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CAUTION OF USE CLOPIDOGREL (PLAVIX ®) IN CARDIAC SURGERY

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ABSTRACT:

Introduction*: Clopidogrel (Plavix ®) is the most potent and popular anti-platelet agent available in the United States and Europe. This medication has been primarily used for patients undergoing coronary stenting and well known to cardiologists; however, little knowledge has been share with cardiac surgeons in Japan. Thus, a literature search was performed to evaluate the risk of clopidogrel administration in patients undergoing coronary artery bypass grafting.*

Methods*: Medline literature search was performed, focusing on the effect of clopidogrel against postoperative bleeding, transfusion and reoperation. A total of 9 papers were found and a total of 4469 patients (503 patients in the clopidogrel group and 3966 patients in the control group) were pooled for analysis. Chi-square tests, Mantel-Haenszel methods or general variance-based methods were utilized to calculate relative risk (RR) with 95% confidence limit (CL), as appropriate.*

Results*: The clopidogrel group demonstrated 703 ml (95% CL 630-755 ml) more drainage than the control group. The transfusion rate was greater in the clopidogrel group: packed red blood cells (78% vs 46%, RR 3.96, 95% CL 2.98-5.27) , fresh frozen plasma (41% vs 15%, RR 4.19, 95% CL 3.06-5.76), and platelet (60% vs 12%, RR 11.63, 95% CL 8.35-16.19). The incidence of postoperative reexploration was also higher in the clopidogrel group than in the control group (8.2% vs 1.4%, Odds ratio 4.87, 95% CL 2.86-8.31), p<0.0001.*

Conclusion*: The preoperative administration of clopidogrel increases postoperative coagulopathy-related complications. At least a 5-days interval after stopping clopidogrel is recommended to avoid clopidogrel-induced coagulopathy, otherwise the risk of bleeding should be carefully explained to the patients.*

Key words:

coronary artery disease, antiplatelet therapy, surgery, complication, transfusion

Introduction

Over the last two decades, anti-platelet drugs have been widely used in patients with cardiovascular disease. The most commonly prescribed drug is aspirin. Randomized prospective control trials (RPCTs) showed that aspirin reduced the incidence of stroke, myocardial infarction and cardiovascular death.[1] In patients undergoing coronary artery bypass grafting (CABG), preoperative use of aspirin was initially found to increase rate of transfusion, reoperation for bleeding and hospital stay, [2, 3, 4] subsequent studies have proven these adverse effects were not related to aspirin. [5, 6, 7] Furthermore, aspirin is now suggested to decrease mortality in CABG patients. [8]

Percutaneous catheter intervention (PCI) using an intracoronary stent has become widely available since the 1990s, and the results were improved with antiplatelet treatment. [9] Recently, drug eluted stent (DES) was developed and its outcomes are known to be optimized with anti-platelet therapy using aspirin and clopidogrel (PLAVIX ®).[10] Unfortunately, clopidogrel is currently unavailable in Japan. Therefore, current protocol for DES antiplatelet treatment in Japan is consistent of aspirin and ticlopidine, accepting the risk of relatively frequent adverse effects of ticlopidine including hepatic, gastrointestinal or dermatologic complications, bone marrow suppression, and thrombotic thrombocytopenic purpura. [11, 12]

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Clopidogrel is an acetate derivative of ticlopidine, expressing anti-platelet function inhibiting adenosine diphosphate (ADP)-related platelet aggregation. Compared to ticlopidine, clopidogrel has demonstrated a more potent antiaggregant effect, more rapid onset of action, lower rate of serious side effects, and better tolerability. [13, 14] Several RPCTs demonstrated that comparable or better efficacy of clopidogrel after stent placement compared to ticlopidine [14, 15, 16, 17]. Because of the better tolerability and equivalent efficacy of clopidogrel over ticlopidine, in the countries where clopidogrel is available, clopidogrel is the most concomitantly used drug of choice followed by aspirin for patients undergoing PCI. Although clopidogrel is currently not in market in Japan, once it become available, it may quickly replace ticlopidine. Every cardiac surgeon in the US is aware of clopidogrel-induced platelet dysfunction observed after CABG; however, little knowledge of this drug has been shared among Japanese cardiac surgeons at the present time.

CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) study, a large double-blind RPCT, has shown that clopidogrel reduces the incidence of ischemic stoke, MI, or vascular death without increasing the major adverse effect compared to aspirin alone.[18] Unfortunately, patients status post-CABG were excluded from these data analyses. Another large double-blind RPCT, CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, demonstrated clopidogrel pretreatment followed by long-term treatment is beneficial in reducing cardiovascular events in patients presenting with acute coronary syndromes.[19] CURE trial identified patients who discontinued clopidogrel within 5 days of coronary artery bypass grafting (CABG) showed significantly increased risk of minor bleeding complications (5.1% vs 2.4%; p<0.001) and a trend towards an increased risk of major bleeding compli-

cations, which was defined transfusion requirement more than 2 units of packed red blood cells, (9.6% vs 6.3%; p=0.06).[20] Although CURE study was not primarily focused on surgical patients, it triggered the attention of cardiac surgeons who operate on patients receiving clopidogrel. Since then, specific studies observing the effects of clopidogrel in patients undergoing CABG have been published. Review of these studies were conducted to evaluate the risk of preoperative administration of clopidogrel in patients undergoing CABG.

Methods

Literature search over Medline was performed using key word interface (coronary artery bypass OR CABG OR cardiac surgery) AND (clopidogrel OR Plavix), looking for human clinical research focusing on postoperative bleeding, transfusion (packed red blood cell [PRBC], fresh frozen plasma [FFP], and platelet) and reoperation, excluding case reports. A total of 9 papers were identified (7 prospective and 2 retrospective studies) and a total of 4469 patients (503 patients in the clopidogrel group and 3966 patients in the control group) were pooled for analysis. [21, 22, 23, 24, 25, 26, 27, 28, 29]

Chi-square tests, Mantel-Haenszel methods or general variance-based methods were utilized to calculate relative risk (RR) with a 95% confidence limit (CL), as appropriate. Missing data in the literature were excluded from the analyses.

Results

Preoperative data are shown in Table 1. The clopidogrel group were a more symptomatic, had more frequent history of coronary intervention and more frequently underwent emergent CABG. Otherwise the pooled data did not significantly differ between the two groups.

Table 1.

Preoperative data of the pooled data. Data are expressed as weighted mean or percent of incidence

Total number of cases	Clopidogrel 503	Control 3966	p
Male	72%	77%	NS
Age	65.7	62.3	NS
Body surface area (m2)	1.9	1.9	NS
Body mass index	27.6	27.1	NS
Hypertension	58%	61%	NS
Diabetes	21%	24%	NS
Previous stroke	11%	10%	NS
Renal dysfunction	6%	4%	NS
Intervention	39%	14%	<0.0001
Canadian cardiac score 3 or 4	75%	30%	<0.0001
Emergent or urgent surgery	31%	11%	<0.0001

Chest tube drainage in the first 24 hours of surgery was 703 ml (95% CL 630-755 ml) more in the clopidogrel group than in the control group (Figure 1). The transfusion rate was greater in the clopidogrel group: PRBC (78% vs 46%, RR 3.96, 95% CL 2.98-5.27) , FFP (41% vs 15%, RR 4.19, 95% CL 3.06-5.76), and platelet (59% vs 12%, RR 11.63, 95% CL 8.35-16.19), as shown in Figure 2. The amount of transfusion per patient was greater in the clopidogrel group than in the control group: 4.2 ± 2.2 units (weighted mean ± pooled standard deviation) vs 1.1 ± 1.1 units of PRBC, 2.3 ± 1.7 vs 1.5 ± 1.5 of FFP, and 4.8 ± 4.3 vs 1.0 ± 2.6 of platelets (Figure 3). Relative risks of transfusion volume of each blood product were 2.41 (95% CL 2.26-2.56, z=31.8) in PRBC, 0.89 (95% CL 0.74-1.04, z=78.9) in FFP, and 2.62 (98% CL 2.45-2.77, z=31.9) in platelets None of the studies demonstrated that either heparin alone or aspirin alone increases the risk of postoperative bleeding, transfusion requirement, or reoperation. [21, 22, 23, 25, 29] The postoperative bleeding, transfusion, and reoperation rates were compared between patients on clopidogrel alone and clopidogrel with aspirin, and the findings were consistent with no significant increase of blood loss, transfusion or reoperation, [22, 23, 29] except in one study showing an isolated increase in PRBC transfusion without increase of blood loss or reoperation rate. [25]

Postoperative reexploration for bleeding or tamponade was also higher in the clopidogrel group than in the control group (8.2% vs 1.4%, RR 7.61, 95% CL 4.73-12.34), as shown in Figure 4. Mode of reexploration was noted in 3

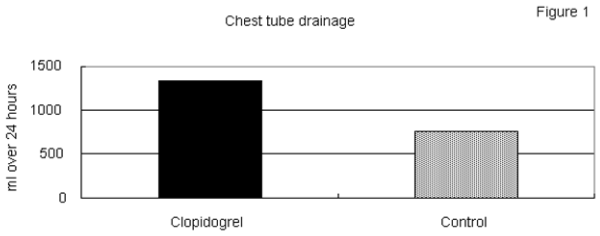

Figure 1.
Chest tube drainage in the first 24 hours after surgery

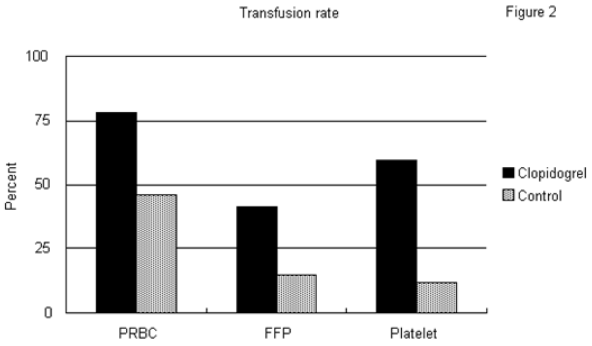

Figure 2
Transfusion rate of blood products. PRBC: packed red blood cell, FFP: fresh frozen plasma

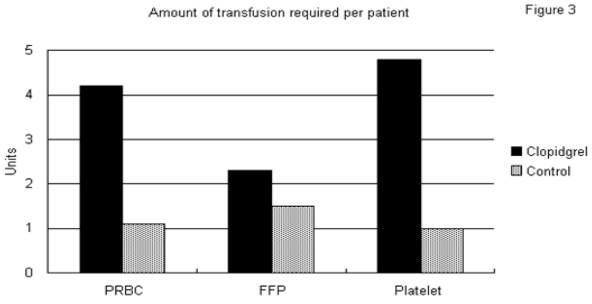

Figure 3
Amount of transfusion required per patient. PRBC: packed red blood cell, FFP: fresh frozen plasma

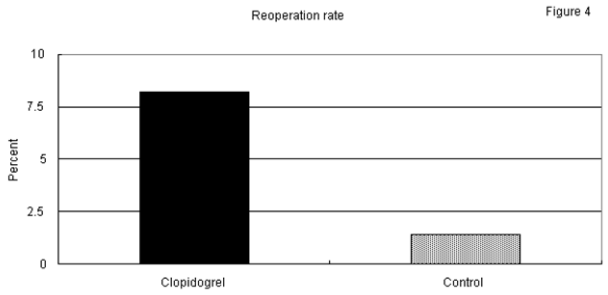

Figure 4
Reoperation rate.

studies and 94% (18/19) of reexploration in the clopidogrel group failed to identify any surgical bleeding sites. [21, 23, 24] Longer intubation time, intensive care unit stay, and/or postoperative hospital stay associated with clopidogrel have reported. [22, 23, 29]

A study showed the blood loss, blood transfusion requirement and reoperation rate returned to the baseline 5 days after discontinuation of clopidogrel. [23]

Discussions

Because clopidogrel has been primarily used for patients undergoing PCI, the pooled clopidogrel group consisted of more patients with a history of PCI and with coronary symptoms. Symptomatic patients may have received a loading dose of clopidogrel prior to catheterization, anticipating PCI which can relief angina. However, PCI is not always successful and sometimes patients may need to undergo emergent or urgent CABG. Patients who recently developed angina despite a previous history of PCI have most likely been prescribed a chronic dose of clopidogrel. If these patients develop a restenosis or denovo coronary lesions amenable to PCI, they are also referred for emergent or urgent surgery. Thus, it is reasonable that emergent or urgent CABG was more common in the clopidogrel group than the other. The majority of studies in our review were prospective consecutive cohort, [21, 22, 23, 24, 25, 26, 28] and none was a randomized prospective study or a matched patients trial. Thus, the clopidogrel group is likely reflect the real population of the patents undergoing CABG on clopidogrel.

As expected, the clopidogrel group had significantly greater volume of postoperative blood loss and higher transfusion requirement, especially PRBC and platelet, than control. Since the clopidogrel dose not effect the coagulation pathway, coagulation profiles (PT, PTT, INR) stay within normal and transfusion of FFP has a minimal effect on stopping bleeding for this particular type of patients, even though a larger amount of FFP was transfused in the clopidogrel group than control. Transfusion of platelets is the only treatment for clopidogrel-related coagulopathy. PRBC should be given as well to replace the blood loss. To correct the clopidogrel-related platelet dysfunction, a previous study showed that a total of 17 units of platelet is required. [27] Cardiopulmonary bypass may cause further deterioration of platelet function. Englberger analyzed patients who underwent off-pump and on-pump CABG with or without clopidogrel, and found that the postoperative blood loss was not related to either off- or on-pump CABG but related to preoperative use of clopidogrel. [24] ADP aggregometry (response <40%) well correlates with platelet dysfunction induced by clopidogrel; [27] however, this laboratory test takes at least 30 minutes to complete and may not always be available. Aprotinin, an antifibrinolytic agent, has been used in cardiac surgery to reduce bleeding and transfusion requirement.[30] Aprotinin is also known to preserve platelet function during cardiopulmonary bypass.[31] Aprotinin has been shown to attenuate the clopidogrel-induced prolongation of bleeding time in animals;[32] however, the benefits of aprotinin in patients who underwent CABG and who were on clopidogrel were not confirmed. [21]

Significant morbidity and mortality can result from postoperative bleeding and subsequent sternal reexploration.[33] Patients undergoing exploration for bleeding also consume considerable resources, including blood products, prolonged intensive care, and overall hospital stay. [33] Patients for suspicious for postoperative bleeding should be carefully monitored for the possible development of tamponade. They may be intubated longer than usual since these patients may eventually go back to the operating room for reexploration. During reexploration of the patients on clopidogrel, usually general oozing is the only finding and there are no specific bleeding sites that can be identified. If a patient requires emergent or urgent CABG with recent clopidogrel administration, the patients should be notified that he or she has an increased risk of bleeding complications.

The action of clopidogrel is irreversible and therefore persists for the entire lifespan of the platelet. Theoretically, it would be optimal to refrain from using clopidogrel within one week before surgery. The drug manufacture recommends that clopidogrel should be discontinued for 7 days prior to elective coronary surgery. However, for unstable patients requiring urgent or emergent CABG, surgeons must balance the risk of ischemic event against the risk of postoperative bleeding complications. Chu found that clopidogrel use within 4 days before CABG is associated with a number of adverse effects including blood loss, transfusion, and reoperation. They found, however, that these adverse effects of clopidogrel decrease to baseline when surgery is delayed for more than 5 days after discontinuation of the drug. Institutional policies for patients receiving clopidogrel and scheduled to undergo open heart surgery should be established. For example, The Cleveland Clinic Foundation has own policy “no clopidogrel at least 5 days prior to CABG if patient is not unstable”. [19] Recently, same rule was applied for Department of Cardiothoracic Surgery, Drexel University College of Medicine. These policies are based on previous publications; however, there has not been any specific data available for Japanese population, whose coagulation and platelet function may slightly differ from those of in Western countries.

Postoperative use of clopidogrel also should be carefully addressed. A loading doses, commonly 300 mg, result in significant platelet inhibition and prolongation of the bleeding time within a few hours. This antiplatelet effects occurs much faster and more effective than ticlopidine. [34] However, if the daily 75 mg dose regimen is used as the sole antiplatelet agent, the platelet inhibition is not achieved within the first five days of treatment.[35] In another word, postoperative use of clopidogrel in patients who was not on preoperatively is safe and it will not effects postoperative adverse outcomes. [35]

In summary, preoperative use of clopidogrel increases postoperative blood loss as well as the risk of reexploration. To avoid these adverse effects, surgeons may have to delay

surgery for a certain period, at least 5 days. If these patients undergo emergent surgery, the risk of the postoperative bleeding should be explained to the patient and blood products for transfusion should be prepared. Institutional regulations should be cautiously established. The day clopidogrel becomes available in Japan is coming soon, and Japanese surgeons should know what this means.

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UNUSUAL LEFT VENTRICULAR TRUE ANEURYSM

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A 67-year-old male with previous myocardial infarction 13 years earlier, hypertension, smoking history, and type II diabetes presented to the emergency room complaining of shortness of breath. The initial work-up ruled out acute myocardial infarction. Echocardiography showed reduced inferior wall motion. Coronary arteriography demonstrated severe stenosis of the proximal left anterior descending artery, severe stenosis of proximal diagonal artery, total occlusion of the first obtuse marginal branch of the circumflex artery, severe stenosis of distal right coronary artery. Left ventriculography demonstrated left ventricular aneurysm (Figure 1).

The patient underwent coronary artery bypass with repair of left ventricular aneurysm. The aneurysm was located between the posterior descending branch of the right coronary artery and the posterolateral brunch of the circumflex artery. The aneurysm was opened and we found an organized thrombus in side (Figure 2). The aneurysm was closed with Teflon strips. Postoperative recovery was uneventful.

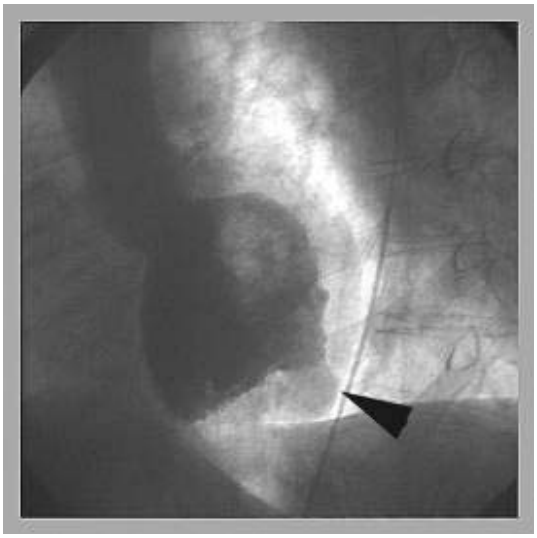
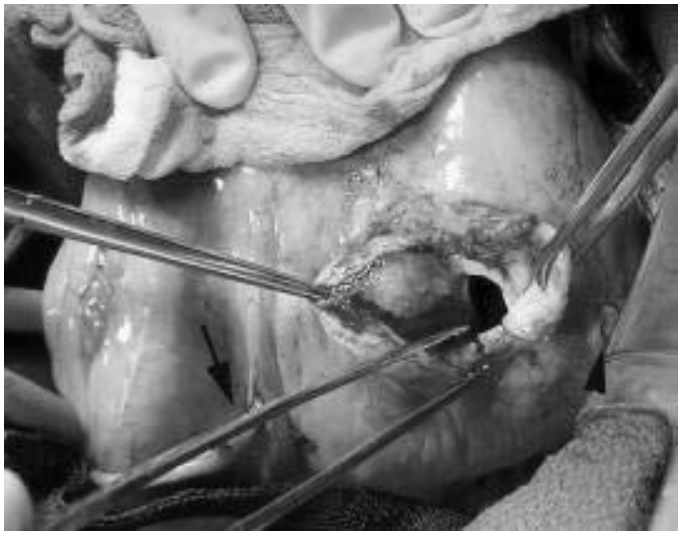


Figure 1.
Preoperative left ventriculography demonstrated left ventricular aneurysm (arrow)

Figure 2.
Intraoperative picture of the left ventricular aneurysm. The large arrow indicates the posterior descending artery, and the short arrow indicates posterolateral branch of the circumflex artery



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