Does Clopidogrel Increase Blood Loss Following Coronary Artery Bypass Surgery?

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Abstract:

Introduction

Clopidogrel treatment is associated with a reduction in thrombotic complications in coronary stent placement, improved outcome after acute coronary syndromes and decreased mortality in patients with coronary artery disease. The purpose of this study was to analyze the effect of preoperative clopidogrel exposure on bleeding complications, blood transfusion requirement and reoperations and ICU and ward stay and mediastinitis in patients undergoing coronary artery bypass grafting (CABG).

Materials and Methods:

This study included 82 patients from a single institution (Shahid Rajaie Hospital) that underwent an isolated CABG who were discharged 2010. The cohort of 82 patients was classified into 2 groups. The control group consisted of 46 patients that did not receive clopidogrel or stopped 5 days before surgery but were treated with aspirin and clopidogrel group consisted of 36 patients that were taking clopidogrel within 5 days of surgery.

Patients were compared based on preoperative data (age, gender, use of clopidogrel, ejection fraction), intraoperative data (cross clamp & CPB time) and postoperative data (chest tube output, rate of reoperation, units of transfused blood length of stay in the intensive care unit and ward).

Results:

There were no significant differences among 2 groups concerning age, sex and ejection fraction. There were no differences in length of intensive care unit and ward stay among 2 groups. Patients in clopidogrel group had more units of platelet transfusion than the control group (P=0.001). There is also a non significant trend toward more chest tube output in clopidogrel group compared with the control group, the mean chest tube output in clopidogrel group was 1185±850 ml and in control group was 1020±590 ml (P=0.305). 7 patients of the total group required reoperation secondly to bleeding, 5 patients in clopidogrel group (13.9%) and 2 patients (4.3%) in control group but was not significant statistically (P=0.125).

Conclusions:

This study demonstrated that clopidogrel within 5 days preoperatively increases the requirement for platelet transfusion and packed cell transfusion only in clopidogrel group that needed reoperation for hemostasis. The reoperation rate of patients that took clopidogrel within 5 days of their procedure was not different from reoperation rate of the patients that did not take clopidogrel.

Our results don't support the recent history of clopidogrel treatment associated with increased blood loss. Transfusion and reoperation was required after CABG.

Key words: CABG; clopidogrel; postoperative blood loss

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Introduction:

Postoperative bleeding following coronary artery bypass surgery necessitates re-exploration in approximately 3% of cases and can cause significant morbidity and mortality. Other than inadequate control of bleeding during surgery, small body size, female gender, concomitant procedures, urgency status, and increased cardiopulmonary bypass time have been previously identified as risk factors [1,2]. In 50% of re-exploration for bleeding no identifiable cause is found[1,3]. Since platelet dysfunction is a crucial part of bleeding after cardiopulmonary bypass[4], antiplatelet agent, adding insult to already dysfunctional platelets, can also affect hemostasis in the postoperative period. Generally these agents are discontinued at the appropriate time before operation to ensure adequate platelet function at the time of operation. However in a group of patients it may not be possible to delay surgery due to ongoing ischemia. Those patients have generally received more potent antiplatelet agents like clopidogrel.

Clopidogrel, a thienopyridine is an irreversible and potent inhibitor of platelet aggregation and has been mainly used to prevent clotting complications immediately before and after intracoronary stenting. Additionally, in patients with acute coronary syndrome, carotid and peripheral vascular disease and acetyl salicylic acid (ASA) intolerance, the cardiologist has been increasingly favoring clopidogrel [5]. As a result more patients are undergoing elective, urgent or emergent CABG while under the influence of clopidogrel. Its beneficial effect on preventing clot formation may return to hazardous on hemostasis in patients who need urgent or emergent CABG. The aim of this study was to evaluate the effects of clopidogrel on blood loss and blood product usage following CABG.

Methods:

2. 1 Patient population

Eighty two consecutive patients underwent isolated coronary artery bypass graft (CABG) by the same surgery team between August 2009 and August of 2010; 36 of those patients had clopidogrel exposure (group 1) within 5 days of operation and remaining 46 patients were not on clopidogrel therapy (group 2) within 5 days of operation. Exclusion criteria included off-pump bypass, reoperations, end stage renal failure, severe liver dysfunction, preexisting bleeding disorders and warfarin usage. Mean age in group 1 was 61±0.6 years and mean age in group 2 was 57.5±8.6 years. There were 52 men (27 in group 1 and 32 in group 2) and 23 women (9 in group 1 and 14 in group 2). Mean LVEF in group 1 (on plavix) was 44%±7.4% and mean LVEF in group 2 (without plavix) was 44.2%±915. The left internal mamuray artery (LIMA) was used in all of 82 patients (100%). Preoperatively intraaortic balloon counter pulsation was not used in any of the patients. All the operations were performed on-pump with the use of a standard circuit and crystalloid prime. Anticoagulation was achieved with heparin. Aprotinin was not used for any of the patients. The degree of hypothermia induced during CPB was monitored by using an nasopharyngeal temperature probe and ranged from 30 to 32±C. Patients were rewarmed to a target temperature of 37±C before CPB was discontinued. After weaning from CPB heparin was neutralized with protamine sulfate (1-1.5 mg/100 U heparin). During extracorporeal perfusion, transfusion of red blood cells was performed when hematocrit value decreased under 0.20. Postoperative transfusion of packed red blood cells was found to be indicated when hematocrit value was lower than 0.21. The clinical criterion for platelet and fresh frozen plasma (FFP) transfusion in the operating room, just before closing the sternum, was excessive microvascular bleeding despite normalized ACT as determined by the surgeon and in the ICU; the clinical criterion was chest tube drainage of greater than 250 ml/h after the first hour despite normalized ACT. In the patients with excessive bleeding, platelet count, bleeding time and ACT were done to assess global coagulation status. Surgical re-exploration was found to be indicated when bleeding exceeded 400ml during the first hour or when it was more than 300 ml/h during the next 3hrs despite ACT and global coagulation status. The pre-operative demographics, preoperative co-merbidities, pre-and postoperative variables of these groups were compared (Table 1). Total chest tube drainage during the first 48 hour, the incidence of re-exploration, the exposure to blood products and the early outcome (The intensive care unit stay and total surgical ward stay) were assessed.

2.2. Statistical analysis

Continuous preoperative, intraoperative and postoperative variable are expressed as the mean ±SD. Dichotomous variables are shown as percentages. Mean differences between

the groups were analyzed using the Fisher exact Chi-square analysis using SPSS statistical soft ware. Variables were considered significant at P values <0.05.

Results:

The baseline characteristics of the patients in each group were comparable in age, gender and body surface area (Table 1).

Table 1: Preoperative variables

	Group 1	Group 2	P value
Age	71±0.7	57.5±8.6	ns
Gender (% male)	27 (75%)	62 (69.6%)	ns
Body mass index	22.4±2.6	25.9±1.4	ns
Diabetes (%)	16 (44.2%)	27 (58.71)	ns
Hypertension (%)	16 (44.4%)	20 (43.5%)	ns
Preoperative EF (%)	44.3±7.4	44.2±9.5	ns
HCT	35±11	36±12	ns
aPTT(s)	32.4±4.4	32.7±4.4	ns

ns: not significant

The baseline hematocrit and platelet levels were also comparable between the groups. The mean number of grafts per patient was 3.6±0.8 in group 1 (on plavix) and in group 2 (without plavix) was 3.5±0.9 without significant difference statistically. We did not find any significant difference in by-pass time, cross-clamping time and use of LIMA (Table 2).

Table 2: Intraoperative variables

	Group 1	Group 2	P value
Number of distal anastomosis	3.6±0.8	3.5±0.9	ns
CPB time (min)	96.7±18.8	99.3±23.6	ns
Cross clamp time (min)	43.1±8.3	46.8±12.5	ns
LIMA (%)	100	100	ns

ns: not significant

Total chest tube drainage was not significantly higher in the patient with clopidogrel exposure (group 1) and an increased amount of transfusion of blood products (platelets) was observed in these patients (Table 3). The mean chest tube in clopidogrel group was 1185±859 Ml and in control group was 1020±590 ml (P=0.305).

Table 3: Postoperative variables

	Group 1	Group 2	P value
Drainage (ml)	1185±850	1020±590	0.305
Re-exploration (%)	13.9%	4.5%	0.202
Packed red blood cells (ml/ patient)	450±626	420±44	0.761
Pletelet (U/patient)	2.5±1.8	0.85±0.5	0.001
Fresh Frozen plasma (U/patient)	1.7±1.06	1.1±0.6	0.132
Length of ICU stay (days)	4.2±2.1	3.9±1.5	0.505
Length of hospital stay (days)	5.5±3.8	4.8±1.5	0.525

The patients with clopidogrel exposure did not have to be taken back to OR significantly more for mediastinal re-exploration. Mediastinal re-exploration for bleeding was required in 5 patients (13.9%) in group 1 and in 2 patients (4.3%) in group 2 (Exact Fisher test, P=0.202). After re-exploration, no specific sources were identified and bleeding was thought to be secondary to coagulopathy in each case. In terms of total length of hospital stay, clopidogrel within 5 days of operation was not associated with prolonged hospitalization. The mean ICU lengths of stay in group 1 was 4.2±2.1 days and in group was 2 3.9±1.5 days and the mean surgical ward stay of group 1 was 5.5±3.8 and in group 2 was 4.8±1.5 days with P value=0.505 and 0.525 respectively.

Discussion

The thienopyridine derivative, clopidogrel, is an antiplatelet agent that inhibits the platelet aggregation induced by adenosine diphosphate, thereby reducing ischemic events. Clopidogrel has a significantly rapid onset of activity and has been the drug-of-choice for acute ischemic events. Clopidogrel has been proven significantly to reduce the risk of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction or strokes; as well as a range of related ischemic events[6]. The CURE trial attests strongly to add clopidogrel to acetyl salicylic acids (ASA) as soon as possible after hospital admission

in patients with unstable angina and myocardial infarction without ST-segment elevation[7-9]. A combination of clopidogrel with ASA, which blocks the thromboxane-mediated pathway, may have an additive effect. Furthermore in patients who are undergoing percutaneous transluminal angioplasty (PTCA) with stenting, short-term ASA treatment plus clopidogrel results in a substantially lower rate of myocardial infarction than does either aspirin alone [7]. These beneficial effects on preventing clot formation may increase the risk of major nonsurgical bleeding in patients who need urgent or emergent CABG [10,11]. Withholding the clopidogrel preoperatively until normal coagulation is restored will be adequate in elective cases. The optimal duration of this delay, however is still unclear. The drug manufacturer recommends that clopidogrel should be discontinued for 7 days prior to elective coronary surgery. In the CURE trial, patients who were withhold from clopidogrel treatment within 5 days prior to CABG had a trend towards more bleeding than these patients in the control placebo group [12]. Chu and associates reported that withholding of clopidogrel for more than 4 days before CABG is not associated with increased blood losses and reoperation for bleeding [11]. However, the management of patients who need urgent or emergency CABG presents a dilemma. Delaying the operation while clopidogrel is withdrawn may end up with a thrombotic episode. On the other hand, if the operation proceeds, surgeon will take the risk of excessive bleeding and possible surgical reexploration and increased blood product which is associated with increased in-hospital morbidity and mortality.

The major objective of this study was to clarify whether blood loss and transfusion requirement would increase in patients undergoing on-pump CABG with a recent history of clopidogrel treatment. Our data and some of others clearly document no excess blood loss in these patients. However, results of the most of others suggested that preoperative use of clopidogrel is associated with increased bleeding and the need for surgical exploration as well as risk of blood and blood product transfusion after CABG [14]. In one of the previous study interestingly, no patients received platelet transfusion and the amount of transfused blood per patient was very low. comparing with other studies, choosing lower hematocrit levels as criterion far blood transfusion and significant difference between the number of the patients on study and control groups might explain this result. Chen and associates recently published study aiming to improve transfusion management of patients undergoing CABG with a recent history of clopidogrel treatment [15]. Some of researchers developed an algorithm based on both clinical and laboratory criteria including two platelet function tests (ADP aggregometry and platelet function analyzer 100). Using this algorithm, they were able to reduce transfusion rate significantly , reoperation per bleeding and hospital stay. However, this algorithm may not be practical for most of the patients with postoperative bleeding since ADP aggregometry takes 45min.

The impact of preoperative acetyl salicylic acid (ASA) exposure on transfusions following CABG is controversial. Preoperative aspirin is now suggested to decrease mortality in CABG patients [16]. In previous studies questioning the effect of clopidogrel after CABG, patients were not grouped to analyze the potential synergistic effect of combination treatment of ASA and clopidogrel. In our study, no significant difference on bleeding and surgical exploration were found neither between patients receiving clopidogrel plus ASA and patients receiving ASA and no other antiplatelet treatment.

Despite our results, most of other studies [10-13, 17] have found longer duration of mechanical ventilation and ICU stay in patients with clopidogrel exposure within five days of surgery. There was also a non-significant trend towards longer postoperative hospitalization in these studies.

Conclusion

Our results do not support that in patients with a recent history of clopidogrel treatment it is associated with excessive blood loss, blood transfusion rate and reoperation for bleeding. Prescribing clopidogrel does not necessarily contraindicate elective CABG. CABG should not be delayed.

Limitations

Limitations of this study include all those inherent to any retrospective single institution analysis. All date elements, however, were prospectively entered in a cardiac surgery research data base according to pre-specified definitions and the data analysis was performed using appropriately risk-adjusted statistical models in order to adjust for differences in preoperative risk factors. One might suggest that surgeons and aesthetics could be a ware of patients who re-

ceived antiplatelet agents preoperatively, possibly lowering their threshold for administering blood products to them. Although such a bias might have occurred with certain secondary end point, it is unlikely to have affected the primary endpoint (need for reexploration due to hemorrhage).

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