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Shervin Ziabakhsh Tabary
Division of Cardiovascular Surgery,
Mazandaran Heart Center,
Medical University of Mazandaran,
Sari, Iran

Does Plavix Have Any Influences on Postoperative Bleeding and Blood Transfusion after Urgent and Emergent Coronary Artery Bypass Grafting

Shervin Ziabakhsh Tabary

The aim of this study was to evaluate the effects of Plavix on blood loss and blood and blood products usage following CABG. Three hundred and ninety two patients underwent urgent or emergent CABG, 364 of those met with inclusion criteria, 56 patients had Plavix exposure (group 1), 98 patients had both ASA and Plavix exposure (group 2) and 136 patients had ASA exposure (group 3) within a week of operation. The remaining 74 patients were on no antiaggregant therapy (group 4). Total chest tube drainage during the first 24 h, the incidence of reoperation for bleeding, blood and blood products usage and the early outcome (duration of mechanical ventilation, the intensive care unit stay and total hospital stay), were assessed. Total chest tube drainage was significantly higher in the patients with Plavix exposure and increased amount of transfusions with blood products were also observed in those patients. The patients with Plavix exposure required significantly more reoperation for bleeding. The duration of controlled ventilation and intensive care unit stay were also significantly longer in the patients with Plavix exposure. Present results support the recent history of Plavix treatment associated with increased blood loss, transfusion and reoperation requirement after CABG.

Key words: CABG, plavix, postoperative bleeding

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Division of Cardiovascular Surgery, Mazandaran Heart Center,
Medical University of Mazandaran, Sari, Iran

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 (Dacey *et al*., 2007; Despotis *et al*., 2004). In 50% of re-exploration for bleeding no identifiable cause is found (Ziabakhsh *et al*., 2004; Woodman and Harker, 2001). Since platelet dysfunction is a crucial part of bleeding after cardiopulmonary bypass (Kestin *et al*., 2000), antiplatelet agents, 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 the surgery due to ongoing ischemia. Those patients have generally received more potent anti-platelet agents like Plavix (CL). Plavix, a thieno-pyridine, 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 Plavix (Yende and Wunderlink, 2001). As a result, more patients are undergoing urgent or emergent CABG while under the influence of Plavix. Its beneficial effects 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 Plavix on blood loss and blood and blood product usage following CABG.

MATERIALS AND METHODS

Patient population: Nine hundred and eighty seven consecutive patients underwent isolated coronary artery bypass graft (CABG) between 10/15/2003 and 10/15/2006. Three hundred ninety two (39.7%) of these patients were operated on an urgent or emergent basis. Of the patients who underwent elective CABG, platelet inhibitors were discontinued a week before surgery. Of the 392 patients who underwent undelayed CABG, 364 met with inclusion criteria, 56 of those patients had Plavix exposure (group 1), 98 patients had both ASA and Plavix exposure (group 2) and 136 patients had ASA exposure (group 3) within three days of operation. The remaining 74 patients were on no antiaggregant therapy (group 4). The majority of patients who were not on antiaggregant therapy, withdrew the medication while a few of them presented without any cardiac related history. Exclusion criteria included: off-pump bypass, reoperations, end stage renal failure, liver dysfunction, preexisting bleeding disorders, warfarin usage and recent glycoprotein llb/llla inhibitors exposure. Since we aimed to clarify the effect of Plavix after cardiopulmonary bypass, the patients who were operated off-pump were excluded. The main reasons for urgent or emergent surgery were critical left main coronary artery (LMCA) stenosis or critical proximal LAD stenosis and the patients with acute coronary syndrome.

Age ranged from 47 to 77 years (mean 63). There were 264 men and 100 women. Main presentation of the patients: angina pectoris in 276 patients; congestive heart failure in 36 patients and both in the remaining. Mean LVEF 39.4% (range 24-55%). The left internal mammary artery (LIMA) was used in 352 patients (96%). Heart failure was defined for the patients in Class III or IV (NYHA). 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 (300 U kg^{-1}). Aprotinin was not used in any patient. The degree of hypothermia induced during CPB was monitored by using a nasopharyngeal temperature probe and ranged from 56 to 32°C. Patients were rewarmed to a target temperature of 74°C before CPB was discontinued. After weaning from CPB, heparin was neutralized with protamine sulfate (1.0-1.5 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 0.26. 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. In the ICU, the clinical criterion was chest tube drainage of greater than 250 ml h^{-1} after the first hour despite normalized ACT. Peri- and postoperative substitution of FFP and platelets was also based on coagulation parameters (platelets <80,000 mL^{-1}, ACT 10% or more than baseline, pathologic thrombin time and/or bleeding time). In the patients with excessive bleeding, platelet count, bleeding time, thrombin time and ACT were done to assess global coagulation status. Surgical re-exploration was found to be indicated when bleeding exceeded 400 mL during the first hour or when it

was more than 300 ml h^{-1} during the next 3 h despite normalized ACT and global coagulation status. The pre-operative demographics, preoperative co-morbidities, operative factors, pre- and postoperative variables of these groups were compared (Table 1). Total chest tube drainage during the first 24 h, the incidence of re-exploration, the exposure to blood products and the early outcome (duration of mechanical ventilation, the intensive care unit stay and total hospital stay) were assessed.

Statistical analysis: Continuous preoperative, intraoperative and postoperative variables are expressed as the mean+SD Dichoto-mous 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 using SPSS statistical software .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). The baseline hematocrit and platelet levels were also comparable between the groups. The mean number of grafts per patient was, in all study population, 2.8. The number of distal anastomosis was comparable among groups. We did not find any significant difference in bypass time, cross-clamping time and use of LIMA (Table 2).

Total chest tube drainage was significantly higher in the patients with Plavix exposure (groups 1 and 2) and an increased amount of transfusions with blood and blood products was observed in those patients (Table 3). However, regarding blood loss and the amount of transfusions, no significant differences were found neither between groups 1 and 2 nor between groups 3 and 4. The patients with Plavix exposure had to be taken back to OR significantly more for mediastinal re-exploration. Mediastinal re-exploration for bleeding was required in 4 patients (6.1%) in group 1, in 6 patients (7.1%) in group 2 and in 2 patient (1.4%) in group 3. Re-exploration was not necessary in group 4. After re-exploration, no specific sources were identified and bleeding was thought to be secondary to coagulopathy in each case.

Also, the patients with Plavix exposure (groups 1 and 2) were less likely to be extubated within 8 h of surgery and the duration of controlled ventilation and intensive care unit stay were significantly longer. There was also a nonsignificant trend toward longer postoperative hospitalization in those patients (Table 3). The main reasons for longer controlled

Table 1: Preparation variables in patients underwent CABG

Preoperative variables	Group 1 n = 56	Group 2 n = 98	Group 3 n = 136	Group 4 n = 74	p-value
Age (years)	63±1.8	64±2.4	62±2.2	66±2.6	ns
Gender (% male)	40 (71%)	70 (71%)	102 (5%)	54 (73%)	ns
Body mass index (kg m^{-2})	27.6±2.9	26.9±3.9	27.2±3.7	27.1±3.4	ns
Angina pect (%)	50 (89.2%)	86 (87.7%)	128 (92.6%)	66 (89.1%)	ns
Diabetes (%)	12 (21.4%)	20 (22.4%)	28 (20.5%)	14 (36.9%)	ns
Hypertension (%)	40 (64.2%)	112 (57.1%)	82 (60.2%)	44 (59.4%)	ns
Preoperative EF (%)	42±3.7	40±4.3	39±3.9	36±3.4	ns
EuroSCORE	3.6±2.8	3.4±2.3	3.0±2.4	3.2±3.0	ns
Platelet count (103 mL^{-1})	265±88	565±92	278±62	562±98	ns
Htc	35±11	74±12	36±14	34±11	ns
aPTT (s)	32.4±4.4	32.7±4.4	31.7±4.3	31.2±4.5	ns

Table 2: Intraoperative variables in patients underwent CABG

Intraoperative variables	Group 1 n = 56	Group 2 n = 98	Group 3 n = 136	Group 4 n = 74	p-value
No. of distal anastomosis	2.6±1.1	2.7±1.0	2.8±1.1	3.1±1.1	ns
CPB time (min) Cross-clamp	42.0±14	40.0±14	38.0±13	38.0±14	ns
Time (min)	27.0±9	25.0±10	56.0±11	26.0±10	ns
LIMA (%)	100.0	98	97.0	97.0	ns

ns: Not significant

Table 3: Postoperative variables in patients underwent CABG

Postoperative variables	Group 1 n = 56	Group 2 n = 98	Group 3 n = 136	Group 4 n = 74	p-value
Drainage (mL/24 h)	1210±260	1360±560	660±110	625±90	<0.05
Re-exploration (%)	7.1	6.1	1.4	0	<0.05
Packed red blood cells (U/patient)	3.7±1.0	3.9±0.8	1.4±0.3	1.2±0.4	<0.05
Platelet (U/patient)	2.2±1.1	2.0±1.2	0.2±0.5	0.3±0.4	
Fresh frozen plasma (U/patient)	1.3±0.7	1.4±0.6	0.7±0.4	0.4±0.3	<0.05
Mech. ventilation >8 h (%)	42.8	48.9	29.4	24.3	<0.05
Length of ICU stay (days)	1.5±0.9	1.6±0.7	1.1±0.5	09±0.3	<0.05
Length of hospital stay (days)	5.9±1.4	5.7±1.4	5.4±1.6	5.1±1.2	NS
Perop. Ml	2 (3.5%)	2 (2.0%)	4 (2.8%)	2 (2.7%)	NS
Postop stroke	0	2 (2.0%)	2 (1.4%)	2 (2.7%)	<0.05

ventilation and intensive care unit stay were found as follow-up for prolonged blood loss and re-exploration, while the reasons for longer hospital stay were renal and respiratory problems, possibly due to excessive blood transfusion.

DISCUSSION

The thienopyridine derivative, Plavix, is an antiplatelet agent that inhibits the platelet aggregation induced by adenosine diphosphate, thereby reducing ischemic events. Plavix has a significantly rapid onset of activity and has been the drug-of-choice for acute ischemic events. Plavix has been proven significantly to reduce the risk of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or stroke, as well as a range of related ischemic events (Yusuf *et al*., 2001). The CURE trial attests strongly to add Plavix to Acetyl Salicylic Acid (ASA) as soon as possible after hospital admission in patients with unstable angina and myocardial infarction without ST-segment elevation (Braunwald *et al*., 2002). A combination of Plavix with ASA, which blocks the thromboxane-mediated pathway, may have an additive effect. Furthermore, in patients who are undergoing percutaneous transluminal coronary angioplasty (PTCA) with stenting, short-term ASA treatment plus Plavix results in a substantially lower rate of myocardial infarction than does either aspirin alone. These beneficial effects on preventing clot formation may increase the risk of major nonsurgical bleeding in patients who need urgent or emergent CABG (Yende and Wunderlink, 2001; Chu *et al*., 2004). Withholding the Plavix 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 Plavix should be discontinued for 7 days prior to elective coronary surgery. In the CURE trial, patients who were withheld from Plavix treatment within 5 days prior to CABG had a trend towards more bleeding than those patients in the control placebo group (Mitka *et al*., 2001). Chu *et al*. (2004) reported that withholding of Plavix for more than 4 days before coronary bypass surgery is not associated with increased blood losses and reoperation for bleeding.

However, the management of patients who need urgent or emergency CABG presents a dilemma.

Delaying the operation while Plavix is withdrawn may end up with a thrombotic episode. On the other hand, if the operation proceeds, surgeons will take the risk of excessive bleeding and possible surgical reexploration and increased blood product use 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 Plavix treatment. Present data and most of others (Yende and Wunderlink, 2001; Mitka *et al*., 2001), clearly document the excess blood loss and transfusion requirements of these patients. However, results of a recent study suggested that preoperative use of Plavix is not associated with increased bleeding and the need for surgical exploration as well as risk of blood and blood product transfusion after CABG (Karabulut *et al*., 2004). In that 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 for blood transfusion and significant difference between the number of the patients on study and control groups might explain this result. Chen *et al*. (2000) recently published a prospective study aiming to improve transfusion management of patients undergoing CABG with a recent history of Plavix treatment.

The researchers developed an algorithm based on both clinical and laboratory criteria including two platelet function tests (Using this algorithm they were able to significantly reduce transfusion rate, reoperation for bleeding and hospital stay. However, this algorithm may not be practical for most of the patients with postoperative bleeding since ADP aggregometry takes 45 min.

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 (Munoz and Johnson, 2000). In previous studies questioning the effect of Plavix after CABG, patients were not grouped to analyze the potential synergetic effect of combination treatment of ASA and Plavix. In this study, no significant differences on bleeding, surgical exploration and blood and blood product transfusion requirement were found neither between patients receiving Plavix alone or combination with ASA, nor between patients receiving ASA and no antiplatelet treatment.

Similarly, most of the other studies (Englberger *et al*., 2004) have also found longer duration of mechanical ventilation and ICU stay in patients with Plavix exposure within three days of surgery. There was also a non-significant trend towards longer postoperative hospitalization in those patients.

CONCLUSION

Present results support that in patients with a recent history of Plavix treatment that it is associated with excessive blood loss, transfusion rate and reoperation for bleeding. Prescribing Plavix necessitates being in strict indications in potential CABG candidates. CABG should be delayed, when possible, to allow platelet function to recover. In urgent or emergent cases, aggressive transfusion of platelets is required if bleeding manifests in the peri-and postoperative period.

LIMITATIONS

The limitations of this study include: (1) patients were not randomized to Plavix exposure and (2) a small cohort of patients may not lead to a meaningful statistical comparison. Additionally, surgeons and anesthesiologists caring for the patients in our study were not blinded to preoperative exposures to antiplatelet medications. This knowledge may have biased their decision on timing and the amount of blood and blood product transfusion.

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