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Impact of Clopidogrel Loading for Coronarography on Bleeding After Urgent First Time CABG

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ABSTRACT

Background: Excessive bleeding impairs outcome after coronary artery bypass grafting (CABG). Clopidogrel in combination with aspirin, given before percutaneous coronary intervention, have become the standard for stent thrombosis prevention. Some premedicated patients, however, are found to need surgical treatment, thus platelet inhibition caused by clopidogrel becomes a concern for post operation major bleeding. **Aims:** This study was designed to evaluate the impact of preoperative clopidogrel on bleeding and outcomes after coronary artery bypass graft surgery (CABG). **Methods:** The study represent a observational retrospective analysis of collected data. The follow up of 223 treated with clopidogrel and aspirin and 77 patients not receiving treatment with platelet antagonist 7 days before CABG are analyzed. **Results:** The groups were comparable in age, gender, body surface area, preoperative hematocrit, preoperative prothrombin time and prior myocardial infarction. The clopidogrel group had higher12h and 24h mean chest tube output (at 12h mean 519.7ml vs 353.1 ml, $p < 0.05$, at 24h mean 756.6 ml vs 563.5 ml, $p<0.05$). Moreover, reoperation for bleeding was 4.5-fold higher in the clopidogrel group (5.9% vs. 1.3%, $p <0.01$), and more transfusions of red blood cells (3.23U vs 2.6 U, $p<0.05$), platelets (1.53U vs 1.23U, $p<0.01$) and fresh frozen plasma (0.84U vs 0.36 U, $p<0.01$). The clopidogrel group also showed a longer mechanical ventilation time (16.9h vs 12.9 h $p = 0.03$) and trend towards more prolonged stay in ICU (2.08 days vs 1.7 days $p= 0.048$). **Conclusions:** Clopidogrel in combination with aspirin before CABG is associated with higher postoperative bleeding, exposure to blood products and morbidity. These findings raise concern regarding the routine administration of clopidogrel before anticipated but undecided coronary stent implantation.

Keywords: Bleeding complications, CABG, Clopidogrel.

1. INTRODUCTION

Bleeding complications are a major concern in patients after cardiac surgery especially after coronary artery bypass grafting. Risk of bleeding complications increases when patients are on antiplatelet therapy. Patients with acute coronary syndrome on antiplatelet therapy who proceed with urgent coronary artery bypass grafting are at higher risk of major bleeding (1, 2).

According to ACC/AHA 2002, 2007 guidelines and updates for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction and other publications, use of clopidogrel in combination with aspirin, given before percutaneous coronary procedure, has become the standard for stent thrombosis prevention (3-5). Premedication with clopidogrel or new potent platelet inhibitors and aspirin (dual antiplatelet therapy–DAPT) has reduced thrombotic complications after percutaneous coronary revascularization procedures (6).

However, evidence of a surgical disease on angiography is a common finding in such premedicated patients. In such patients premedicated with clopidogrel and aspirin irreversible platelet inhibition becomes a concern for upcoming CABG (7). Such a concern is specifically expressed in recommendations that high-risk patients with acute coronary syndrome who are in need of urgent CABG procedure should not receive an ADP-receptor inhibitor until the coronarography is performed and the decision is taken not to proceed with urgent CABG(8). For elective CABG the drug cessation is recommended at least 5 days and preferably 7 days before surgery (9).

Clopidogrel is a nonreversible platelet antagonist. As a prodrug, clopidogrel is rapidly metabolized in

liver to its active form with plasma half-life of approximately 8 hours. Platelet exposure to active form causes prolonged inhibition (7–10 days) of platelet activation and aggregation. Thus, during this period the hemostasis is dependent on supply of fresh produced or transfused platelets (10).

As cardiac surgery is a major hemostatic challenge where more than 15% of patients admitted to the hospital with acute coronary syndrome are in need of CABG, clinicians have to take complex decisions to consider the risk of antiplatelet agents in such patients requiring urgent surgical revascularization (10).

2. AIM

Aim of article was to estimate the prevalence rate, risk factors and antimicrobial resistance pattern of isolates in Acinetobacter spp. from various clinical samples.

This study was designed to evaluate the impact of preoperative clopidogrel and aspirin on bleeding and outcomes after coronary artery bypass graft surgery (CABG).

3. MATERIALS AND METHODS

Major bleeding was defined according to: Bleeding Academic Research Consortium (BARC) (11), Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) (12), PLATelet inhibition and patient Outcomes (PLATO) and PLATO major bleeding (13). In our study major bleedings reported when bleeding resulted in death, reoperation due to bleeding, intracranial haemorrhage, transfusion of 4 or more units of RBC over 24h and/or 5 or more units of RBCs over 48 h, chest tube drainage in excess of 1500 mL/12 h or 2000 mL/24h or drop in haemoglobin of ≥5.0 g/L. Bleeding volume was defined as chest drainage volume. A thrombotic event was defined as ischaemic stroke with duration exceeding 24hand verified by CT/MRI, pulmonary embolism or deep vein thrombosis evidenced during the same hospitalization. Urgent surgeries defined as within first five days of hospitalization for ACS.

The study represent an observational retrospective analysis of data collected from January 2014 to December 2017 from patients operated for CABG at Hygeia Hospital, Tirana. There were 223 patients treated preoperatively complying to standard protocol with clopidogrel and aspirin at least 7 days before first time CABG. Second group of 77 patients operated for first time CABG were without antiplatelet therapy for at least 7 days before operation. Tendency to intervene as soon as possible correcting the ischemic cardiac event explains the major number of patients in clopidogrel group. Patients with a history of previous cardiac surgery, concomitant valvular surgery, preoperative exposure to either oral anticoagulants or platelet glycoprotein IIb/IIIa inhibitors were excluded. There were a very small number of patients who did not receive aspirin who are excluded, too.

Evaluation of postoperative bleeding and clinical outcomes is performed in both groups. All patients were operated with cardiopulmonary bypass, and mean cardiopulmonary bypass time was lower in the clopidogrel group (106±36 vs 110±43min). Total operation time was not significantly different between groups (193±67 vs. 203±77min) and neither was duration of aortic cross clamp (57±22 vs.64+23 min). The number of distal anastomoses did not differ between the groups.

Bleeding is assessed as chest tube outputs at 12h, 24h and 48h after surgery. Hemograme, ABE, kidney function, neurological status as well as transfusion of red blood cells, platelets, fresh frozen plasma and cryoprecipitate were recorded.

Clinical outcomes after surgery specific to CABG recovery are considered reoperation for bleeding, severe low cardiac output, mortality, acute myocardial infarction (confirmed with enzymes elevation), stroke and postoperative atrial fibrillation. Need for multiple vasopressors or intra-aortic balloon pump after surgery was defined as severe low cardiac output. Duration of intubation/mechanical ventilation and postoperative length of stay in the ICU were evaluated as general postsurgical outcomes.

Risk factors for postoperative bleeding were assessed including advanced age, female gender, small body surface area and kidney failure (14). Baseline hematocrit and prothrombin time were assessed, too. Kirklin and Barrat-Boyes criteria for re-exploration for postoperative bleeding were considered as the guide line (15).

Statistical analysis

Continuous variables are expressed as mean SD. Dichotomous variables are shown as percentages. Mean differences between the groups were analyzed using the Student ***t*** test. Proportional differences were analyzed using the Fisher exact chi-square analysis and p value of 0.05 was considered statistically significant.

4. RESULTS

Patient characteristics were comparable in age, gender and body surface area in both groups (Table 1). The baseline hematocrit, prothrombin time and creatinine levels were also comparable between the groups. There was a significantly prevalence of class III to IV angina (68.6% vs. 52.6%, p=0.01) in the clopidogrel group.

	Clopidogrel+ Aspirin (n = 223pts)	Non Clopidogrel+Aspirin (n = 77pts)	P value
Age (years)	66.62±8,32	68.60±12,15	0.18
Gender (female)	30.45%	28.73%	0.64
Body surface (m^2)	1.82±0.34	1.80±0.24	0.75
Preoperative Hb (gr/L)	138.2±14.2	137.6±15.3	0.45
Prothrombine time (sec)	11.6±1.2	11.2±1.3	0.28
Preop platelet count (x 10^9)	232±86	245±105	0.12
Preop creatinine (mg/L)	10.3±5.4	11.3±6.1	0.38
History of MI*	55.8%	48.4%	0.086
History of CVA**	6.7%	4.6%	0.10
History of CHF***	16.9%	20.7%	0.12
Class III or IV angina	68.6%	52.6%	0.01

Data are shown as mean ±SD or percentage, *MI – myocardial infarction, **CVA – cerebral vascular accident, ***CHF – congestive heart failure,

Table 1. Baseline Characteristics

The postoperative measures of bleeding and blood product transfusions are shown in Table 2. Patients in clopidogrel group had a significantly higher mean chest tube output at all time intervals compared to other group (12h and 24h p<0.05,48h p<0.01). Blood products used showed a significant statistic difference between the groups (p=0.036). Differences are statistically significant for every type of blood products used, especially for platelet transfusion (p= 0.015).

	Clopidogrel+ Aspirin (n = 223pts)	Non Clopido-grel+Aspirin (n = 77pts)	P value
Major bleeding(pts)	18.8%	7.8%	0.008
Chest tube output (ml)			
12 h	519.7±373.6	353.1±209.8	0.016
24 h	756.6±412.8	563.5±347.1	0.012
48h	1137.5±565.4	894.2±452.7	0.008
Transfusions (U/pt)			
Red blood cells	3.23±3.1	2.6±2.2	0.036
Platelets	1.53±0.98	1.23±0.87	0.005
FFP*	0.84±1.03	0.36±0.65	0.003
Cryoprecipitate	0.21±0.18	0.18±0.16	0.033
Blood products exposure			
Red blood cells	92.3%	73.2%	0.032
Platelet	46.5%	28.7%	0.015
Any blood product	95.8%	76.3%	0.036
*FFP – fresh frozen plasma			

Table 2. Post operation Bleeding and Transfusions

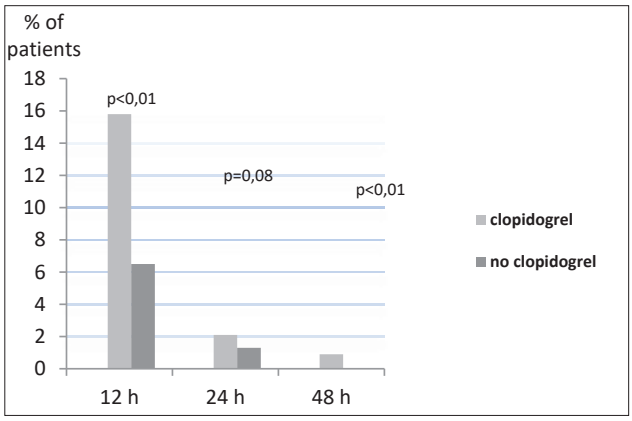

Figure 1. Time when major bleeding is referred

Referred incidence of major bleeding was significantly higher at any moment of monitoring in the patients received clopidogrel within 7 days before operation (Figure 1).

The most striking finding was a 4.5-fold higher incidence of reoperation for bleeding in the clopidogrel group (5.9% vs. 1.3%, p<0.01). In all cases reoperation was performed within first 24 hours. It was observed that patients of non clopidogrel group had a shorter time of mechanical ventilation and length of stay in ICU.

More than 99% of all cases with major bleeding were manifested during first 24 hours after CABG in both groups and mainly during first 12h. Difference in frequency of major bleeding is statistically significant almost all the time span (p<0.01).

Higher mortality rate was observed in the clopidogrel and aspirin group (p=0.864) and higher frequency of myocardial infarction in non clopidogrel group (p<0.05). Post operation cerebral vascular accidents and acute renal failure were more frequent in the non clopidogrel group of patients. Septic complications were significantly higher (p<0.05)in patients of the clopidogrel group, as well as length of stay in ICU. The clinical outcomes are shown in Table 3.

	Clopidogrel+ Aspirin (n = 223pts)	Non Clopido-grel+Aspirin (n = 77pts)	P value
Reoperation for bleeding	5.9%	1.3%	0.002
Severe low cardiac output	5.5%	5.2%	0.42
Mortality	4.97%	3.9%	0.02
MI*	2.2%	5.2%	0.012
CVA**	2.2%	2.7%	0.07
Sepsis	2.2%	1.3%	0.04
Acute renal failure	1.7%	2.6%	0.09
Mechanical ventilation (h)	**16.9**±9.87	**12.9**±8.88	0.03
Length of stay in ICU (days)	**2.08**±1.68	**1.7**±1.5	0.048
*MI-myocardial infarction, **CVA- cerebral vascular accident			

Table 3. The clinical outcomes

5. DISCUSSION

Aggressive antiplatelet therapy with a combination of an ADP receptor inhibitor and aspirin is a well established practice for coronary stent thrombosis prevention (8, 9, 16, 17). The results of our study support such a standard, as post operation myocardial infarction (2.2% vs 5.2%, p=0.012) and cerebral vascular accidents (2.2% vs 2.7%, p=0.07) were higher in non clopidogrel group. Considering the pharmacological properties of clopidogrel, many clinics use it widely in combination with aspirin as antiplatelet therapy before the diagnostic coronary angiography whenever there was a probability of subsequent stent implantation (18-20).

There are many publications demonstrating the efficacy of clopidogrel therapy in prevention of stent thrombosis in acute coronary syndrome and non-ST elevation myocardial infarction (21-23). Standard use of clopidogrel and aspirin before coronarography, as aggressive antiplatelet therapy, produced an increasing number of patients presenting for CABG within first seven days after clopidogrel and aspirin treatment (6).

Clopidogrel loading dose of 300 mg displays 30% antiplatelet activity in 5 h, close to the 40% steady-state antiplatelet activity achieved with a 75 mg daily dose (24). CURE study showed survival benefit starting from 2 h after the single 300 mg dose (18).

Such implication produces a hemostasis problem of major importance. In our study, we found that patients exposed to clopidogrel and aspirin, before acute or urgent first-time CABG had significantly more postoperative bleeding and subsequent transfusions.

The results of the study also confirm the detrimental effect of major bleeding complications on outcome after CABG. The unadjusted 30-day mortality was almost 6

times greater in patients with major bleeding compared with those without bleeding complications (6.7% vs. 1.1%). These findings support previous studies about the effects of bleeding complications (25, 26). It emphasizes the importance of avoiding excessive bleeding after CABG and, if possible, to avoid aggressive antiplatelet premedication for coronarography prior to acute or urgent CABG.

Out of total amount, 95.8% of patients in the clopidogrel group were exposed to different blood products. Reoperations for bleeding were significantly higher in the clopidogrel group (5.9% vs. 1.3%, p<0.01). These findings raise the concern, in particular, the practice of starting clopidogrel and aspirin therapy before possible but undecided coronary stent implantation.

Standard use of aggressive platelet inhibition in coronary disease imposes a major challenge to optimal management of patients receiving clopidogrel presenting for CABG. Results of this study suggest that these patients should delay the surgery, when possible. The delay to allow platelet function recover was subject to many studies. Most of the studies converge to CURE study results, supported by European guidelines (23), which showed that patients who stopped taking clopidogrel within five days of CABG had a trend towards more major bleeding than those on placebo (16). Other publications showed that discontinuation of ticagrelor or 3 days before surgery did not increase the incidence of major bleeding complications, opposing to data for clopidogrel used within 5 days before CABG. The difference is due to different pharmacokinetic profiles of the drugs (23, 24).

Our data show significant statistical correlation between 12h, 24h and 48h mediastinal drainage output and duration of delay to surgery after discontinuation of antiplatelet therapy. All reoperations occurred in patients within 24h or less after CABG with clear predominance of incidence in patients who were treated with anti platelet agents within 5 days before CABG .

If CABG cannot be safely delayed, platelet transfusions are considered when rapid reversal of clopidogrel effect is needed to control bleeding. In contrast to a bciximab exposure before CABG, in clopidogrel exposure prophylactic platelet transfusions are used safely without the possibility of acute reversal of the clinical benefits of platelet inhibition (27).

Tranex (tranexamic acid) is widely used as an effective and safe drug in prevention and treatment of bleeding in adult patients undergoing cardiac surgery. Use of tranex during cardiopulmonary bypass is shown to be effective in prevention of massive bleeding. Patients receiving high-dose (80 mg/kg total dose) of tranex also require fewer units of blood product transfusion and are less likely to undergo repeat surgery to achieve haemostasis (28). However, data from numerous observational studies demonstrate that tranexamic acid use is associated with an increased risk of postoperative seizure (28).

Patients with a high risk of bleeding should receive high-dose tranexamic acid, while those at low risk of bleeding should receive low-dose tranex with considering potential dose-related seizure risk (29).

Aortocoronary grafts have a significant rate of acute thrombotic occlusion. Aspirin therapy after CABG was used as standard for our patients unless its use was specifically contraindicated. Antiplatelet therapy significantly reduces the rate of graft occlusion at 30 days (30, 31). Aspirin therapy started immediately after CABG not only improves early graft patency but also improves survival (32).

Women suffered a higher incidence of major bleeding complications than in men (20.2% vs 16.5%). This may be due to the higher risk of transfusions in women. The higher risk of transfusion in women is mainly caused by lower preoperative haemoglobin levels and smaller blood volume, leading to a higher grade of hemodilution during cardiopulmonary by pass while the same definitions for major bleeding as males are used (33, 34).

Actual guidelines recommend discontinuation of the antiplatelet therapy 5 days before surgery (35, 36). Use of platelet function tests optimize better the timing of the procedure. This strategy is supported by studies, where are shown a significant association between the grade of ADP-dependent platelet aggregability and CABG-related bleeding complications in clopidogrel-treated patients (37).

6. STUDY LIMITATIONS

The present study has inherent limitations of an observational study. Unregistered confounders may include, e.g. history of previous bleeding, COPD, undiscovered liver disease (alcoholism), previous undiagnosed CVA and incipient renal failure.

The imbalance of class III to IV angina (68.6% vs. 52.6%, p < 0.01) raises concern that there may be differences in the use of antiplatelet agents between the groups that may influenced the outcomes. Patients receiving either GP IIb/IIIa inhibitors or oral anticoagulants were excluded from the study. Nonetheless, because patients were not randomized to clopidogrel exposure, not considered confounding factors may exist. Considering the structure of the study the effect of aspirin on post operation bleeding in our patient groups is unknown. Synergy of clopidogrel and aspirin has been described (37), which could not be assessed in this study. The results of this study essentially reflect the effects of the combination of clopidogrel with aspirin and cannot be generalized to patients that are receiving clopidogrel alone.

7. CONCLUSION

Clopidogrelin combination with aspirin used before first-time CABG was associated with higher postoperative bleeding and morbidity. Our findings confirm, as other publications, the great concern regarding the routine administration of clopidogrel before anticipated but undecided coronary stent implantation. It may be reasonable to delay surgery, when possible, in patients recently exposed to the combination of clopidogrel and aspirin. Introduction of new P2Y12-receptor antagonist – ticagrelor, offers a new possibility, considering the shorter period of time needed for cessation of its antiplatelet effect. Bleeding after first time CABG remains a

major concern and further studies will be needed to better define the role of platelet antagonists before CABG.

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- Conflict of interest: Authors declare no conflict of interest.
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