

## The clinical application of clopidogrel in current coronary artery surgery

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### Abstract

The article presents an overview of the current clinical application of clopidogrel in coronary artery surgery. The viewpoint is that clopidogrel can reduce preoperative and postoperative ischemic events of coronary artery bypass grafting(CABG). With the development of standardized medication and the corresponding preventive technique, it will be of great value to reduce hemorrhage complications and obtain the maximum benefit from clopidogrel's anti-platelet properties.

*Key words:* clopidogrel; coronary artery bypass grafting; hemorrhage

### INTRODUCTION

Clopidogrel is one of the thienopyridine agents that functions as an adenosine diphosphate(ADP) receptor antagonist. It markedly reduces ADP induced activation of the glycoprotein II b/ III a complex, thereby inhibiting platelet activation. It is one of the most widely prescribed anti-platelet agents used for the treatment of coronary artery disease(CAD), stroke and particularly symptomatic peripheral arterial disease. With changing treatment for coronary disease, the application of perioperative drug therapy is an area requiring continuing consideration. The purpose of the present review is to describe the application of clopidogrel to coronary artery surgery.

#### Preoperative Application

With a greater understanding of the treatment of CAD, the application of anti-platelet-aggregation drugs has gained more and more attention by clinicians. Anti-platelet-aggregation therapy has also been included in the treatment guidelines for patients with acute coronary syndrome(ACS). With the expansion of indications for clopidogrel, this drug has been used in an increasing number of patients whose coronary arterial angiographies suggest a requirement for surgical treatment,

especially those in high risk categories, such as unstable angina and main trunk disease<sup>[1-5]</sup>. Clopidogrel has a potent anti-platelet action and many clinical trials have demonstrated that it can significantly reduce major adverse cardiovascular and cerebrovascular accidents pre and post coronary artery bypass grafting(CABG)<sup>[6-11]</sup>.

#### Scheduled Operation

In those patients requiring coronary artery surgery, the majority have received drug treatment for a period of time, including the anti-platelet agent clopidogrel. The interval for discontinuing clopidogrel prior to operation is generally for 2-7 days depending on the cardiac treatment center<sup>[4,7,8, 12-25]</sup>. Some patients at high risk receive low molecular weight heparin for anticoagulation during the period when clopidogrel is withdrawn<sup>[26]</sup>. The purpose of drug withdrawal is to recover platelet function and thereby reduce inter- and post-operation bleeding.

The interval for discontinuing clopidogrel before coronary artery surgery is the main factor in determining inter-operative bleeding complications. In the guidelines of American College of Cardiology(ACC) and American Heart Association(AHA), it is suggested that clopidogrel should be withheld for 5 days before performance of CABG surgery, if clinical circumstances permit<sup>[11, 27, 28]</sup>.

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### Urgent or Emergency Operations

Administration of clopidogrel in combination with aspirin is the standard care for patients at high risk. However, as many as 5% of patients indicated for CABG may require urgent or emergency surgery<sup>[29]</sup>. It is impossible for these patients to delay an operation until the platelet function recovers because of their continued cardiac ischemia<sup>[16, 21, 22]</sup>. Cardiac surgeons are then facing a dilemma: whether the patient should have surgery delayed for several days, risking acute ischemic events, or operate earlier, risking increased bleeding. So weighing the risk of hemorrhage complications in these patients is very important<sup>[7, 16, 22, 30-33]</sup>.

### Intraoperative Countermeasures

Intraoperative and postoperative bleeding, associated transfusion requirements and surgical re-exploration to control bleeding are side effects of clopidogrel use in patients requiring coronary artery surgery, and pose serious problems for the cardiac surgeon.

Patients scheduled for CABG discontinue clopidogrel for a period of time, so that platelet functions recovers sufficiently. They do not bleed more when compared with patients without clopidogrel<sup>[10, 34]</sup>. However, these kinds of patients who need urgent or emergency revascularization surgery are at increased risk of bleeding complications because they are administered anti-platelet agents, such as aspirin combined with clopidogrel. Withholding anti-platelet therapy for a shorter time before coronary surgeries may prevent ischemic events including death<sup>[6, 16]</sup>, but it obviously increases the risk of bleeding complications. It has been demonstrated that Aprotinin can significantly reduce clopidogrel-induced bleeding and transfusion requirements in patients undergoing urgent or emergency CABG<sup>[4, 6, 20, 21, 29]</sup>. Enoch and his colleagues reported 49 ACS patients undergoing urgent CABG surgery. Twenty five patients (treatment group) remained on aspirin and clopidogrel until surgery, and also received intraoperative aprotinin. Others (placebo group) received placebo for 5 days before surgery and received placebo infusions intraoperatively. The postoperative blood loss was significantly greater in the placebo group ( $702 \pm 120$  ml versus  $446 \pm 62$  ml,  $P = 0.004$ ), and the cardiac events before surgery were also greater in the placebo group<sup>[6]</sup>. A clinical trial described 75 patients administered clopidogrel for 5 days before CABG surgery. Thirty-seven patients received full dose aprotinin during surgery, while the remaining patients received saline. Bleeding ( $760 \pm 350$  ml versus  $1200 \pm 570$  ml,  $P < 0.001$ ) and transfusions (erythrocytes  $1.2 \pm 1.5$ U versus  $2.8 \pm 3.2$ U,  $P = 0.02$ , platelet  $0.1 \pm 0.4$ U versus  $0.9 \pm 1.4$ U,  $P = 0.002$ ) were all significantly less in the aprotinin group compared with the saline

group<sup>[16]</sup>. Lindvall and colleagues reported on 33 patients with preoperative clopidogrel exposure less than 5 days before surgery who underwent urgent CABG. Among them, there were 18 patients who received a full dose aprotinin regime intraoperatively whereas the other 15 patients did not. The two groups were comparable. The aprotinin group exhibited significantly less postoperative bleeding (710 ml versus 1210 ml,  $P = 0.004$ ), and required significantly less blood products (packed red blood cells 0.9U versus 2.7U,  $P = 0.01$ , platelet 0.1U versus 0.6U,  $P = 0.02$ ), and fewer re-operations for bleeding (3 versus 0,  $P = 0.05$ ). Overall the aprotinin group exhibited significantly less postoperative bleeding<sup>[29]</sup>.

Off-pump CABG can eliminate the deleterious effects of cardiopulmonary bypass, as it results in less postoperative bleeding compared to traditional CABG<sup>[31, 36, 37]</sup>. Shim et al reported 106 patients scheduled for off-pump CABG were divided into three groups: aspirin and clopidogrel discontinued more than 6 days before surgery; aspirin and clopidogrel continued until 3 to 5 days before surgery, and both medications continued within 2 days of surgery. During surgery a cell salvage device was used and salvaged blood was reinfused. The amounts of perioperative blood loss and blood transfusion required were similar among all groups. They concluded preoperative clopidogrel and aspirin exposure even within 2 days of surgery did not increase perioperative blood loss and blood transfusion requirements in patients undergoing elective off-pump CABG<sup>[38]</sup>.

Auto-transfusion<sup>[29, 38]</sup> and transfusion of principal blood products, including packed red cell, fresh frozen plasma, platelet and hemostatic agents are useful operative and postoperative measures. It was reported that platelet adenosine diphosphate receptor antagonist with a heparin infusion might have been attributable to a conservation of coagulation factors (plasma fibrinogen), thereby reducing postoperative bleeding<sup>[24]</sup>.

### Perioperative Observation Targets

Values of blood loss, intraoperative and postoperative transfusion of blood products (packed red cell, fresh frozen plasma, and platelet), and the rate of re-exploration for bleeding are usually used to evaluate the effect of clopidogrel. Some platelet ADP receptor inhibition testing modalities, such as thromboelastography, platelet aggregation, and whole blood aggregation are useful, but they are not generally used in clinical practice<sup>[1, 6, 21, 32, 37-39]</sup>. McLean and Cannon have pointed out that a point-of-care device could accurately and rapidly measure the degree of platelet inhibition among patients taking clopidogrel, alerting the physician to such situations as "clopidogrel resistance". The device would have the potential of allowing thera-

peutic decision-making based on the degree of platelet inhibition<sup>[40]</sup>. Additionally, the length of ICU stay, mechanical ventilation, and hospital stay can also indirectly reflect the influence of clopidogrel.

### Postoperative Application

A recent clinical study provided information on postoperative clopidogrel administration. Sixty-three patients undergoing CABG received daily clopidogrel, 75mg, and aspirin, 81mg, when postoperative chest tube drainage was  $<$  or  $=$  50 ml/h for 2 hours. In the same study another 54 patients received aspirin alone. The clopidogrel group did not exhibit an increase in the incidence of re-exploration, transfusion, or the quantity of blood products transfused. Mortality, myocardial events or length of stay in hospital were not different in the two groups. It was concluded that early postoperative clopidogrel could be administered safely<sup>[41]</sup>. Halkos and his colleagues also reported on 364 patients who underwent off pump CABG and received aspirin 4 hours after surgery if their chest tube output was less than 100 ml/h for 4 hours. Of these patients, 193 also received clopidogrel. There were no differences in mean chest tube drainage, total number of blood units transfused or mortality at 6 months between groups. It was concluded that off pump CABG patients could safely receive clopidogrel in the early postoperative period without increased risk for mediastinal hemorrhage<sup>[42]</sup>. Similarly, Shennib, Endo and Benhameid reported on 135 patients who underwent off pump CABG, and were administered clopidogrel, 75 mg/day, and aspirin, 325 mg/day, orally or initially through a nasogastric tube, commencing within 6 hours of surgery. All patients were followed up for 3 months. It was concluded that administration of a combined regimen of clopidogrel and aspirin following off pump CABG was safe and was associated with a relatively low incidence of major adverse cardiac events, bleeding, pulmonary embolism, and deep vein thrombosis. They recommended their routine administration after off pump CABG<sup>[43]</sup>. Curbuz et al reported on 591 patients who underwent CABG and received aspirin in the first 6 hours after surgery. Among them, 325 patients were administered clopidogrel 1 day after surgery. Postoperative clopidogrel independently decreased symptom recurrence ( $P < 0.0001$ , OR 0.3[0.15-0.99]; 95% CI) and adverse cardiac events ( $P < 0.0001$ , OR 0.2[0.10-0.45]; 95% CI)<sup>[44]</sup>. Clopidogrel caused fewer gastrointestinal complications than aspirin in those patients with no previous history of gastric or duodenal ulceration. But, in patients with a previous history of gastrointestinal complications, this study found that clopidogrel alone is not a safer alternative than aspirin alone. When combined with a proton pump inhibitor, these two

agents can be effective and safe<sup>[45]</sup>.

### Evaluation

Many clinical trials demonstrated that clopidogrel had early and long-term benefits for patients. ACS patients are recommended to receive clopidogrel combined with aspirin as early as possible. Clopidogrel did reduce the relative risk of cardiovascular events, such as angina, MI, and stroke, when it was administered prior to surgery. Operation-associated bleeding was related to the interval of discontinuing clopidogrel. Clopidogrel administration after CABG was of benefit for early graft patency by preventing thrombus formation and reducing cardiovascular events<sup>[3, 7, 30, 44, 46-48]</sup>.

Many studies have demonstrated that patient exposure to clopidogrel just before coronary artery surgery was the single most important predictive factor for increasing intraoperative and postoperative bleeding and transfusion requirements, especially for urgent or emergency surgery without any prior protection<sup>[1, 6, 8, 12, 14-18, 22-24, 30, 31, 33, 37, 49, 50-52]</sup>. It is very important to balance the benefit of clopidogrel therapy and the risk of bleeding. The CURE (clopidogrel in unstable angina to prevent recurrent events), is a randomized, double blind, placebo controlled study, that has demonstrated the safety of withdrawing clopidogrel 5 day prior to CABG<sup>[7, 8, 10]</sup>. No study has specifically demonstrated the influence of clopidogrel on operative mortality<sup>[1, 2, 17, 30, 31, 36]</sup>, but it is of interest that the risk of cardiovascular death, MI, and stroke was more likely to be reduced in patients who were prescribed this drug<sup>[6-8, 16, 34, 53]</sup>.

Clopidogrel is now extensively used. With standardized usage this agent can be applied to many new cardiovascular surgical techniques. However, the problem of bleeding remains a challenge<sup>[4, 8, 19, 32, 35]</sup>. Pre- and postoperative administration of clopidogrel is definitely beneficial and its use has become routine in some cardiac treatment centers<sup>[8, 35, 54]</sup>.

### Application Prospect

Clopidogrel can decrease postoperative platelet thrombus formation. Some animal models showed it could reduce C-reactive protein (CRP), platelet-mediated intimal proliferation and smooth muscle hyperplasia, which may improve the grafts' patency rates<sup>[55-57]</sup>. Therefore, a Canadian multicenter study was recently conducted to evaluate the efficacy of clopidogrel and aspirin therapy in the prevention of saphenous vein graft intimal hyperplasia following coronary artery bypass surgery<sup>[48]</sup>.

Clopidogrel is a potent anti-platelet agent that as many clinical trials have demonstrated can reduce the pre- and postoperative ischemic events of CABG. Although the hemorrhage that occurs during surgery is inevitable,

standardized medication and the corresponding preventive technique can be of great value in reducing hemorrhagic complication, so as to allow the maximum benefit from the anti platelet properties of this drug.

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