Institutional report - Coronary
Impact of clopidogrel on postoperative blood loss after non-elective coronary bypass surgery

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Abstract

The aim of this study was to evaluate the effects of clopidogrel on blood loss and blood and blood products usage following CABG. One hundred and ninety-six patients underwent urgent or emergent CABG, 182 of those met with inclusion criteria, 28 patients had clopidogrel exposure (group 1), 49 patients had both ASA and clopidogrel exposure (group 2), and 68 patients had ASA exposure (group 3) within a week of operation. The remaining 37 patients were on no antiagregant therapy (group 4). Total chest tube drainage during the first 24 h, the incidence of reoperation for bleeding, 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 clopidogrel exposure and increased amount of transfusions with blood products were also observed in those patients. The patients with clopidogrel 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 clopidogrel exposure. Our results support the recent history of clopidogrel treatment associated with increased blood loss, transfusion and reoperation requirement after CABG.

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Keywords: CABG; Clopidogrel; Postoperative blood loss

1. 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 [3,4]. Since platelet dysfunction is a crucial part of bleeding after cardiopulmonary bypass [4], 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 antiplatelet agents like clopidogrel (CL). 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 intraconorary 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 urgent or emergent CABG while under the influence of clopidogrel. 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 clopidogrel on blood loss and blood and blood product usage following CABG.

2. Methods

2.1. Patient population

One thousand and thirty-eight consecutive patients underwent isolated coronary artery bypass graft (CABG) by the same surgeon (FN) between 10/15/2002 and 10/15/2004. One hundred and ninety-six (18.8%) 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 196 patients who underwent undelayed CABG, 182 met with inclusion criteria, 28 of those patients had clopidogrel exposure (group 1), 49 patients had both ASA and clopidogrel exposure (group 2), and 68 patients had ASA exposure (group 3) within three days of operation. The remaining 37 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 IIb/IIIa inhibitors exposure. Since we aimed to clarify the effect of clopidogrel 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 132 men and 50 women. Main presentation of the patients: angina pectoris in 138 patients; congestive heart failure in 18 patients; and both in the remaining. Mean LVEF 39.4% (range 24–55%). The left internal mammary artery (LIMA) was used in 176 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). 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 28 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 (1.0–1.5 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 after the first hour despite normalized ACT. Peri- and postoperative transfusion of FFP and platelets was also based on coagulation parameters (platelets <80,000/ml, 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 during the next 3 h despite normalized ACT and global coagulation status. The pre-operative demographics, pre-operative co-morbidities, operative factors, pre- and post-operative 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.

2.2. Statistical analysis

Continuous preoperative, intraoperative, and postoperative variables are expressed as the mean ± S.D. 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 using SPSS statistical software (SPSS Inc, Chicago, IL). Variables were considered significant at P-values < 0.05.

3. 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 clopidogrel 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 clopidogrel exposure had to be taken back to OR significantly more for mediastinal re-exploration. Mediastinal re-exploration for bleeding was required in two patients (6.1%) in group 1, in three patients (7.1%) in group 2, and in one 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 clopidogrel 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 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.

4. 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 mortality 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 most of others [10–13], clearly document the excess blood loss and transfusion requirements of these patients. However, results of a recent study suggested that preoperative use of clopidogrel is not associated with increased bleeding and the need for surgical exploration as well as risk of blood and blood product transfusion after CABG [14]. 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 and associates recently published a prospective study aiming to improve transfusion management of patients undergoing CABG with a recent history of clopidogrel treatment [15].

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Intraoperative variables</th>
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<tbody>
<tr>
<td>Group 1 n:28</td>
<td>Group 2 n:49</td>
</tr>
<tr>
<td>Number of distal anastomosis</td>
<td>2.6±1.1</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>42±14</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>27±10</td>
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<tr>
<td>LIMA (%)</td>
<td>100</td>
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ns, not significant.

<table>
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<th>Table 3</th>
<th>Postoperative variables</th>
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<tr>
<td>Group 1 n:28</td>
<td>Group 2 n:49</td>
</tr>
<tr>
<td>Drainage (mL/24 h)</td>
<td>1210±260</td>
</tr>
<tr>
<td>Re-exploration (%)</td>
<td>7.1</td>
</tr>
<tr>
<td>Packed red blood cells (U/patient)</td>
<td>3.7±1.0</td>
</tr>
<tr>
<td>Platelet (U/patient)</td>
<td>2.2±1.1</td>
</tr>
<tr>
<td>Fresh frozen plasma (U/patient)</td>
<td>1.3±0.7</td>
</tr>
<tr>
<td>Mech. ventilation &gt;8 h (%)</td>
<td>42.8</td>
</tr>
<tr>
<td>Length of ICU stay (d)</td>
<td>1.5±0.9</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>5.9±1.4</td>
</tr>
<tr>
<td>Perop. MI (%)</td>
<td>1 (3.5%)</td>
</tr>
<tr>
<td>Postop stroke</td>
<td>0</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; ns, not significant; MI, myocardial infarction.
The authors 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 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 [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 differences on bleeding, surgical exploration and blood and blood product transfusion requirement were found neither between patients receiving clopidogrel alone or combination with ASA, nor between patients receiving ASA and no antiplatelet treatment.

Similarly, most of the other studies [10–13] have also found longer duration of mechanical ventilation and ICU stay in patients with clopidogrel exposure within three days of surgery. There was also a non-significant trend towards longer postoperative hospitalization in those patients.

5. Conclusion

Our results support that in patients with a recent history of clopidogrel treatment that it is associated with excessive blood loss, transfusion rate, and reoperation for bleeding. Prescribing clopidogrel 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.

6. Limitations

The limitations of this study include: (1) patients were not randomized to clopidogrel 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.

References