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Središnja medicinska knjižnica

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Abstract

Objectives: Individual variability in the response to antiplatelet therapy (APT), frequently administered preoperatively, has been established by various platelet function assays and could reflect bleeding tendency after coronary artery bypass surgery (CABG). Our hypothesis is that multiple electrode whole-blood aggregometry (MEA) can identify patients at risk for excessive bleeding.

Methods: We enrolled 211 patients (155 male and 56 female) undergoing isolated CABG in a prospective observational study. Patients were divided into 4 groups with respect to their preoperative APT management. MEA, using the ASPI and the ADP test, was performed prior to surgery. The primary endpoint was chest tube output (CTO) and the secondary endpoint was perioperative packed red blood cell concentrate (PRBC) administration. Patients were characterized as bleeders if their 24 hour CTO exceeded the 75th percentile of distribution.

Results: 24 hour CTO value of 11.33 mL/kg presented 75th percentile of distribution, thus cut-off value for "bleeder category". The proportion of patients characterized as bleeders was significantly different among the groups in regard to preoperative APT (p=0.039). Significant differences in both ASPI (p<0.001) and ADP (p=0.038) tests were observed between different preoperative APT groups. Significant correlations between the ASPI test (r=-0.170, p=0.014) and ADP test (r=-0.206, p=0.003) with 24 hour CTO were found. The receiver operating curve revealed an ASPI test value of < 20 area under curve (AUC) units (AUC 0.603, p=0.023) and an ADP test <73 AUC (AUC 0.611, p=0.009) as a "bleeder" determinant. The proportion of patients transfused with PRBC did not significantly differ among the groups in regard to preoperative APT (p=0.636). Comparison of the ASPI test values between patients with respect to PRBC administration revealed lower values in the ASPI test in a group of patients transfused with PRBC (mean, 27.88 *vs.* 40.32 AUC, p=0.002)

Conclusions: Our study showed that MEA is a useful method of predicting CABG patients with excessive postoperative bleeding.

Keywords: Blood loss; Multiple electrode aggregometry; Platelet aggregation inhibitors; Coronary artery bypass surgery

Introduction

Antiplatelet therapy (APT) is widely used for secondary prevention of ischemic events associated with established coronary atherosclerotic disease. The bleeding risk has become more problematic with the advent of widespread and prolonged therapy with the combination of acetylsalicylic acid (ASA) and clopidogrel (CLO). Several studies suggest cardiac surgical patients are at an increased risk of adverse outcomes, transfusion and hemorrhagic complications when receiving CLO preoperatively [1, 2]. Cardiac surgery patients who experience significant postoperative bleeding or receive blood transfusions are at increased risk for other adverse outcomes [3, 4]. Blood transfusions have been associated with increased rates of clinically significant infections, ischemic events, and 30-day mortality [5]. Patients receiving APT have different degrees of platelet inhibition. Widespread variability in platelet response to ASA or CLO has been established by various platelet function assays [6]. This observation argues against a uniform approach to patients recently exposed to APT who need CABG. Platelet function monitoring may play an important role in reducing bleeding events in patients receiving APT who require CABG by identifying patients with pronounced platelet inhibition who are prone to excessive bleeding after CABG. Previous publications have reported on the inadequacy of conventional coagulation tests in predicting postoperative bleeding [7, 8]. Classic light transmission aggregometry (LTA) performed in platelet rich plasma is the "gold standard" for platelet function testing, but this method is time consuming and is not always available. Alternatively, multiple electrode aggregometry (MEA), a bedside platelet function test, may quantify platelet function in 10 minutes using tests sensitive to the effects of different antiplatelet drugs. Velik-Salcher et al demonstrated that the results of the bedside MEA and LTA did not differ in their ability to detect the effects of ASA and dual antiplatelet therapy (DAT) in patients scheduled for elective cardiac surgery [9]. The use of platelet function monitoring to guide the timing of surgery after the discontinuation of APT could be useful in terms of delaying surgery if the patient is at high risk of bleeding. The aim of our study was to investigate whether it was possible to identify patients at high risk for excessive bleeding based on MEA findings. The study evaluated the impact of APT, assessed by MEA, on bleeding tendency or transfusion requirements in patients following CABG.

Materials and methods

Patient selection

This prospective observational study was approved by the Institutional Research Ethics Review Board. After

obtaining informed consent, 216 adult patients scheduled for elective CABG requiring cardiopulmonary bypass (CPB)

between August 2009 and January 2011 were enrolled in the study. Five patients were excluded from data analysis

due to a lack of reagents (n=2), sudden hemodynamic instability followed by intraaortic balloon pump insertion prior

to the procedure (n=1), incomplete data collection (n=1), and chest re-exploration due to an obvious surgical cause of

bleeding (n=1). The final sample consisted of 155 male and 56 female patients. Type and daily dose of APT, received

preoperatively, and the interval from the last dose of CLO to CABG were meticulously documented. In our study

cohort, APT was administered by the referring cardiologist. In groups of patients recieving ASA preoperatively, ASA

was continued up to date of surgery. In patients receiving CLO, the drug was discontinued at admission to cardiac

surgery department, prior to surgery at variable intervals. Time from CLO cessation to surgery varied individually,

from 2 to 8 days, based on the date of admission to department of cardiac surgery and the date of procedure. All

patients with preoperative APT received APT continuously at least for 10 days prior to admission to department of

cardiac surgery. Patients were divided into subgroups according to preoperative APT: group 1 (n=103) received ASA

100mg/day, group 2 (n=82) received ASA 100 mg/day + CLO 75mg/day, group 3 (n=13) received CLO 75 mg/day

monotherapy and, group 4 (n=13) did not have any exposure to APT prior to surgery. Exclusion criteria were: patients

with cardiac surgical procedures other than isolated CABG, APT other than ASA or CLO, hematological disorders,

patients on non-steroidal anti-inflammatory drugs, patients with missing data, urgent and emergent surgery, off-pump

CABG and Re-Do CABG.

Perioperative management

All patients had the same anesthetic and perfusion teams and were admitted at least 1 day before surgery. Surgery was

performed in a single unit with standard surgical techniques. Anesthesiologists and surgeons were blinded to the

results of the MEA measurements. Results of platelet mapping were not available to the operating room staff or the

intensive care unit team. Surgical re-exploration of the mediastinum for excessive bleeding was noted, along with any surgical explanation of bleeding.

The patients received diazepam and morphine 30 min prior to the induction of anesthesia. Endotracheal tube, urinary catheter, as well as radial artery and pulmonary artery catheters were inserted. The anesthetic regime included induction and maintenance of anesthesia with midazolam, fentanyl and pancuronium bromide. This was coupled with sevoflurane inhalation. The initial ventilator settings included a tidal volume of 8 ml/kg, and a respiratory rate of 12 breaths per minute. Typically, the FiO2 was set to 50%. The critical components of the employed cardiopulmonary circuit were the Medtronic Affinity Trillium membrane oxygenator, venous reservoir, PVC tubing (Medtronic, Minneapolis, MN, USA), and a Stoeckert III roller pump (Stoeckert, Munich, Germany). The ascending aorta and right atrium were cannulated for CPB. Myocardial protection consisted of both antegrade and retrograde cold blood cardioplegia. Systemic heparinization aiming at an activated clotting time >480 s was used, followed by full reversal with protamine after decannulation. A dose of 1 g tranexamic acid was given at the induction of anesthesia and after protamine administration. Tepid CPB was employed, targeting the flow at 2.2 l/min/m^2. The target mean arterial pressure during CPB was 60 mmHg. If necessary, norepinephrine was employed to reach this value. Distal coronary anastomoses were performed on an arrested heart during a single period of aortic cross-clamping. Weaning from CPB was initiated once the patient's rhythm had stabilized and normothermia had been achieved. Inotropic support was initiated in order to maintain a cardiac index greater than 2.2 l/min/m^2. The preferred inotropic agent was dobutamine. Norepinephrine was used if dobutamine produced excessive vasodilatation. Epinephrine was used if the hemodynamic performance remained inadequate with the previously mentioned catecholamines. Packed red blood cells (PRBC) were added into the CPB circuit if the Hct was <20% during extracorporeal circulation, or if it was <25% after the patient was weaned off CPB. If activated clotting time was > 170 seconds after heparin reversal, a supplementary dose 50 mg of protamine was given. Surgical hemostasis was aimed for in every case. We regularly used bone wax and diathermy for bleeding control. The left pleural space was open for left internal mammary artery harvesting. Low voltage unipolar electro-cautery complemented with generous usage of hemostatic clips was utilized. Volume

replacement in the intensive care unit was administered as deemed necessary by the consultant anesthesiologist using hydroxyethyl starch 6% 130/0.4 and lactated Ringer's solution.

Blood sampling

Blood samples were obtained 1 hour prior to surgery using venipuncture, and 4 ml blood was collected in 4 ml heparin (Lithium Heparin 68 IU) coated BD Vacutainer plastic tubes.

Multiple-electrode aggregometry (MEA)

Whole blood platelet aggregation was determined using MEA (Multiplate®, Verum Diagnostica GmbH and Dynabyte Informationssysteme GmbH, Munich, Germany)[10]. Increase in impedance is expressed in arbitrary area under curve (AUC) units, highlighted as the parameter with the highest diagnostic power [10, 11]. We incubated 3 min and measured platelet aggregation 6 min after stimulation. Platelet aggregation was determined in response to stimulation with arachidonic acid with a final concentration of 0.5 mM (ASPI test designed to evaluate ASA effect) and adenosine diphosphate (ADP) with a final concentration of 6.4μM (ADP test designed to evaluate thienopyridines, such as CLO, effect). The same person, not directly involved in patient care, performed all the measurements.

Primary and secondary outcome

Chest tube output (CTO) adjusted to body weight (ml/kg) during the first 24 postoperative hours was defined as the study's primary outcome. Although some authors offer definitions of abnormal blood loss [8], we decided to make our own definition in order to adapt the volume of postoperative CTO to our study cohort. We believe that such a definition makes the most reliable correlation, and is not distorted to different perfusionistic, surgical and anesthetic techniques described by other authors. Patients were characterized as bleeders if their CTO in the first 24 hours (ml/kg) exceeded 75th percentile of distribution. A similar definition has already been described in the literature [12]. The secondary endpoint was perioperative packed red blood cell concentrate (PRBC) administration and is shown in the form of binary variables (transfused or not transfused PRBC's).

Statistical analysis

The Kolmogorov-Smirnov test was used for evaluating the normality of distribution of all continuous variables. Correlation between CTO during the first postoperative 24h and MEA parameters was evaluated by Pearson's

correlation coefficient. Receiver operating characteristic curve (ROC) was constructed to assess the ability of MEA

parameters to predict excessive postoperative blood loss [13]. One way ANOVA was used to assess differences

between antiplatelet therapy groups. Post hoc Least Square Difference (LSD) method tests were carried out if the

initial ANOVA were significant. A two-way ANOVA test was used to analyze the effect of the independent variables

on the expected outcome along with their relationship to the outcome itself. A value of $p<0.05$ was considered

statistically significant. For statistical analysis we used MedCalc® For Windows (MedCalc Software, Broekstraat 52,

9030 Mariakerke, Belgium).

Results

Descriptive statistics of patient groups regarding basic demographic and laboratory data are shown in Table 1. Patient characteristics according to primary outcome are shown in Table 2. Significant differences in both ASPI and ADP test values were observed between different preoperative APT groups (Table 3). The proportion of patients characterized as bleeders was significantly different among the groups in regard to preoperative APT (p=0.039). Patients characterized as bleeders had lower ASPI (mean 24.62 *vs.* 32.63 AUC, p=0.028) and ADP (mean 60.82 *vs.* 69.63 AUC, p=0.018) tests values. Significant correlations were found between both the ASPI (r=-0.170, p=0.014) and ADP test (r=-0.206, p=0.003) values with 24 hour CTO divided by the patient's weight (mL/kg) as shown in Figure 1 and Figure 2, respectively. Both the ADP and ASPI tests were tested for accuracy in predicting excessive postoperative bleeding with ROC analysis. The accuracy of the ASPI test (AUC 0.603, p=0.023) is shown in Figure 3, and the accuracy of the ADP test (AUC 0.611, p=0.009) is shown in Figure 4.

161 patients (76.3%) received PRBC with no significant differences in PRBC administration among the preoperative APT administration groups (p=0.636). However; comparison of the ASPI and ADP test values between patients with respect to PRBC administration revealed significantly lower ASPI test values in the group of patients exposed to PRBC (mean, 27.88 *vs.* 40.32 AUC, p=0.002). We found no differences in ADP test values between patients exposed and not exposed to PRBC (mean, 67.55 *vs.* 67.24 AUC, p=0.94). Subsequent analysis within groups with respect to preoperative APT management is shown in Table 4a. Two-way Anova with ASPI test and ADP test as a dependent variable is shown in Table 4b and 4c, respectively.

The proportion of 45.02% (95 from 211 patients) had recent exposure to CLO, as administered by the referring cardiologist. In group of patients receiving CLO preoperatively, the drug was discontinued immediately at admission to cardiac surgery department. Time from CLO cessation to surgery varied individually, from 2 to 8 days, based on the date of admission to cardiac surgery department and the date of surgery. In group of patients with recent preoperative CLO exposure, we found no significant correlation between MEA ADP test values and number of days after CLO cessation (Pearson Correlation r=0.029, p=0.783).

Discussion

In our study there was a significant difference in ASPI (p=0.028) and ADP (p=0.018) test values based on bleeding status. APT is the mainstay of treatment in patients with coronary artery disease and inevitably contributes to acquired platelet dysfunction in patients after CABG. Postoperative bleeding remains one of the major complications of cardiac surgery, and the pivotal role of platelet function has to be taken into consideration. Patients undergoing cardiac surgery are at high risk for excessive micro vascular bleeding and re-exploration [14]. Although this study showed a statistically significant correlation between the ASPI test and the ADP test and CTO, correlations between MEA tests and CTO were not strong (correlation coefficient was -0.17 for ASPI and -0.21 for ADP test values). The reason could be that blood loss measured from the chest and mediastinal tubes consists of a mixture of fluids, including actual blood loss, serous drainage and fluid left in the pleural cavity. Also the actual blood loss through these tubes is the sum of coagulopathic bleeding and surgical bleeding from wound edges. Unfortunately, it is impossible to differentiate bleeding volume according to surgical or coagulopathic cause. In addition to, MEA tests were performed prior to surgery and the effect of CPB on platelet function and the consequent risk of bleeding were not explored. Blood product transfusion for excessive postoperative bleeding is associated with a significant impact on perioperative morbidity and mortality. There is a nearly linear correlation between the mortality of cardiac surgical patients and the number of PRBC transfusions [3]. In the present study, the group of patients with PRBC transfused had significantly lower ASPI test values compared to the patients not exposed to PRBC (p=0.002). Of note, there was no difference in PRBC administration based on APT group (p=0.636). The fact that patient was exposed to APT does not inevitably suggest the need for PRBC transfusion. Platelet function is rather grading scale than dichotomous variable (*i.e.* inhibited *vs.* non inhibited), and widespread variability in platelet response to APT exists, from deep platelet function inhibition to high residual platelet reactivity following APT administration. The prevalence of low response to aspirin as defined by different platelet function tests, varies widely, generally ranging from 1% to 45% [6] . This can result in diminished bleeding tendency in group of patients with high residual platelet reactivity regardless of APT administered. On the other hand, there is evidence that certain patients have an accentuated response to the usual doses of preoperative aspirin that may result in increased perioperative blood loss requiring PRBC transfusion

[15]. Those facts can argue that quantified platelet function can be predictive of transfusion requirements rather than administration of antiplatelet drugs *per se*.

However, we found no differences in ADP test values between patients exposed and not exposed to PRBC (mean, 67.55 *vs.* 67.24 AUC, p=0.94). We have no explanation for a discrepancy that the ADP test was a better predictor of CTO than ASPI, but only ASPI showed a difference based on PRBC use. Transfusion of PRBC's, defined as a secondary outcome, presents only indirectly the extent of bleeding. When analyzing causal relationship between MEA test values and PRBC transfusion, results should be interpreted with caution due to many factors (*i.e.* baseline preoperative hemoglobin and hematocrit laboratory findings, intravascular volume status and fluid management, hemodynamic instability and respiratory (oxygen delivery) issues) which may sometimes require PRBC transfusion regardless of perioperative bleeding extent. When comparing ADP test values between preoperative APT groups, the difference in ADP test values was only significant between dual antiplatelet therapy group (Group 2) and group of patients without exposure to antiplatelet therapy (Group 4) (p=0.012) as shown in Table 3. The efficacy of platelet inhibition with ASA and CLO varies widely among patients, from intensive platelet inhibition to poor platelet response [16]. The effect of CLO cessation mainly depends on two factors: (1) achieved platelet inhibition, which is related to inherent platelet activity prior to CLO administration and platelet ADP inhibitory response to administered CLO, and (2) an ability to restore normal function after CLO withdrawal [16]. At present study, in group of patients receiving CLO preoperatively, the drug was discontinued immediately at admission to cardiac surgery department. Time from CLO cessation to surgery varied individually, from 2 to 8 days, based on the date of admission to cardiac surgery department and the date of surgery. Such variability in a timeframe from CLO discontinuation to MEA measurements which were performed prior to surgery could explain variability in ADP test values observed within subgroup of patients exposed to CLO. In contrast to our expectations, the duration of the interval between CLO withdrawal and surgery was not predictive of ADP test values (p=0.783). However, patients in "bleeder" category had significantly lower MEA ADP test values (mean, 60.82 *vs.* 69.63 AUC, p=0.018). We believe that widespread variability in platelet response to APT, as well as differences in inherent platelet activity result in a similar variability in observed MEA ADP test values, thus bleeding diathesis. For this reason, quantification of platelet aggregation

status may help individualize the surgical approach, thus facilitating the appropriate timing of the operation in relation to the risk of micro vascular bleeding[16].

Different platelet function assays have already been used to assess platelet function and different devices and techniques of blood sample preparation are hindering study result comparisons. In contrast to many devices that use platelet rich plasma, MEA analyzes platelet function in whole blood, their physiologic environment. There are limited sources of literature regarding the predictive value of MEA in recognizing patients at high risk of bleeding and/or transfusion requirements. Rahe-Meyer et al monitored platelet function with MEA in 60 patients undergoing elective open-heart surgery. Pre-bypass ADP induced aggregation correlated to transfusion requirements [17]. In contrast to them, we found no differences in ADP test values between patients exposed and not exposed to PRBC (p=0.94). Valuable data concerning MEA guided hemostatic management of patients receiving thienopyridines has been previously published [18]. Ranucci et al [18] have found on an independent association between the MEA ADP test and postoperative bleeding and procoagulant blood products transfusion. The authors did not report on the proportion of patients that were also receiving ASA in addition to thienopyridines nor were ASPI test values obtained [18]. Furthermore, the heterogenicity of the observed patient population in Ranucci's paper makes it somewhat difficult to exclude the effect of the complexity of cardiac pathology and the duration of CPB on postoperative CTO [19]. Finally, the authors have performed thromboelastography in a select population of patients, and desmopresin was administered according to MEA ADP test in the presence of micro vascular bleeding [18]. This can markedly influence the primary outcome, as much as secondary outcome, and thus create a bias since not all patients had the same hemostatic management [19]. In the present study, only isolated CABG patients were included which enhanced the robustness of the results. Ferraris and coworkers supported the premise that enhanced platelet inhibition following ASA administration results in bleeding tendency [15]. Our findings suggest a similar phenomenon. In the group of patients receiving only ASA prior to surgery, patients with ASPI test values below the lowest quartile range had a significantly greater volume of 24 hour chest tube output (p= 0.017) in comparison to patients in the upper quartile ranges of ASPI test values.

Limitations of study

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Our study provides only platelet function assessment prior to surgery. The effect of CPB on platelet function and the consequent risk of bleeding were not explored. Intraoperative assessment of platelet function during CPB can reveal a further degree of platelet function deterioration and its relation to bleeding tendency. CPB inevitably causes a hemostatic disorder and platelet function impairment. Reduction in platelet function, assessed with MEA, during and after CPB was described by Velik- Sacher et al [9]. Preoperative and intraoperative assessment of platelet function can distinguish the influence of preexisting, APT related, and CPB-acquired platelet function disorders.

Due to many different factors influencing blood loss after cardiac surgery, we cannot expect strong predictions from a bed-side test assessing only one part of hemostasis. Although, there is overall consensus regarding the dominant role of platelets in hemostasis after cardiac surgery, we believe that adequate interaction of all coagulation components is crucial to achieve adequate hemostasis. For this reason, concomitant use of the MEA and thromboelastometry, both pre- and intraoperatively, could provide a more complete and reliable picture of hemostatic disturbances. This would shed light on the role of fibrinogen and its interaction with platelets.

According to our routine clinical practice we do not administer fresh frozen plasma, cryoprecipitate, and platelet transfusion for elective isolated CABG procedures. Inclusion of patients requiring urgent CABG with recent exposure to loading dose of CLO, and therefore accentuated platelet inhibition, could provide correlations of MEA tests with administration of procoagulant blood products such as fresh frozen plasma or cryoprecipitate which is often administered in urgent cases. An alternative hemostatic approach to patients recently exposed to DAT could be transfusion of platelets. However, we do not argue that approach due to two reasons: first, previous studies have shown that prophylactic use of platelet transfusion does not change chest tube output [20], secondly, it has been shown that platelet transfusion in the perioperative period of CABG is associated with increased risk for serious adverse events [21]. When considering appropriate preoperative APT management for patients undergoing CABG, possibility for both excessive bleeding and adverse ischemic events should concomitantly be assessed and platelet function test results should inextricably be included into consideration [22]. In the present study, none of the patients experienced adverse ischemic events while awaiting surgery. Based on our findings, we believe that it might be possible to form a tailored approach in the timing surgery for CABG patients based upon MEA results, if clinical

condition allows. Such an approach requires MEA testing at admission to the department and, if pronounced platelet inhibition occurs, early APT discontinuation should be done in order to restore platelet function. Hemostatic interventions (*i.e.* desmopresin administration in patients with pronounced platelet inhibition) on the basis of MEA should also be evaluated. However, such a novel approaches should be evaluated through prospective randomized trials.

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Table 1.

Patient characteristics and preoperative laboratory parameters in 211 study participants.

	Antiplatelet therapy group	Mean	SD[*]	P[†]
Age (years)	Group 1	64.98	8.09	0.507
	Group 2	63.77	8.89	
	Group 3	63.69	7.09	
	Group 4	61.77	4.94	
Euro Score (%)	Group 1	3.58	3.32	0.371
	Group 2	2.92	2.44	
	Group 3	2.67	1.25	
	Group 4	2.87	2.64	
Body mass index (kg/m^2)	Group 1	28.59	3.85	0.007
	Group 2	28.44	3.38	
	Group 3	32.26	4.27	
	Group 4	28.57	4.19	
Body surface area (m^2)	Group 1	1.97	0.22	0.133
	Group 2	1.97	0.18	
	Group 3	2.11	0.19	
	Group 4	1.99	0.21	
Hemoglobin (g/L)	Group 1	135.89	15.99	0.170
	Group 2	138.02	14.39	
	Group 3	131.15	9.70	
	Group 4	143.00	11.99	
Hematocrit	Group 1	0.41	0.04	0.217
	Group 2	0.41	0.04	
	Group 3	0.39	0.03	
	Group 4	0.42	0.03	

Platelet count (x10^9/L)	Group 1	217.03	58.92	0.405
	Group 2	221.67	67.10	
	Group 3	198.85	53.96	
	Group 4	238.69	62.11	
Fibrinogen (g/L)	Group 1	4.00	1.21	0.888
	Group 2	3.95	1.23	
	Group 3	4.24	2.01	
	Group 4	4.10	1.15	
ASPI test (AUC)	Group 1	24.84	18.57	<0.001
	Group 2	23.98	15.61	
	Group 3	67.92	28.35	
	Group 4	82.85	26.52	
ADP test (AUC)	Group 1	69.10	24.13	0.038
	Group 2	62.45	24.85	
	Group 3	73.54	33.78	
	Group 4	81.31	20.77	
Aortic cross clamp (min)	Group 1	60.90	22.27	0.669
	Group 2	59.39	20.17	
	Group 3	53.54	12.26	
	Group 4	62.31	30.17	
Cardiopulmonary bypass time (min)	Group 1	88.46	25.89	0.365
	Group 2	84.45	25.03	
	Group 3	81.85	21.05	
	Group 4	96.31	40.37	
Number of grafts	Group 1	2.66	0.52	0.626
	Group 2	2.56	0.65	
	Group 3	2.54	0.66	
	Group 4	2.69	0.63	

Group 1 - acetylsalicylic acid monotherapy (n=103), Group 2 -dual antiplatelet therapy (n=82), Group 3- clopidogrel monotherapy (n=13), Group 4 -no antiplatelet therapy (n=13). [*]Standard deviation

[†]One-way ANOVA

Table 2.

Patient characteristics according to primary outcome

	24 hour chest tube output (ml/kg)	N	Mean	Std. Deviation	P†	
Age (years)	<=75 percentile	161	63.65	8.07	0.065	
	>75 percentile	50	66.10	8.45		
Aortic cross clamp time (min)	<=75 percentile	161	60.65	22.43	0.394	
	>75 percentile	50	57.68	18.18		
Cardiopulmonary bypass time (min)	<=75 percentile	161	87.39	27.32	0.683	
	>75 percentile	50	85.64	23.35		
24 hour chest tube output (mL)	<=75 percentile	161	619.69	166.88	<0.001	
	>75 percentile	50	1360.20	525.11		

		24 hour chest tube output (mL/kg)				P*
		<=75 percentile		>75 percentile		
		Count	Column N %	Count	Column N %	
Gender	Male	118	73.3%	37	74.0%	0.921
	Female	43	26.7%	13	26.0%	
Diabetes mellitus	No	95	59.0%	37	74.0%	0.056
	Yes	66	41.0%	13	26.0%	
Packed red blood cells concentrate	No	42	26.3%	8	16.0%	0.137
	Yes	118	73.8%	42	84.0%	
Antiplatelet therapy groups	Group 1	83	51.6%	20	40.0%	0.039
	Group 2	56	34.8%	26	52.0%	
	Group 3	9	5.6%	4	8.0%	
	Group 4	13	8.1%	0	0%	

Group 1 - acetylsalicylic acid monotherapy (n=103), Group 2 -dual antiplatelet therapy (n=82), Group 3- clopidogrel monotherapy (n=13), Group 4 -no antiplatelet therapy (n=13).

[†] Independent t test

*Pearson chi square test

Table 3.

LSD post hoc analysis of ASPI test and ADP test value differences between different preoperative antiplatelet therapy groups.

Dependent Variable	APT groups (I)	APT groups (J)	Mean Difference (I-J)	Std. Error	$p^{†}$
ASPI test (AUC)	Group 1	Group 2	.869	2.779	0.755
		Group 3	-43.078*	5.527	<0.001
		Group 4	-58.001*	5.527	<0.001
	Group 2	Group 1	-.869	2.779	0.755
		Group 3	-43.947*	5.605	<0.001
		Group 4	-58.871*	5.605	<0.001
	Group 3	Group 1	43.078*	5.527	<0.001
		Group 2	43.947*	5.605	<0.001
		Group 4	-14.923*	7.365	0.044
	Group 4	Group 1	58.001*	5.527	<0.001
		Group 2	58.871*	5.605	<0.001
		Group 3	14.923*	7.365	0.044
ADP test (AUC)	Group 1	Group 2	6.646	3.684	0.073
		Group 3	-4.441	7.327	0.545
		Group 4	-12.211	7.327	0.097
	Group 2	Group 1	-6.646	3.684	0.073
		Group 3	-11.087	7.432	0.137
		Group 4	-18.856*	7.432	0.012
	Group 3	Group 1	4.441	7.327	0.545
		Group 2	11.087	7.432	0.137
		Group 4	-7.769	9.765	0.427
	Group 4	Group 1	12.211	7.327	0.097
		Group 2	18.856*	7.432	0.012
		Group 3	7.769	9.765	0.427

Group 1 - acetylsalicylic acid monotherapy (n=103), Group 2 -dual antiplatelet therapy (n=82), Group 3- clopidogrel monotherapy (n=13), Group 4 -no antiplatelet therapy (n=13).

[†]Post hoc LSD analysis

Table 4.

Table 4 a.

Differences between ASPI and ADP test values within groups with respect to red blood cells concentrate administration.

	Groups	PRBC (+/-)	N	Mean	Std. Deviation	P
Group 1	ASPI test (AUC)	0	24	33.46	22.242	0.010
		+	79	22.41	16.616	
	ADP test (AUC)	0	24	68.71	24.084	0.950
		+	79	69.06	24.420	
Group 2	ASPI test (AUC)	0	18	32.28	20.046	0.010
		+	64	21.64	13.399	
	ADP test (AUC)	0	18	59.33	25.594	0.550
		+	64	63.33	24.772	
Group 3	ASPI test (AUC)	0	3	89.00	11.358	0.037
		+	10	61.60	29.159	
	ADP test (AUC)	0	3	96.67	31.342	0.234
		+	10	66.60	32.729	
Group 4	ASPI test (AUC)	0	5	73.00	19.404	0.265
		+	8	89.00	29.636	
	ADP test (AUC)	0	5	71.00	21.059	0.186
		+	8	87.75	19.039	

Group 1 - acetylsalicylic acid monotherapy (n=103), Group 2 -dual antiplatelet therapy (n=82), Group 3- clopidogrel monotherapy (n=13), Group 4 -no antiplatelet therapy (n=13), PRBC – packed red blood cells (+ administered, 0 not administered)

Table 4b

Two way ANOVA for ASPI test value as a dependent variable:

Source	Type III Sum of Squares	df	Mean Square	F	p
Corrected Model	66718.239[a]	7	9531.18	29.020	<0.001
Intercept	201821.90	1	201821.90	614.498	<0.001
Antiplatelet therapy groups	48326.02	3	16108.67	49.047	<0.001
Packed red blood cells administration	1238.27	1	1238.27	3.770	0.048
Antiplatelet therapy groups * packed red blood cells administration	2800.94	3	933.65	2.843	0.039
Error	66343.58	202	328.43		
Total	332831.00	210			
Corrected Total	133061.81	209			

Table 4c

Two way ANOVA for ADP test value as a dependent variable:

Source	Type III Sum of Squares	df	Mean Square	F	p
Corrected Model	8442.067	7	1206.01	1.949	0.064
Intercept	383764.98	1	383764.98	620.302	<0.001
Antiplatelet therapy groups	5852.63	3	1950.88	3.153	0.026
Packed red blood cells administration	90.94	1	90.94	.147	0.702
Antiplatelet therapy groups * Packed red blood cells administration	3122.82	3	1040.94	1.683	0.172
Error	124972.31	202	618.67		
Total	1089552.00	210			
Corrected Total	133414.38	209			

Figures:

Figure 1.

Significant correlation was found between the ASPI (r=-0.170, p=0.014) test value and 24 hour chest tube output divided by the patient's weight (mL/kg).
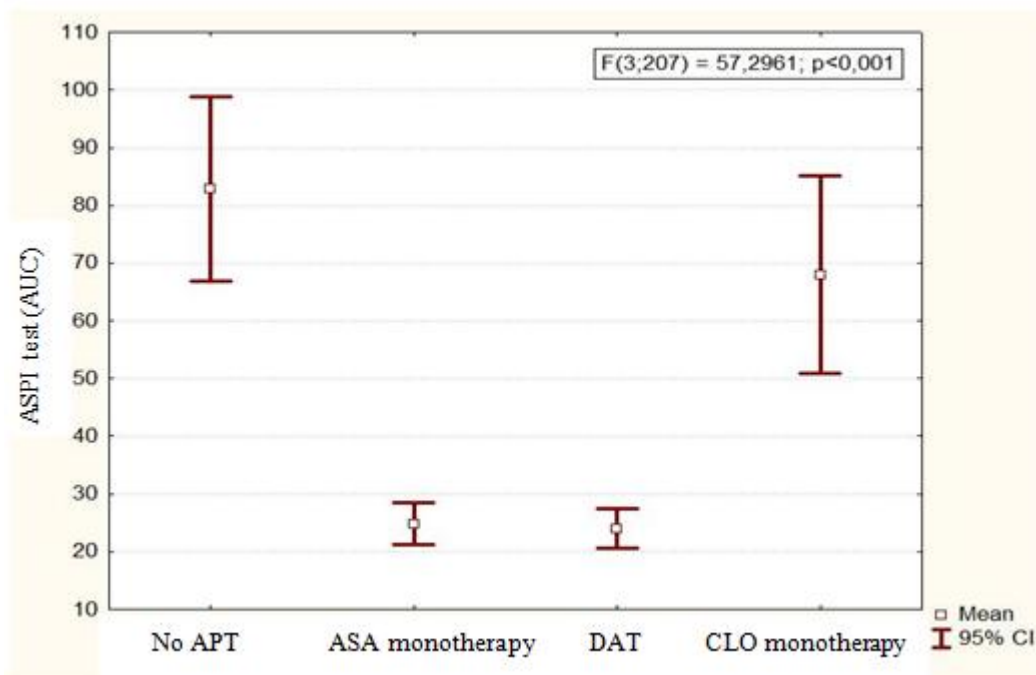
Figure 2.

Significant correlation was found between the ADP test (r=-0.206, p=0.003) test value and 24 hour chest tube output divided by the patient's weight (mL/kg).

Figure 3.
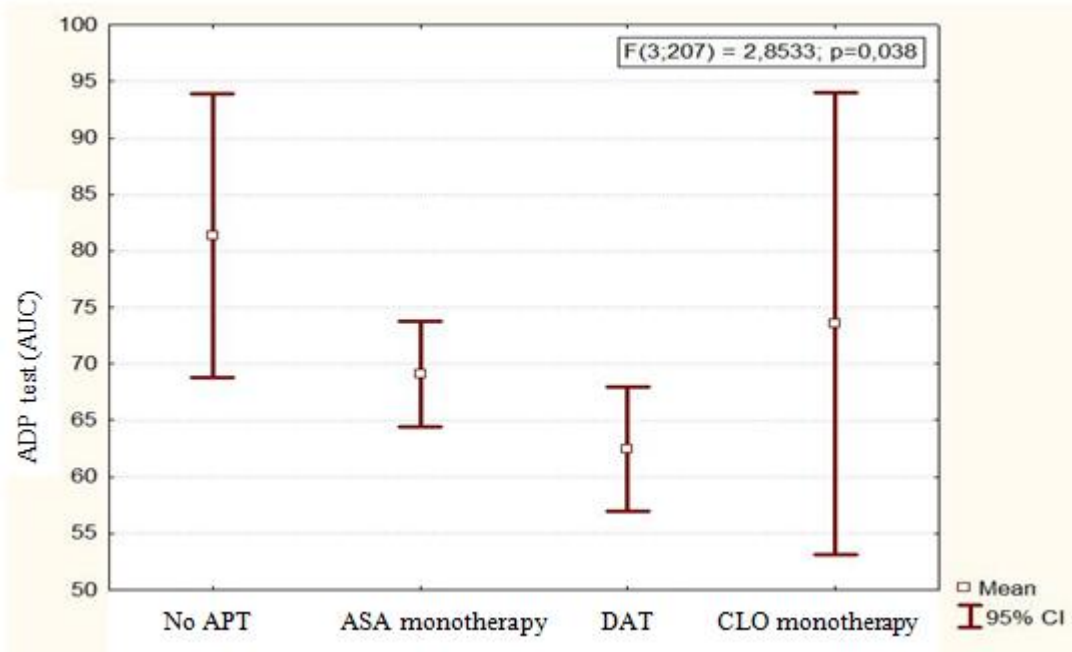
Receiver operating characteristic curve analysis for excessive bleeding prediction by the Multiplate ASPI test. The best predictive value corresponds to an ASPI test value of equal or less than 20 AUC (Area under the curve 0.603. 95% Confidence Interval 0.533-0.669. p=0.02).
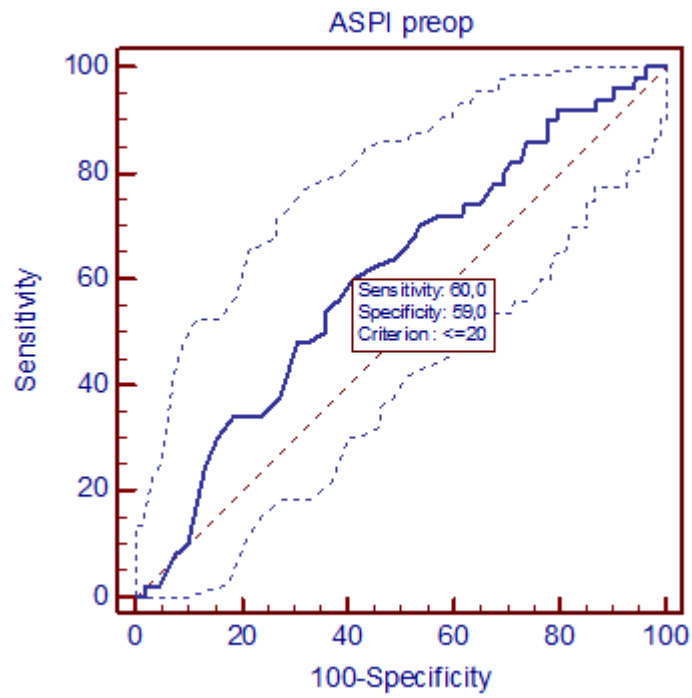
Figure 4.

Receiver operating characteristic curve analysis for excessive bleeding prediction by the Multiplate ADP test. The best predictive value corresponds to an ADP test value of equal or less than 73 AUC (Area under the curve 0.611. 95% Confidence Interval 0.541-0.677. p=0.009).