ORIGINAL PAPER

doi: 10.5455/medarh.2018.72.31-35
MED ARCH. 2018 FEB; 72(1): 31-35
RECEIVED: OCT 10, 2017 | ACCEPTED: JAN 05, 2018

A Difference in Bleeding and Use of Blood and Blood Products in Patients who Were Preoperatively on Aspirin or Dual Antiplatelet Therapy Before Coronary Artery Bypass Grafting

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ABSTRACT

Background: Postoperative bleeding in patients who underwent elective coronary artery bypass surgery (CABG) may increase due to preoperative anticoagulant therapy indicative of their disease - acute coronary syndrome or implanted coronary artery stent. Increased bleeding in many cases requires the use of blood and blood derivatives, and sometimes even reoperation. Their use poses the risk of complications, may extend the hospitalization. **Methods:** Our observation retrospective study included 131 patients, 41 treated with aspirin and 90 treated with aspirin and clopidogrel. All underwent for the first time elective on-pump isolated CABG surgery at Clinic for cardiovascular surgery of Clinical Center University of Sarajevo, in period June 2016 to September 2017. The data were collected from patient's records. **Results:** Out of 131 patients,73.3% were male. The average age was 62. The average total drainage during the first 48 postoperative hours in ASA group was 1027.4±404.9ml and 1049.8±371.3ml in DAPT group. The mean number of whole blood transfusions in the DAPT group washigher compared to ASAgroup. The average number of fresh frozen plasma were higher in the DAPT group 0.84±0.51 compared to the group ASA 0.39±0.07, as well the average thrombocytes transfusions were slightly higher in the DAPT group. Statistical analysis suggests that there is no significant difference between the observed groups ($p>0.05$). Also, our study did not show a statistically significant difference between arrhythmia onset, the length of mechanical ventilation, use of protamineand tranexamic acid. Reoperation due to postoperative bleeding was recorded in 2 cases in the DAPT group as well as 2 lethal cases. **Conclusion:** In our study, we could not demonstrate less postoperative bleeding and use of blood and blood products in a group of patients who were preoperatively treated with aspirin compared to patients with dual antiplatelet therapy in the elective isolated CABG surgery.

Keywords: preoperative anticoagulants,CABG, postoperative bleeding.

1. INTRODUCTION

Ischemic heart disease is the result of a disproportion between the need for myocardial oxygen and the supply of myocardium through coronary circulation. The leading cause of ischemic heart disease is the process of atherosclerosis. Although atherosclerosis represents the athletic process, in the last decades, more and more occur in the younger population. In the last decade, there has been a dramatic increase in coronary disease, which today is the leading cause of morbidity and mortality.

The introduction of new diagnostic and therapeutic procedures in cardiology and cardiac surgery has led to significant progress in the treatment of patients with ischemic heart disease. Modern pharmacological therapy, new invasive percutaneous coronary intervention (PCI), and advanced cardiac surgeries have significantly changed access to these patients and their prognosis.

Patients referred to coronary bypass grafting (CABG) are commonly treated with antiplatelet agents, aspirin (ASA) and adenosine diphosphate (ADP) receptor antagonists (clopidogrel). The standard of care for patients with coronary artery disease is ASA, while ASA with clopidogrel, so called dual antiplatelet therapy (DAPT), is used as treatment for patients with acute coronary syn-

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drome (ACS) and percutaneous coronary intervention (PCI).

The use of antiplatelet agents at the time of CABG carries benefits and risks. Drugs reduce ischemic events, but aggravate the bleeding in cardiac surgery (1).

Antiplatelet drugs such as aspirin (ASA) and clopidogrel, used alone or in combination prevent heart disease and stroke by preventing the formation of blood clots in the arteries. These drugs can be used as a therapy for myocardial infarction, ischemic stroke, unstable angina, non-ST-elevation myocardial infarction, acute coronary syndrome, chronic atrial fibrillation and ST-elevation myocardial infarction. Antiplatelet drugs have become essential therapy for the treatment of conditions mentioned above (2).

In patients who have had a heart attack low-dose aspirin is recommended as a lifelong therapy that should never be interrupted. In some cases these patients and those who have had PCI with placement of bare-metal or drug-eluting stents put in one or more of their arteries are prescribed low-dose aspirin and an additional antiplatelet drug, usually clopidogrel (3). In the perioperative period, the indication for antiplatelet agents is reinforced by the increased platelet activity following surgery, but they also increase the risk of surgical bleeding. Elective surgery should be postponed, whereas vital or urgent surgery should be performed under continued dual antiplatelet therapy. The risk of surgical hemorrhage is increased approximately 20% by aspirin or clopidogrel alone, and 50% by dual antiplatelet therapy.

Aspirin cessation is associated with an increased risk of cardiac complications. Even if clopidogrel treatment must be interrupted in high-risk surgical situations, aspirin must be continued without interruption. Heparin has no antiplatelet activity and therefore is not an adequate substitution for aspirin or clopidogrel treatment (4).

The management of antiplatelet agents in the perioperative period of cardiac surgery requires close collaboration between cardiologists, surgeons and anesthesiologists. It is necessary to avoid thrombotic complications maintaining the anti-aggregation, but balancing bleeding complications.

Patients treated with long-term treatment of these drugs could be at risk for increased bleeding if it is maintained until surgery, mainly if there are any other outstanding variable as indicator of risk: advanced age, preoperative anemia,reoperative procedures, emergency operations or non-cardiac patient comorbidities.

If the patient is under the effect of one or more of these drugs the associated bleeding risk might be carefully balanced and an alternative anti-aggregation protocol could be considered. So, for patients scheduled for CABG, the recommendation is to stop clopidogrel at least 5 days and, preferably, 10 days prior to surgery to minimize blood loss. In the case of aspirin, the recommendation is to maintain it up to surgery and beyond the time of surgery (5).

2. METHODS

Our observation retrospective study included 131 patients underwent elective CABG procedure between June 2016 and September 2017. All patients were treated at Clinic for cardiovascular surgery at the Clinical Center University of Sarajevo. Data were obtained from hospital registries and included detailed patient, surgery, anesthesia and intensive care related information.

Patients were divided into two groups: aspirin treated patients - ASA group with 41 patients and patients treated with aspirin and clopidogrel medication - so called dual antiplatelet therapy - DAPT group with 90 patients.

Primary end point was to evaluate postoperative bleeding after elective CABG and use of blood and blood products in patient in ASA compared with DAPT group.

Secondary end point included appearance of arrhythmias, the length of mechanical ventilation, reoperation due to postoperative bleeding.

Including criteria were the age between 18 and 80 years, both gender, isolated on-pump CABG for the first time. Excluding criteria were redo CABG and off pump CABG.

Routine protocols for anesthetic and surgical procedures were used, making circumstances standardized and comparable for all patients. Full median sternotomy was made, using loadingdose of unfractioned heparin with the goal to achieve an activated clotting time-ACT>450 s beforeinitiating cardiopulmonary bypass (CPB). Body temperature was kept at 32°C-36°C. Myocardial protection was achieved using crystalloid cardioplegia. Intraoperative blood management included the use of a cell saverfor reinfusion of washed residual blood from the cardiotomy reservoir at termination of CPB. Blood transfusion during CPB was given at hemoglobin levels <5.0 mmol/l. After CPB discontinuation, heparin was reversed by administration of 1 ml protamine for each 1000 IU heparin.

In the intensive care unit red blood cell transfusion was used if hemoglobin level was < 7.0 mmol/l. In the presence of significant bleeding fresh frozen plasma (FFP) was administrated and platelet concentrate transfusion if platelet count $<100 \times 10^9$/l. Prophylactic heparin wasstarted 12 hours after admission to ICU, and APTT was monitored for adjustment of heparin therapy. Surgical re-exploration was considered if drainage exceeded 800 ml/h in the first hour postoperatively. All data were taken intraoperative and in the first 48 hours postoperatively.

Statistical analysis

The results are shown in form of tables and charts by the number of cases, percentages, mean with standard deviation and range of values. The comparison between the observed groups was performed using the chi-square and Student's t test at a significance level set at $p<0.05$ or with 95% confidence. The analysis was carried out using the statistical package IBM statistics SPSS v 23.0.

3. RESULTS

In total sample of 131 patientsthe analysis of mean age was 62.1±6.7 years with the youngest patients at age of 41 and the oldest at age of 81 years. Patients in ASA

	N	Mean	SD	p value	t test
Age					
ASA group	41	62.44	6.37		
DAPT group	90	62.00	7.15	0.737	0.337
Total	131	62.14	6.89		
Gender		Male	Female		
ASA group / N(%)	41	32 (78%)	9 (22%)	0.271	0.271
DAPT group / N(%)	90	64 (71.1%)	26 (28.9)		
Aspirin vs. Aspirin+ Clopidogrel		STOP (days)			
ASA group	41	14.39	2.63	0.349	
DAPT group	90	10.97	7.62		0.941
Total	131	12.04	9.31		

Table 1. Preoperative factors

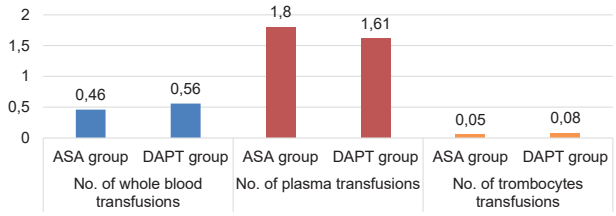

Figure 1. Intraoperative use of blood and blood products

group were slightly older with an average age of 62.4±6.4 years (49-78 years) compared to patients in the DAPT group with an average age of 62±6.9 years (51-81 years). Men were more represented in the total sample,73.3% to 26.7% of female (*Table 1).*

The average interruption of aspirin application before surgery in the total sample was 12±9.3 days (1-130 days) and was longer for ASA group–14.4±2.6 days (1-120 days) compared to the DAPT group–11±7,6 days (1-130 days). Statistical analysis as shown in *Table 1.* suggests that there is no significant difference between the observed groups (p>0.05).

The mean number of whole blood transfusions was higher in the DAPT group - 0.56±0.068 compared to the ASA group - 0.46±0.05. Likewise, the average fresh frozenplasma transfusions were higher in the ASA group - 1.8±1.5 compared to the DAPT group - 1.6±1.5. The average number of concentrated thrombocytes transfusions was slightly higher in the DAPT group - 0.08±0.06 compared to the ASA group - 0.05±0.05, without statistically significant difference (p>0.05) (*Figure1).*

The average total drainage during 48h was 1042.8±380.8 ml (170-2220 ml) in the total sample and was slightly higher in the DAPT group - 1049.8±371.3 ml (440-2220 ml) compared to ASA group - 1027.4±404.9 ml (170-2060 ml) (*Table 2).* Statistical analysis suggests that there is no significant difference between the observed groups (p>0.05).

Repeated surgery was only recorded in two cases or 2.2% in the DAPT group as well as in two cases of lethal outcome, without significant difference between groups (p>0.05).

As in *Figure 2,* the mean number of whole blood transfusions was higher in the DAPT group - 1.39±1.06 compared to ASA group - 1.22±1.03. Likewise, the average fresh frozenplasma transfusions were higher in the DAPT group - 0.84±0.51 compared to the ASA group - 0.39±0.07. The average of concentrated thrombocytes transfusions were slightly higher in the DAPT group - 0.1±0.08 compared to the ASAgroup - 0.02±0.01. Statistical analysis suggests that there is no significant difference between the observed groups (p>0.05).

Statistical analysis of postoperative ICU factors was shown in *Table 2.* The duration of mechanical ventilation in ICU was slightly higher in the ASAgroup - 629.6±491.6 minutes (0-2880) compared to the DAPT group - 565.3±272.4 minutes (240-1440), while the mean duration of mechanical ventilation averaged 585.4±354.9 minutes (0-2880) in the total sample. Statistically there was no significant difference between the observed groups (p>0.05).

Arrhythmias were more common in the ASA group–24.4% compared to 21.1% of the DAPT group. The postoperative use of tranexamic acid and protamine sulfate were slightly higher in the ASA group but not statistically significant in any of ICU factros (p>0.05).

ICU factors	N	Mean	SD	p value	t test
Total drainage in 48 h (ml)					
ASA group	41	1027.44	404.98		
DAPT group	90	1049.76	371.33	0.757	0.310
Total	131	1042.77	380.75		
Repeated surgery		Yes	No		
ASA group / N		0	0	0.470	0.925
DAPT group / N		2	0		
Mechanical ventilation (minutes)					
ASA group	41	629.6	491.6		
DAPT group	90	565.3	272.4	0.338	0.962
Total	131	585.4	354.9		
Arrhytmia		N	%		χ2 test
ASA group		10	24.4		
DAPT group		19	21.1	0.418	0.176
Total		29	22.1		
Tranexamic acid		N	%		χ2 test
ASA group		11	26.8		
DAPT group		21	23.3	0.411	0.186
Total		32	24.4		
Protamine		N	%		χ2 test
ASA group		21	51.2		
DAPT group		36	40.0	0.230	1.443
Total		57	43.5		

Table 2. Postoperative factors in the ICU

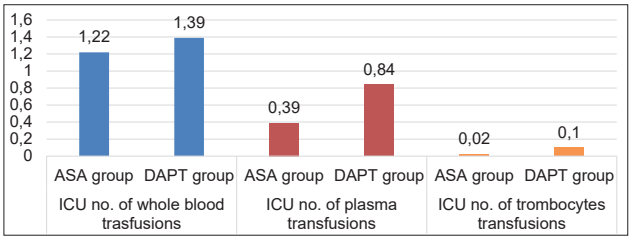

Figure 2. Use of blood, fresh frozen plasma and platelets in intensive care unit

4. DISCUSSION

In cardiac surgery we still face the dilemma whether to stop the antiplatelet treatment to avoid bleeding and risk postoperative thrombotic stent events, or to maintain the antiplatelet therapy preoperatively to avoid the stent thrombosis, thus risking major blood loss and increased transfusion rate. There are some controversies in the pre-operative antiplatelet therapy, especially aspirin maintenance prior to coronary artery bypass surgery regarding bleeding risk and need for transfusions (5).

In this observation retrospective study our primary goal was to investigate if patients treated with dual antiplatelet therapy (aspirin and clopidogrel) shortly prior to undergoing CABG are at a higher risk of bleeding-related complications when compared with patients exposed to aspirin only (ASA group). Many studies like the one by Tomšić et al. have shown that exposure to clopidogrel within 120 h (5 days) prior to surgery was associated with increased needs for blood and blood products transfusions. In our trial dual antiplatelet therapy was stopped 11 days prior coronary artery surgery (*Table 1*), following the recommendations for CABG surgery. The authors above underlined that patient who discontinued clopidogrel > 5 days prior to surgery did not experience bleeding-related complications more often compared with patients on aspirin only (5, 6).

In our trial we found that the average chest drainage volumes in the 48 postoperative hours were not significantly different in the aspirin and dual antiplatelet therapy group, but we had a slightly larger chest tube extent, also therefor greater rate of blood transfusions in the DAPT group (Table 2), what is in line with the results recently published by Petricevica et al. (7).

Transfusion requirements followed the severity of postoperative bleeding. Although mean chest drainage volumes was similar in the aspirin and dual therapy group, patients in the clopidogrel group received more blood and blood products than those in the aspirin group (*Figure 2*).

Regarding the intraoperative use of blood and blood products, more doses of whole blood were given to the DAPT group compared to ASA patients, but with no significant difference. Fresh frozen plasma was intraoperatively frequently used in ASA patients (Figure 1). In the intensive care unit the need for fresh frozen plasma in presence of greater postoperative drainage was slightly higher in the DAPT group, but with no significant difference between compared groups (*Figure 2*).

We discovered that slightly more DAPT patients required thrombocyte substitution, intraoperatively as well in the ICU, but we did not find statistical significance in this study. The second goal of our study was to investigate the requirement of reoperation due to the postoperative bleeding. Higher mediastinal chest tube drainage was in relation to the increased incidence of chest re-opening. Surgical chest re-exploration based on drainage volume was performed in two patients of the DAPT group, while we did not have indications for reoperation in the ASA group *(Table 2).* Similar results were shown in the recent meta-analysis of observational studies by Biancari et al. that propound that recent exposure to clopidogrel before CABG was associated with a higher operative mortality and this was related to blood loss, blood transfusion and re-exploration for bleeding (1, 8).

Dual antiplatelet treatment is a cornerstone in the treatment of coronary disease but the optimal treatment duration is unclear. The risk of bleeding was higher in treatment groups with longer DAPT duration (9). In our trial the interruption time of dual antiplatelet therapy prior to coronary surgery was shorter than the aspirin only therapy before surgery what is in correlation with the Miceli et al. study, who pointed out the risk of re-exploration for bleeding increased with decreasing time from the last dose of clopidogrel and aspirin prior CABG surgery (10). As there are many clinical studies comparing cardiovascular risk in correlation with the transfusion use and cessation of antiplatelet therapy prior the cardiac surgery, we analyze postoperative ICU factors like length of mechanical ventilation, arrhythmia, requirement for additional dose of tranexamic acid and protamine sulfate. Patients in the highest quintile of risk accounted for more than 50% of overall blood usage were those who also experienced the highest rates of postoperative complications. Optimization of patient blood management in the CABG context requires identification of predictors of blood loss and transfusion requirements (11).

Therefore, patients in the ASA group show more common onset arrhythmia, duration of mechanical ventilation in intensive care unit, but with in significant difference between observed groups (*Table 2*). The additional dose of fibrinolytic was slightly higher but not significant in the ASA group. As in many studies examined, the administration of a single dose of transexamic acid before cardiopulmonary bypass significantly reduced postoperative bleeding and inhibited fibrinolysis in patients treated with aspirin. This effect is not consistent in all the studies, which in the prophylactic tranexamic acid use did not result in any significant decrease in postoperative bleeding. Another ICU factor we investigate was the frequencyof use of protamine in presence of elevated ACT and higher chest drainage, what was more common in the ASA group. As known the antiplatelet therapy in patients at high risk of occlusive vascular events reduce the combined outcome of any serious vascular event as well non-fatal myocardial infarction, non-fatal stroke and vascular mortality (5, 12). In our study we did not have any cases of cardiovascular events mentioned above. Two lethal outcomes in the DAPT group were high risk patients preoperatively low ventricular ejection fraction, comorbidities, were also on high-dose inotropic support in the first 48 postoperative hours.

5. CONCLUSION

We did not manage to demonstrate less postoperative bleeding and use of blood and blood products in a group of patients who were preoperatively treated with aspirin compared to patients with dual antiplatelet therapy in the elective coronary artery bypass grafting surgery. Therefore, anindividual and optimal patient-relatedtherapeutic approach for discontinuation management

of each antiplatelet agent preoperatively is crucial in perioperative bleeding risk assessment and in prediction of the use of blood and blood products.

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