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Off-Pump Coronary Artery Bypass Grafting Attenuates Postoperative Bleeding Associated with Preoperative Clopidogrel Administration

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ABSTRACT

Background: Clopidogrel is being increasingly administered as primary therapy for acute coronary syndromes and prior to planned percutaneous coronary intervention (PCI). In these settings, surgical revascularization results in significantly increased postoperative bleeding, transfusion, and reexploration. Off-pump coronary artery bypass grafting (OPCAB) may decrease the extent of postoperative bleeding in patients exposed to clopidogrel.

Methods: The cases of 78 consecutive patients undergoing OPCAB by a single surgeon were retrospectively analyzed, and the patients were divided into 2 groups, those with immediately preoperative clopidogrel exposure (clopidogrel OPCAB, n = 15) and those without (control OPCAB, n = 63). Multiple perioperative parameters were statistically compared. The clopidogrel OPCAB group also was compared with a group of previously described on-pump coronary bypass patients who made up a historical control group (n = 59).

Results: Postoperative bleeding, transfusion requirements, reexploration rates, duration of mechanical ventilation, and length of stay were markedly less for clopidogrel OPCAB patients than for historical controls and were statistically equivalent to those of control OPCAB patients.

Conclusion: Among these 15 OPCAB patients with immediately preoperative administration of clopidogrel and aspirin, outcome was improved compared with published results for on-pump coronary bypass patients and was equivalent to results among OPCAB patients not exposed to clopidogrel. Published, recommended approaches to clopidogrel administration, such as avoidance of pre-PCI clopidogrel, delay of surgery, and platelet transfusion do not appear to be necessary with OPCAB.

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INTRODUCTION

The potent antiplatelet agent clopidogrel, together with aspirin, has been shown to improve outcome in acute coronary syndromes and periprocedurally during percutaneous coronary intervention [CURE 2001, Steinhubl 2002]. A proportion of patients presenting with acute coronary syndromes will need surgical revascularization. In addition, a proportion of patients with presumed PCI-amenable disease will be found to have coronary anatomy more amenable to surgery. Patients exposed to clopidogrel who subsequently undergo coronary artery bypass grafting (CABG) experience markedly increased postoperative bleeding and transfusion requirements as well as a nearly 10-fold increase in reexploration rate [Yende 2001, Hongo 2002]. These complications are apparent even up to a week after clopidogrel is discontinued, prompting suggestions to reexamine the practice of preangiography clopidogrel administration, delay surgery, and transfuse platelets [Hongo 2002]. OPCAB is associated with decreased rates of postoperative bleeding and transfusion requirements, presumably in part because of avoidance of bypass pump–induced blood component dilution and dysfunction [Puskas 2001]. This study was performed to evaluate the potential role of OPCAB in eliminating the need to delay surgery and in decreasing postoperative bleeding in patients recently exposed to clopidogrel.

MATERIALS AND METHODS

All patients undergoing OPCAB by a single surgeon during a 1-year period were evaluated. Those receiving clopidogrel 1 to 4 days prior to surgery made up the clopidogrel group. These patients received either 300 mg orally prior to coronary angiography or had been on a daily oral regimen of 75 mg. The remaining patients made up the control group. All patients in both groups received aspirin prior to surgery. Patients exhibited similar preoperative characteristics and underwent statistically equal numbers of grafts (clopidogrel, 2.8 ± 0.3; control, 2.8 ± 0.1) Patients were compared with respect to multiple perioperative parameters. The clopidogrel and control groups were compared by statistical analyses with the unpaired Student *t* test.

The clopidogrel group was then further compared with respect to the same parameters against published results for a

Results*

Parameter	Historical Control	Clopidogrel OPCAB	Control OPCAB	*P* Value for Clopidogrel OPCAB versus Control OPCAB
n	59	15	63	—
8-h chest tube output, mL	775 ± 727	387 ± 65	423 ± 27	NS
24-h chest tube output, mL	1224 ± 1119	868 ± 100	797 ± 39	NS
Packed red blood cells, units	2.5 ± 2.4	1.7 ± 0.5	1.6 ± 0.3	NS
Platelets, units	0.9 ± 1.2	0	0	NS
Fresh frozen plasma, units	0.7 ± 1.7	0	0	NS
Cryoprecipitate, units	0.2 ± 1.3	0	0	NS
Reexploration	6.8%	0	0	NS
Extubation ≤8 h	54%	73%	71%	NS
Myocardial infarction	0%	0%	1.6%	NS
Mortality	1.7%	0%	0%	NS
Length of stay ≤5 d	34%	87%	84%	NS

*OPCAB indicates off-pump coronary artery bypass grafting; NS, not significant.

group of 59 patients undergoing on-pump CABG who received clopidogrel within a week prior to surgery [Hongo 2002]. Fifty-one of these 59 patients also received preoperative aspirin. This group of patients served as a historical control group.

RESULTS

Clopidogrel OPCAB patients in comparison with historical controls demonstrated a marked reduction in postoperative bleeding, transfusion requirements, reexploration rate, duration of mechanical ventilation, and length of stay (Table). All parameters were statistically equivalent between clopidogrel OPCAB and control OPCAB groups, suggesting that clopidogrel exposure was not a pertinent factor in outcome when off-pump revascularization techniques were used. No OPCAB patients received platelets, fresh-frozen plasma, or cryoprecipitate. There were no reexplorations and no deaths among OPCAB patients.

DISCUSSION

In this brief, preliminary study investigators found decreased rates of postoperative bleeding, transfusions, and reexploration in OPCAB patients preoperatively exposed to clopidogrel in comparison with historical control patients undergoing on-pump CABG. Furthermore, these OPCAB patients had statistically similar outcomes compared with OPCAB patients not exposed to clopidogrel. To the best of our knowledge, this is the first report of the utility of OPCAB in patients preoperatively exposed to clopidogrel.

Clopidogrel is a potent antiplatelet agent that inhibits the platelet fibrinogen receptor glycoprotein IIb/IIIa. A 75-mg daily dose results in a 40% reduction in adenosine diphosphate–induced platelet aggregation [Izaguirre-Avila 2002]. The onset of action is very fast. A 300-mg oral loading dose results in up to 30% reduction in platelet activity within 5 hours [Savcic 1999]. This inhibition of platelet activity manifests as elevated bleeding times. The addition of 150 mg clopidogrel to aspirin increases mean bleeding time from 8 minutes to 18 minutes, and 300 mg results in a bleeding time of 25 minutes [Payne 2002]. Clinically the use of clopidogrel is associated with a slight increase in major and minor bleeding events.

The clinical application of clopidogrel is expanding. There are 3 major categories of cardiovascular patients.

1. Primary therapy for coronary artery disease (CAD). In the CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events), patients presenting with acute coronary syndromes without ST-segment elevation were randomized to clopidogrel therapy versus placebo. Clopidogrel patients experienced lower rates of cardiovascular death, myocardial infarction, stroke, and refractory ischemia [CURE 2001]. These results have been further analyzed and found to be applicable across all risk groups, low, intermediate, and high [Budaj 2002].
2. Periprocedural PCI. In a large randomized study of pre-PCI clopidogrel and aspirin (Clopidogrel for the Reduction of Events During Observation [CREDO]), patients receiving clopidogrel 6 or more hours prior to PCI experienced a 35% reduction in the combined events of death, myocardial infarction, or urgent target-vessel revascularization [Steinhubl 2002]. These findings correlate with the known onset of action of clopidogrel and are among multiple studies of the benefits of periprocedural clopidogrel [Nikhil 2002].
3. Peripheral vascular disease. More frequently, patients with peripheral vascular disease are being managed with long-term clopidogrel therapy [Hiatt 2002]. This group includes patients with cerebrovascular, visceral, and lower extremity disease as well as patients undergoing percutaneous and surgical revascularization procedures of these territories [Criado 2002].

With the expanding applications of clopidogrel therapy there is an understanding that there is a growing population of patients in whom surgery in general and cardiac surgery in particular are associated with significant increases in postoperative bleeding and in transfusion requirements. Specific

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perioperative anesthetic recommendations have been devised for management of patients exposed to clopidogrel prior to cardiac surgery [Levy 2001].

Avoidance of cardiopulmonary bypass may be the most effective management strategy. Overall, off-pump coronary revascularization techniques have been associated with decreased postoperative bleeding and transfusion requirements [Nader 1999, Puskas 2001]. These findings are likely due in part to the absence of bypass pump–induced dilutional coagulopathy, plasminogen activation, and platelet aggregation, consumption, and dysfunction [Casati 2001].

OPCAB applied specifically to each of the above 3 categories of patients would have significant potential utility. With the recent advocacy of clopidogrel efficacy in reducing morbidity and mortality from CAD, albeit therapy with this drug is less cost-effective on a population level, there exists an ever-increasing pool of patients who present for evaluation of CAD who are already taking clopidogrel [CURE 2001, Gaspoz 2002]. These patients, if found to have surgical CAD, would likewise either need a delay in surgery or accept increased risk of postoperative bleeding. The median delay until surgery among CURE trial patients was 5 days. OPCAB could be utilized to address treatment of this group of patients.

The utility of an OPCAB approach would potentially be most applicable to care of patients undergoing planned PCI. Patients who present with presumed CAD potentially amenable to PCI face 3 possible scenarios:

1. Diagnostic coronary angiography, identification of PCI-appropriate anatomy, administration of clopidogrel, and subsequent repeated angiography with PCI;
2. Diagnostic coronary angiography, identification of PCI-appropriate anatomy, immediate PCI, and postprocedural administration of clopidogrel;
3. Administration of clopidogrel, diagnostic coronary angiography, identification of PCI-appropriate anatomy, and immediate PCI.

None of these options is optimal, for each has a clear disadvantage. Scenario 1 requires a repeated procedure. Scenario 2 has a slightly increased risk of stent thrombosis compared with pre-PCI platelet inhibition. In scenario 3, if CABG-appropriate anatomy is instead identified, then patients who need surgical revascularization within the next few days are at significantly increased risk of postoperative bleeding, transfusion, and reexploration. OPCAB may provide an effective means of surgical revascularization in the setting of recent clopidogrel exposure and thereby comfortably permit scenario 3. Although specific percentages are difficult to estimate, it is known that approximately 20% of patients undergoing coronary angiography are found to have surgical anatomy. Thus among patients undergoing coronary angiography who are already thought likely to have at least PCI-amenable disease, the proportion of patients found to have surgical disease is likely even higher than 20%.

Finally, vascular disease in extracoronary territories often is diagnosed with significant coexistent coronary disease, thus the patients may need surgical revascularization, forming another group of patients in whom OPCAB may have specific utility.

In this study, the proportion of patients exposed to clopidogrel preoperatively was nearly 20% (15 of 78 patients). This proportion extrapolated to a general population of patients with surgical CAD implies that preoperative clopidogrel exposure is a major issue. Results very similar to those among patients serving as the historical controls have been published with a 9.8% reexploration rate among CABG patients preoperatively exposed to clopidogrel and aspirin as well as a mean packed red blood cell transfusion rate of 2.3 units per patient [Yende 2001].

Patients in the clopidogrel OPCAB group all received clopidogrel within 4 days of surgery, and most underwent OPCAB within 1 or 2 days after exposure to clopidogrel. This narrower window adds even greater emphasis to the marked decrement in postoperative bleeding among OPCAB patients compared with the historical controls. The latter patients were operated on within a 7-day window. CURE data clearly demonstrated that patients undergoing CABG 6 or more days after discontinuing clopidogrel did not experience increased bleeding.

There were several limitations to our study. The total number of clopidogrel OPCAB patients was small, but the number is steadily increasing. There was no retrospective on-pump control clopidogrel group from our institution, because the general practice was to delay surgery for at least 5 days. There was no available concurrent on-pump clopidogrel group, because patients now undergo OPCAB. Although results of a randomized trial might have been more definitive, it might have been unethical to subject patients to on-pump CABG after clopidogrel administration. We knew that the rate of transfusion and reexploration was significantly elevated.

The findings of this study have thus far significantly influenced our clinical practice. All patients with suspected PCI-amenable coronary disease receive preangiography clopidogrel. If found to have surgical disease instead, patients undergo OPCAB without delay. Patients who present during clopidogrel therapy also undergo diagnostic angiography and, if applicable, immediate PCI or OPCAB. Published suggested practices of clopidogrel avoidance, delay of surgery, and platelet administration are not necessary.

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