage value was significantly associated with a fall in preoperative INR. The multivariate linear regression analysis confirmed the preoperative value of INR as the only factor significantly associated with changes in total drainage value. The increase in preoperative INR value is associated with an increase in the total drainage value. A major dilemma in bleeding patients is whether coagulopathy or mechanical bleeding is the cause of the increase drainage and whether it is necessary to continue with the administration of hemostasic therapy and blood products or perform revision in the operating room. In less than ten minutes, ROTEM test guide doctors in which direction they should work.

The number of transfused allogeneic blood products is declining year after year, which points to the importance of modern monitoring in the indication of blood transfusions by the doctors. Transfusion of fresh plasma is also reduced. Transfusion of concentrated platelets remained at the same level, but percentage of cryoprecipitate transfusions increased year after year (37).

Despite improvements made with existing new techniques, most surgeons tend to accept a significant amount of blood loss as a feature of cardiac surgery (38). It is important to ensure adequate drainage and removal of blood from pericardium and pleura (it has high fibrinolytic activity and tissue factor of coagulation). Removing this blood and clot probably not only reduces the chance of excessive blood loss by preventing systemic coagulopathy, but it is likely to have beneficial effects on several other factors associated with surgery such as, for example, inflammation, atrial fibrillation, pericardial effusion (tamponade), and development of the adhesions (39). After careful evaluation, hemodilution appears to be the most pronounced factor associated with the development of coagulopathy after cardiac surgery, and probably plays an important role in the occurrence of blood loss after heart surgery (40). Fibrinogen is one of the most important factors in coagulation and it is possible that the clotting process falls below the critical level during hemodilution and therefore care should be taken and, if necessary administration of fibrinogen concentrate initiated (41).

Fibrinogen is an acute phase protein the level of which gradually increases during and after surgery in response to a surgical trauma and the use of ECC. The increased concentration of D-dimer and prothrombin fragment 1 + 2 together with increased thrombin production indicate that the hypercoagulable state develops up to 5 days after cardiac surgery. The combination of these two factors (hypercoagulable state and the use of fibrinogen concentrates) can increase the risk of thromboembolic complications in the postoperative period. Therefore, adequate anticoagulant and (or) antiaggregation therapy to prevent the occurrence of thromboembolic complications in the postoperative course is necessary, especially in patients who do not receive vitamin K antagonists, even in patients without prior bleeding. A delicate balance between bleeding and hypercoagulable states must be maintained. The use of POC evaluation can provide a quicker and more complete insight into this delicate balance, creating more individualized treatment oriented to each patient in particular. A large variation in the patient's sensitivity to the use of clopidogrel often results in very different individual results before surgery, which requires further use and determination of the POC before, during and after cardiac surgery. An individual approach oriented to each patient can contribute to the reduction of perioperative and postoperative blood loss and minimizes the need for transfusion to a minimum (42).

Transfusion of red blood cells is common in cardiac surgery. The percentage of patients receiving blood transfusion during the perioperative period varies in literature: from 95%, up to 10 years ago, to 49% of CABG patients over the past few years. Blood transfusion can improve systemic transport and distribution of oxygen, relieve regulation of vasomotor response, improve delivery of oxygen to the myocardium. On the other hand, there are data in the literature that indicate that transfusion damage is probably more serious than it has been valued so far and that blood transfusions are used more often than necessary (43). Even transfusion of one blood unit is associated with a significant risk of serious postoperative morbidity, the immediate goal should be to avoid transfusion whenever possible and not to apply it just to treat low hemoglobin levels, which is a common practice in over 50% of all patients receiving transfusion. Traditional concern over transfusion of blood and blood derivatives is reduced to the possibility of transmitting viral and bacterial infections or the occurrence of haemolytic reactions, which is rarely occurring. However, immunosuppression, lung damage, or dysfunction of the organs can occur with each recipient. Recently, Cleveland Clinic investigators have found that the administration of erythrocytes that have been stored for a longer period (> 14 days) is independently associated with an increased risk of complications and increases the estimated risk of death (30). This happens because the erythrocytes over time develop lesions and release cytokines, cell membranes fragment and release hemoglobin and free oxygen radicals. Obviously, there is a challenge to determine the circumstances in which transfusion is used. Unfortunately, the existing evidence is scarce, and the existing guidelines and recommendations are based on a low level of evidence. Assuring doctors to change their practice is not an easy task and an appropriate clinical assessment is used as a justification for transfusion.

Numerous strategies exist to minimize the need for a transfusion of blood and blood products in the perioperative period.

Some of the existing guidelines recommend: discontinuation of preoperative application of antithrombotic drugs, applying a restrictive attitude about the level of hemoglobin requiring red blood cell transfusion, the application of intraoperative blood savage techniques, and offpump CABG as one of the of surgical techniques that can reduce bleeding in the postoperative course. The study we conducted showed that using the POC and Rotem methods in the

preoperative and postoperative period, can reduce postoperative bleeding to an acceptable level that in most patients does not require the use of blood and blood derivative transfusion. Antiagregation therapy was stopped before surgery and was re-administered after taking drains out. Reinfusion of the remaining blood at the end of the CPB and the use of the Cell Saver system were applied to all patients involved in our study. But perhaps most importantly, doctors should be encouraged to use a restrictive hemoglobin compensation model, which is also recommended in special guidelines: patients should be given blood transfusions when hemoglobin is less than 7 g / dL, where transfusion is not indicated for improving oxygen transport and when the hemoglobin concentration was higher than 10 g / dL. About 20% of all CABG operations are in off-pump technique. The use of CPB during CABG is associated with more harmful effects, including hemodilution, activation of coagulation factors, and a decrease in the number and function of platelets, leading to coagulopathy that can lead to extensive bleeding and the need for massive blood transfusions. Because of this, off-pump procedures would be expected to lead to a reduction in the incidence of postoperative complications, and are also recommended to reduce the need for transfusion. However, in our study, we did not notice the significant differences between individual patient groups in whom increased bleeding could be expected in the intra and postoperative period. The number of platelets and their function was tracked at 8 different time points. Our study did not show that there was statistically significant correlation between individual groups of patients compared to basic biochemical and inflammatory parameters with the number and function of platelets. There has been a decrease in platelet counts intraoperatively, and a gradual increase in their number in the immediate postoperative period. Increased perioperative bleeding was associated only with a reduced number and platelet function as well as elevated ACT rates.

The only parameter in our study that was associated with increased postoperative drainage was increased preoperative value of INR. In our study, only 4 patients (14.28%) received platelets while 12 patients received a blood supply (42%), an average of 583 ml. We didn't have any reintervention because of bleeding. Our study could not show independent prognostic factors of greater postoperative drainage compared to the classic operational parameters that are being monitored (aortic cross-clamp and ECC time...), nor in relation to the parameters of inflammation.

Conclusion

Based on the conducted research and the obtained results, it can be concluded:

- Surgical myocardial revascularization is a safe technique with a minimum morbidity rate.
- By using of modern methods for preoperative hemostasis monitoring (Multiplate, Rotem), the risk of postoperative bleeding can be significantly reduced, as well as the need for transfusion of red blood cells and other blood derivatives.
- The only preoperative independent prognostic parameter for increased postoperative drainage was INR.
- ACT was an independent postoperative prognostic parameter of increased postoperative drainage, probably due to delayed or prolonged heparin activity
- Inflammation parameters did not show association with the occurrence of postoperative complications.
- Diabetes was significantly more common in patients without bleeding. The same conclusion was for patients with higher BMI.
- In patients with bleeding significantly higher values of urea and the difference in APTT preoperatively and at the end of the follow-up period were detected compared to patients without bleeding.
- Multivariate logistic regression analysis confirmed the difference in APTT values preoperatively and at the end of the monitoring period, as the only factor significantly associated with the risk of bleeding.
- Correlation analysis showed that the increased values of total allogeneic transfusion were significantly associated with the elevated values of urea and increased differences in APTT and CK MB values preoperatively and at the end of the follow-up period.
- Multivariate linear regression analysis confirmed the urea value as the only factor significantly associated with the change in the total transfusion value. The increase in urea levels is associated with the increase in the total amount of allogeneic transfusion.
- The correlation analysis showed that the increased number of days in the intensive care was significantly associated with female gender, high number of grafts and prolonged ECC and aortic cross -clamp time, HCT, PT, and INR values preoperatively and at the end of the follow-up period.

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References

1. De Backer G. Epidemiology and prevention of cardiovascular disease: Quo vadis? Eur J Prev Cardiol 2017; 24(7): 768-72. [CrossRef][PubMed]
2. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 2014; 35(42): 2929. [CrossRef][PubMed]
3. Fuster V, Kelly BB, editors. Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health. Washington (DC): National Academies Press (US); 2010.
4. Incidencija i mortalitet od akutnog koronarnog sindroma u 2006, 2007, 2008, 2009, Srbija. Institut za javno zdravlje republike Srbije „Dr Milan Jovanović Batut"; Available from: http://www.batut.org.rs.
5. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardialrevascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010; 31(20): 2501-55. [CrossRef][PubMed]
6. Herzog CA, Ma JZ, Collins AJ. Comparative survival of dialysis patients in the United Statesafter coronary angioplasty, coronary artery stenting, and coronary artery bypass surgery andimpact of diabetes. Circulation 2002; 106(17): 2207-11. [CrossRef][PubMed]
7. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. Guidelines on themanagement of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006; 27(11): 1341-81. [CrossRef][PubMed]
8. Trullàs JC, González-Franco Á. Major developments in the 2016 european guidelines for heart failure. Rev Clin Esp 2017; 217(7): 405-9. [CrossRef][PubMed]
9. US Department of Health and Human Services: The 2011 national blood collection and utilization survey report. Washington, DC: US Department of Health and Human Services, Office of the Assistant Secretary for Health. 2011; 15 Available from: https://www.aabb.org/research/hemovigilance/bloodsurvey/Documents/11-nbcus-report.pdf
10. Robich MP, Koch CG, Johnston DR, Schiltz N, Chandran Pillai A, Hussain ST, et al. Trends in blood utilization in United States cardiac surgical patients. Transfusion 2015; 55(4): 805-14. [CrossRef][PubMed]
11. Geissler RG, Rotering H, Buddendick H, Franz D, Bunzemeier H, Roeder N, et al. Utilisation of blood components in cardiac surgery: a single-centre retrospective analysis with regard to diagnosis-related procedures. Transfus Med Hemother 2015; 42(2): 75-82. [CrossRef][PubMed]
12. Stoicea N, Bergese SD, Ackermann W, Moran KR, Hamilton C, Joseph N, et al. Current status of blood transfusion and antifibrinolytic therapy in orthopedic surgeries. Front Surg 2015; 2:3. [CrossRef][PubMed]
13. Koch CG. Tolerating anemia: taking aim at the right target before pulling the transfusion trigger. Transfusion 2014;54(10 Pt 2):2595-7. [CrossRef][PubMed]
14. Ad N, Massimiano PS, Burton NA, Halpin L, Pritchard G, Shuman DJ, et al. Effect of patient age on blood product transfusion after cardiac surgery. J Thorac Cardiovasc Surg 2015; 150(1): 209-14. [CrossRef][PubMed]
15. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002; 288(12): 1499-507. [CrossRef][PubMed]
16. Anía BJ, Suman VJ, Fairbanks VF, Rademacher DM, Melton LJ 3rd.. Incidence of anemia in older people: an epidemiologic study in a well defined population. J Am Geriatr Soc 1997; 45(7): 825-31. [CrossRef][PubMed]
17. Dejam A, Malley BE, Feng M, Cismondi F, Park S, Samani S, et al. The effect of age and clinical circumstances on the outcome of red blood cell transfusion in critically ill patients. Crit Care 2014; 18(4): 487. [CrossRef][PubMed]
18. Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. J Crit Care 2001; 16(1): 36-41. [CrossRef][PubMed]
19. Corwin HL, Parsonnet KC, Gettinger A. RBC transfusion in the ICU. Is there a reason? Chest 1995; 108(3): 767-71. [CrossRef][PubMed]
20. Littenberg B, Corwin H, Gettinger A, Leichter J, Aubuchon J. A practice guideline and decision aid for blood transfusion.Immunohematology 1995; 11(3): 88-94. [PubMed]
21. Lako A, Bilali S, Memishaj S, Daka A, Dedej T, Nurka T, et al. The impact of blood use on patients undergoing coronary artery bypass surgery: a prospective study. G Chir 2014; 35(1-2): 20-6. [CrossRef][PubMed]
22. Westenbrink BD, Kleijn L, de Boer RA, Tijssen JG, Warnica WJ, Baillot R, et al. Sustained postoperative anaemia is associated with an impaired outcome after coronary artery bypass graft surgery: insights from the IMAGINE trial. Heart 2011; 97(19): 1590-6. [CrossRef][PubMed]
23. Patel NN, Avlonitis VS, Jones HE, Reeves BC, Sterne JA, Murphy GJ. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. Lancet Haematol 2015; 2(12): e543-53. [CrossRef][PubMed]
24. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007; 116 (22): 2544-52. [CrossRef][PubMed]
25. Litmathe J, Boeken U, Feindt P, Gams E. Predictors of homologous blood transfusion for patients undergoing open heart surgery. Thorac Cardiovasc Surg 2003; 51(1):17-21. [CrossRef][PubMed]
26. Pattakos G, Koch CG, Brizzio ME, Batizy LH, Sabik JF 3rd, Blackstone EH, et al. Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. Arch Intern Med 2012; 172(15): 1154-60. [CrossRef][PubMed]
27. Loor G, Li L, Sabik JF, 3rd, Rajeswaran J, Blackstone EH, Koch CG. Nadir hematocrit during cardiopulmonary bypass: end-organ dysfunction and mortality. J Thorac Cardiovasc Surg 2012; 144(3): 654-662. [CrossRef]
28. Paone G, Herbert MA, Theurer PF, Bell GF, Williams JK, Shannon FL, et al. Red blood cells and mortality after coronary artery bypass graft surgery: an analysis

of 672 operative deaths. Ann Thorac Surg 2015; 99(5): 1583-9. [CrossRef][PubMed]
29. Shaw RE, Johnson CK, Ferrari G, Zapolanski A, Brizzio M, Rioux N, et al. Balancing the benefits and risks of blood transfusions in patients undergoing cardiac surgery: a propensity-matched analysis. Interact Cardiovasc Thorac Surg 2013; 17(1):96-102. [CrossRef][PubMed]
30. Kuduvalli M, Oo AY, Newall N, Grayson AD, Jackson M, Desmond MJ, et al. Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. Eur J Cardiothorac Surg 2005; 27(4): 592-8. [CrossRef][PubMed]
31. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg 2002; 74(4): 1180-6. [CrossRef][PubMed]
32. Möhnle P, Snyder-Ramos SA, Miao Y, Kulier A, Böttiger BW, Levin J, et al. Postoperative red blood cell transfusion and morbid outcome in uncomplicated cardiac surgery patients. Intensive Care Med 2011; 37 (1): 97-109. [CrossRef][PubMed]
33. Loor G, Rajeswaran J, Li L, Sabik JF 3rd, Blackstone EH, McCrae KR, et al. The least of 3 evils: exposure to red blood cell transfusion, anemia, or both? J Thorac Cardiovasc Surg 2013; 146(6): 1480-1487. [CrossRef][PubMed]
34. Schwann TA, Habib JR, Khalifeh JM, Nauffal V, Bonnell M, Clancy C, et al. Effects of Blood Transfusion on Cause-Specific Late Mortality After Coronary Artery Bypass Grafting-Less Is More. Ann Thorac Surg 2016; 102(2): 465-73. [CrossRef][PubMed]
35. Du Pont-Thibodeau G, Harrington K, Lacroix J. Anemia and red blood cell transfusion in critically ill cardiac patients. Ann Intensive Care 2014; 4: 16. [CrossRef][PubMed]
36. Azarfarin R, Ashouri N, Totonchi Z, Bakhshandeh H, Yaghoubi A. Factors influencing prolonged ICU stay after open heart surgery. Res Cardiovasc Med 2014; 3(4): e20159. [PubMed]
37. Mehta RH, Grab JD, O'Brien SM, Glower DD, Haan CK, Gammie JS, et al. Clinical characteristics and in-hospital outcomes of patients with cardiogenic shock undergoing coronary artery bypass surgery: insights from the Society of Thoracic Surgeons National CardiacDatabase. Circulation 2008; 117(7): 876-85. [CrossRef][PubMed]
38. Jubelirer SJ, Mousa L, Reddy U, Welch CA. Coronary artery bypass grafting (CABG) in patients with immune thrombocytopenia (ITP): a community hospital experience and review of the literature. W V Med J 2011; 107(6): 10-4. [PubMed]
39. Engoren M, Arslanian-Engoren C. Long-term survival in the intensive care unit after erythrocyte blood transfusion. Am J Crit Care 2009; 18(2): 124-31. [CrossRef][PubMed]
40. Vamvakas EC, Carven JH. RBC transfusion and postoperative length of stay in the hospital or the intensive care unit among patients undergoing coronary artery bypass graft surgery: the effects of confounding factors. Transfusion 2000; 40(38): 832-9. [CrossRef][PubMed]
41. Koster A, Zittermann A, Borgermann J, Knabbe C, Diekmann J, Schirmer U, et al. Transfusion of 1 and 2 units of red blood cells does not increase mortality and organ failure in patients undergoing isolated coronary artery bypass grafting. Eur J Cardiothorac Surg 2016; 49(3): 931-6. [CrossRef][PubMed]
42. Haanschoten MC, van Straten AH, Verstappen F, van de Kerkhof D, van Zundert AA, Soliman Hamad MA. Reducing the immediate availability of red blood cells in cardiac surgery, a single-centre experience. Neth Heart J 2015; 23(1): 28-32. [CrossRef][PubMed]
43. Ferraris VA. Blood transfusion in cardiac surgery: who should get transfused? Lancet Haematol 2015; 2(12). [CrossRef][PubMed]

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POREMEĆAJI KOAGULACIONOG STATUSA I HEMOSTAZE KAO PROGNOSTIČKI PARAMETRI NEPOSREDNIH I RANIH REZULTATA NAKON HIRURŠKE REVASKULARIZACIJE MIOKARDA

Dragan Milić[1,2], Milan Lazarević[1], Dragan Bogdanović[3], Zoran Damnjanović[4], Saša Živić[1], Dejan Perić[1], Aleksandar Kamenov[1], Vladimir Stojiljković[1], Mlađan Golubović[5]

[1]Klinika za kardiohirurgiju, Klinički centar Niš, Niš, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija
[3]Institut za javno zdravlje Niš, Niš, Srbija
[4]Klinika za vaskularnu hirurgiju, Klinički centar Niš, Niš, Srbija
[5]Klinika za anesteziologiju, Klinički centar Niš, Niš, Srbija

Kontakt: Dragan Milić
Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija
E-mail: drdraganmilic@gmail.com

Hirurška revaskularizacija miokarda predstavlja jednu od najčešće izvođenih hirurških procedura u svetu. Vremenom, razvojem tehnologije i savremenih dijagnostičkih postupaka kao i unapređenjem hirurške tehnike, stopa smrtnosti kod elektivnih nekomplikovanih slučajeva pala je na ispod 2%. Ipak, i pored izuzetnog razvoja hirurške metode, stopa postoperativnih komplikacija koje mogu ugroziti bolesnike kreće se i preko 10%. Cilj ovog istraživanja bio je da se definiše grupa bolesnika sa povećanim rizikom od postoperativnih komplikacija u zavisnosti od poremećaja koagulacionog statusa i hemostaze.

Sprovedeno je prospektivno, nerandomizovano istraživanje koje je obuhvatilo 28 bolesnika koji su podvrgnuti hirurškoj revaskularizaciji miokarda u Klinici za kardiohirurgiju KC Niš od januara do aprila meseca 2017. godine. Preoperativno, kao i tri sata, 24 sata, 48 sati, tri dana i pet dana postoperativno, određivani su sledeći parametri: krvna slika, parametri inflamacije (C reaktivni protein, presepsin); koagulacioni status (protrombinsko vreme, International Normalized Ratio, aktivisano parcijalno tromboplastinsko vreme, fibrinogen, anti-trombin III, D dimer).

Jedini preoperativni nezavisni prognostički parametar povećane postoperativne drenaže bio je INR. ACT je bio nezavisni postoperativni prognostički parametar povećane postoperativne drenaže verovatno zbog odloženog ili protrahovanog dejstva heparina. Parametri inflamacije nisu pokazali povezanost sa nastankom postoperativnih komplikacija. U odnosu na bolesnike bez krvarenja, kod onih sa krvarenjem evidentirane su značajno više vrednosti uree i razlike vrednosti APTT preoperativno i na kraju perioda praćenja. Multivarijantna logistička regresiona analiza je kao jedini faktor značajno povezan sa rizikom za nastanak krvarenja potvrdila razliku vrednosti APTT preoperativno i na kraju perioda praćenja. Multi-varijantna linearna regresiona analiza je kao jedini faktor značajno povezan sa promenom vrednosti ukupno date alogene transfuzije potvrdila vrednost uree. Povećanje nivoa uree povezano je sa porastom vrednosti ukupno date alogene transfuzije. Korelaciona analiza je pokazala da je povećan broj dana boravka u intenzivnoj nezi bio značajno povezan sa ženskim polom, povećanjem broja graftova i povišenim vrednostima trajanja EKK, vremena klemovanja, vrednosti HCT, PT, INR preoperativno i na kraju perioda praćenja.

Hirurška revaskularizacija miokarda je bezbedna i sigurna metoda sa minimalnom stopom morbiditeta. Primenom savremenih metoda za preoperativni monitoring hemostaze može se značajno smanjiti rizik postoperativnog krvarenja i smanjiti potreba za transfuzijom crvenih krvnih zrnaca i drugih derivata krvi.

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Ključne reči: *kardiohirurgija, koagulacioni status, parametri inflamacije, faktori rizika*