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Bleeding Outcomes in Patients Given Clopidogrel Within 5 Days of Robotic Coronary Artery Bypass Graft Procedure

Sophia Vainrub, PharmD[1], **Asad E. Patanwala, PharmD**[1], **Richard Cosgrove, PharmD**[2], **Robert Poston, MD**[1], and **Paul E. Nolan Jr, PharmD**[1]

[1]University of Arizona, Tucson, AZ, USA

[2]University of Arizona Medical Center, University Campus Tucson, AZ, USA

Abstract

Background—Current guidelines recommend that clopidogrel should be held for 5 days prior to coronary artery bypass graft (CABG) procedure. However, it is unknown if this recommendation should apply to robotic-assisted (rCABG), which is less invasive because it does not involve sternotomy and thus reduces the risk of bleeding.

Objective—To compare postoperative bleeding for rCABG patients who were taking clopidogrel within 5 days of the procedure with those who were not taking clopidogrel.

Methods—This was a retrospective cohort study conducted between January 1, 2012 and December 31, 2012 of consecutive patients undergoing rCABG. Patients were categorized into 2 groups based on whether or not clopidogrel was administered within 5 days prior to the date of surgery. The primary outcome measure was the occurrence of the Bleeding Academic Research Consortium (BARC) definition for CABG-related bleeding. The secondary outcome measure was a comparison of chest tube output during the first 24-hour postoperative period.

Results—A total of 136 rCABG patients were included in the final analyses. Of these, 39 (29%) received clopidogrel within 5 days of surgery. CABG-related bleeding using the BARC definition occurred in 26% of patients who received clopidogrel and 8% of patients who did not (P = .011). Median chest tube output during the first 24-hour postoperative period was also greater in patients who received clopidogrel (900 vs 735 mL, P = .002).

Conclusions—The use of clopidogrel within 5 days of rCABG is associated with greater postoperative bleeding and chest tube output, as defined by the BARC criteria.

Keywords

clopidogrel; coronary artery bypass; platelet aggregation inhibitors; bleeding

Corresponding Author: Asad E. Patanwala, Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, 1295 N Martin, PO Box 210202, Tucson, AZ 85721, USA. patanwala@pharmacy.arizona.edu.

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Introduction

Coronary artery bypass graft (CABG) procedures have been used widely since the 1970s to improve morbidity and mortality in patients with multivessel heart disease.[1] This procedure is associated with significant complications, including bleeding risks. It is estimated that even if a restrictive transfusion strategy were used, close to half of patients undergoing traditional CABG would require blood transfusions postoperatively.[2] This has led to the introduction of less-invasive techniques, such as robotic CABG (rCABG), which is fully endoscopic, with low rates of morbidity and mortality.[3] Compared with traditional CABG, this technique may be associated with decreased blood transfusions, hospital length of stay, and mortality.[4,5]

Because of their previous cardiovascular history, patients who require a CABG procedure are often chronically taking P2Y12 platelet inhibitors such as clopidogrel. After myocar-dial infarction (MI), clopidogrel has been shown to reduce the risk for subsequent MI, stroke, and death.[6,7] In addition, P2Y12 inhibitors, such as clopidogrel, are routinely recommended after percutaneous coronary intervention (PCI) to prevent stent thrombosis.[8] However, clopidogrel use at the time of CABG may increase the risk for bleeding, transfusions, and need for reoperation. Given this risk, the American Heart Association recommends that clopidogrel should be held for at least 5 days prior to a CABG.[9] However, this guidance may not be necessary for rCABG because it is minimally invasive and is associated with less bleeding. This would enable the continuation of clopidogrel therapy during the pre-operative period. Thus, there is a gap in the literature regarding the need for cessation of clopidogrel prior to rCABG.

The purpose of this study was to evaluate bleeding-related outcomes in patients who had undergone rCABG. Patients who stopped their clopidogrel for at least 5 days prior to robotic CABG were compared with patients who did not stop their clopidogrel in the preoperative period. The primary outcome measure was the occurrence of the Bleeding Academic Research Consortium (BARC) definition for CABG-related bleeding.[10] The secondary outcome measure was a comparison of chest tube output during the first 24-hour postoperative period.

Methods

Study Design and Patient Selection

This was a retrospective cohort study conducted in a tertiary care academic institution in the United States. Institutional review board approval was obtained prior to data collection. All patients 18 years and older who underwent rCABG at the study site between January 1, 2012, and December 31, 2012, were included. Patients were categorized into 2 groups: those who (1) received clopidogrel within the 5 days preceding surgery (clopidogrel group) and (2) did not receive clopidogrel or any other P2Y12 inhibitor within 5 days preceding surgery (control group). The use of clopidogrel was assessed in the preanesthesia clinic or on hospital admission by an anesthesiologist or nurse.

Data Collection

Data were collected from the patients' electronic medical records and from a database of rCABG procedures performed at the institution, on standardized data collection forms. Prior to data collection, all fields and locations were identified in the medical record and the rCABG database to ensure consistency of data collection. Data collected included information on patient demographic parameters, comorbidities, anticoagulants and antiplatelets used in the perioperative period, transfusions (platelets, packed red blood cells, cryoprecipitate, and fresh frozen plasma), and postoperative chest tube output. In addition, postoperative and daily hemoglobin values were recorded. If several hemoglobin values were reported on any given day, the final value in that 24-hour period was recorded. Conversion from a thoracotomy to a partial sternotomy modality was recorded because this would increase postoperative bleeding. Also, the need for reoperation after closure of sternotomy for bleeding control was recorded.

Outcome Measures

The primary outcome measure was the occurrence of the BARC definition for CABG-related bleeding.[10] This definition was created based on consensus from academic research organizations from the United States and Europe, representatives from the FDA, and representatives from device manufacturers to standardize clinical outcomes. Based on this definition, CABG-related bleeding is said to occur if any of the following are present: (1) perioperative intracranial bleeding within 48 hours, (2) reoperation after closure of sternotomy for the purpose of controlling bleeding, (3) transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period, or (4) chest tube output of 2 L within a 24-hour period. The secondary outcome measure in this study was chest tube output with the first 24-hour period after surgery. Outcomes in terms of TIMI (thrombolysis in myocardial infarction) major and minor bleeding[10] were also reported to enable comparison with other studies. TIMI major bleeding includes any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI), clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL, and fatal bleeding directly resulting in death within 7 days. TIMI minor bleeding is defined as clinically overt bleeding (including in imaging), resulting in a hemoglobin drop of 3 to <5 g/dL.

Data Analysis

Fisher's exact test was used to compare the incidence of CABG bleeding and other categorical variables between the 2 groups. Student's *t* test was used to compare normally distributed continuous variables between groups, and data were reported as means with standard deviations (SDs). Continuous variables that were not normally distributed were compared using the Wilcoxon rank-sum test, and data were reported as medians with interquartile ranges (IQRs). A logistic regression analysis was performed to adjust for baseline differences between groups. All statistical analyses were conducted in STATA 11 (StataCorp, College Station, TX). A 2-tailed $\alpha<.05$ was considered to be statistically significant for all analyses.

Results

Study Patients

A total of 136 patients underwent rCABG during the study time period. No patients were excluded. The mean age of the cohort was 68 ± 11 years, and 89 (65.4%) were male. The majority of rCABG cases involved 1-vessel (n = 80, 58.8%) or 2-vessel (n = 51, 37.5%) revascularization on the beating heart via a small left thoracotomy. A few patients (n = 10, 7.5%) required a partial sternotomy approach.

Overall, 39 (28.7%) received and 97 (71.3%) did not receive clopidogrel within 5 days of rCABG. The groups were similar with regard to baseline demographic characteristics, with the exception of current smoking status, which was more common in the clopidogrel group (Table 1). All but one of the patients in the clopidogrel group had undergone preoperative, staged PCI as part of a hybrid procedure. Clopidogrel is expected in these cases because it is strongly indicated early after stent placement. The groups were similar with regard to number of vessels operated on or type of rCABG used (Table 2). Also, preoperative (within 24 hours of surgery) use of other antiplatelets and anticoagulants was similar between groups, with the exception of aspirin, which was more commonly used in the clopidogrel group and likely related to previous PCI in this group (Table 2).

Outcomes

The primary outcome of CABG-related bleeding per the BARC definition occurred in more patients in the clopidogrel group than in the no-clopidogrel group (25.6% vs 8.3%, respectively; $P = .011$), as also seen by the odds ratio (OR) after adjusting for smoking status and aspirin use (OR = 3.4; 95 % CI = 1.2 to 10.1; $P = .027$). The clopidogrel group had significantly greater bleeding during the first 24-hour postoperative period as measured by median chest tube output (900 mL [IQR = 700-1340 mL] vs 735 mL [IQR = 490-980 mL]; $P = .002$) and by chest tube output adjusted for smoking status and aspirin use (coefficient = 319 mL; 95% CI = 39 to 599 mL; $R^2 = 0.060$; $P = .026$).

A comparison of bleeding at other time points (intraoperative and up to 96 hours postoperatively) and hemoglobin levels are reported in Table 3. The clopidogrel group had greater intraoperative bleeding and lower hemoglobin levels postoperatively, even though these were similar at baseline (Table 3). There were significantly more patients in the clopidogrel group who required intraoperative transfusions of fresh frozen plasma and platelets, with a trend toward more red blood cell transfusions (Table 3). TIMI minor bleeding occurred in 3 patients in the clopidogrel group and 1 patient in the no-clopidogrel group ($P = .071$). No patient had TIMI major bleeding, such as intracranial or fatal bleeding. One patient in each group had a reoperation for bleeding. The median length of hospital stay was 5 days (IQR = 3-9 days) in the clopidogrel group and 4 days (IQR = 3-6 days) in the no-clopidogrel group ($P = .137$). Patients who had CABG-related bleeding as defined by BARC had a longer hospital length of stay (6.5 days [IQR = 5-13 days] vs 4 days [IQR = 3-7 days]; $P = .005$). All patients survived to hospital discharge.

Discussion

To our knowledge, this is the first study that examines the effect of clopidogrel taken within 5 days of a rCABG procedure on bleeding-related outcomes. The effect was consistent across measured outcomes, indicating greater bleeding with clopidogrel use. This included a well-accepted definition of CABG-related bleeding per BARC,[10] chest tube output, transfusions, and hemoglobin levels.

Most research related to the perioperative use of clopidogrel is from studies conducted in patients with traditional CABG. It is recommended that patients with acute coronary syndromes be given P2Y12 antagonists, such as clopidogrel, because this has been shown to improve outcomes associated with MI, stroke, and death.[6,7] Unfortunately, a subset of these patients may require a subsequent CABG based on their coronary anatomy. These patients taking clopidrogrel have an increased risk for bleeding resulting in reoperation and transfusions after a traditional CABG.[11] This has led to a less-than-expected use of clopidogrel for acu te coronary syndromes.[12] The American Heart Association (AHA) recommends that when patients are referred for elective CABG, clopidrogrel should be held for greater than 5 days.[9] However, this is not possible for urgent CABG, for which the recommendation is to discontinue clopidogrel for at least 24 hours prior to CABG to minimize the risk of bleeding. Our investigation expands the concerns about the bleeding risks of clopidogrel by demonstrating that rCABG does not entirely circumvent this risk, suggesting that it should be discontinued for 5 days prior to the date of surgery. However, the less-invasive technique may reduce the magnitude of bleeding caused by clopidogrel.

In our study, there were more patients in the clopidogrel group who were also taking aspirin within 24 hours prior to surgery. Thus, it is possible that the increased postoperative bleeding in the clopidogrel group was also related to coad-ministered aspirin. However, after adjusting for aspirin use in our multivariate analysis, clopidogrel was independently associated with bleeding. In addition, in a recent large multicenter cohort study of more than 6000 patients, preoperative aspirin use prior to CABG was not associated with postoperative bleeding. However, patients with preoperative clopidogrel use had increased postoperative bleeding and reoperation rates.[13] The AHA recommends that aspirin should be administered to CABG patients preoperatively.[9] This is because studies have shown that aspirin use preoperatively has been associated with decreased in-hospital mortality in these patients.[14,15] In addition, aspirin use in these studies was not associated with increased postoperative bleeding, need for blood product transfusions, chest tube output, or surgical re-exploration. Thus, it is reasonable that this recommendation by the AHA would apply to rCABG as well, and our findings were likely related to clopidogrel.

The study has a few limitations related to its study design. This was a retrospective, single-center study. Thus, the results are hypothesis generating and should be extrapolated with caution to other centers. These results need to be verified in larger prospective trials. It is possible that there were other unmeasured factors that could have influenced our outcomes. However, there was a large difference in effect between the treatment groups, and important variables that could influence bleeding such as demographics, medication use and procedure data were reported. Overall, the groups were well matched with regard to these variables,

and multivariate analysis was conducted to adjust for baseline differences. Information such as dosing of clopidogrel prior to surgery was not available. This could also influence bleeding, especially if patients were given higher-than-standard doses. Postoperative hemoglobin values could have been influenced by transfusions. However, patients in the clopidogrel group had lower hemoglobin values even after receiving more transfusions. Thus, the difference in hemoglobin values between groups is likely conservative.

Conclusion

The use of clopidogrel within 5 days of rCABG is associated with greater postoperative bleeding and chest tube output. These data may prove helpful when considering the timing of rCABG in patients who are actively treated with clopidogrel. Future prospective studies are needed to confirm these findings.

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Table 1

Demographic Characteristics.

Variable	Clopidogrel (n = 39), n (%) or Mean ± SD	No Clopidogrel (n = 97), n (%) or Mean ± SD	*P* Value
Age, years	66.4 ± 11.6	68.8 ± 10.2	.268
Weight, kg	81.8 ± 18.3	86.6 ± 26.0	.227
Sex			.844
Male	25 (64.1)	64 (66.0)	
Female	14 (35.9)	33 (34.0)	
Race			.174
Caucasian	29 (74.4)	82 (84.5)	
Hispanic	8 (20.5)	14 (14.4)	
Other	2 (5.1)	1 (1.0)	
Past medical history			
Percutaneous coronary intervention	38 (97.4)	38 (39.2)	<.001
Hypertension	36 (92.3)	88 (90.7)	1.000
Myocardial infarction	23 (59)	47 (48.5)	.343
Diabetes	15 (38.5)	40 (41.2)	.848
Smoker (within past 2 weeks)	10 (25.6)	9 (9.3)	.026
Congestive heart failure	6 (15.4)	18 (18.6)	.805
Peripheral arterial disease	5 (12.8)	10 (10.3)	.763
Stroke	3 (7.7)	10 (10.3)	.757
Previous coronary arterial bypass graft	3 (7.7)	9 (9.3)	1.000
Atrial fibrillation/flutter	3 (7.7)	8 (8.3)	1.000
Transient ischemic attack	1 (2.6)	3 (3.1)	1.000

Table 2

Medication and Procedure Information.

Variable	Clopidogrel (n = 39), n (%) or Mean ± SD	No Clopidogrel (n = 97), n (%) or Mean ± SD	*P* Value
Preoperative medications[a]			
Aspirin	30 (76.9)	44 (45.4)	.001
GIIb/IIIa inhibitor	3 (7.7)	3 (3.1)	.353
Heparin infusion	1 (2.6)	4 (4.1)	1.000
Prophylactic unfractionated heparin	0 (0)	3 (3.1)	.557
Prophylactic enoxaparin	0 (0)	1 (1)	1.000
Warfarin	0 (0)	1 (1)	1.000
Procedure information			
Partial sternotomy performed	4 (10.3)	6 (6.2)	.472
Valve repair or replacement	0 (0)	4 (4.1)	.578
Transmyocardial laser revascularization	1 (2.6)	2 (2.1)	1.000
Number of vessels operated on			.115
1	20 (51.3)	60 (61.9)	
2	19 (48.7)	32 (33)	
3	0 (0)	5 (5.2)	
Status of rCABG procedure			.087
Elective	24 (61.5)	75 (77.3)	
Urgent[b]	15 (38.5)	22 (22.7)	

Abbreviations: GIIb/IIIa inhibitor, glycoprotein IIb/IIIa inhibitor; rCABG, robotic-assisted coronary artery bypass graft.

[a] Medications are within 24 hours prior to surgery.

[b] Defined as urgent if performed during the index admission.

Table 3

Comparison of Blood Loss and Transfusions.

Variable	Clopidogrel (n = 39), Median (IQR) or Mean ± SD or n (%)	No Clopidogrel (n = 97), Median (IQR) or Mean ± SD or n (%)	*P* Value
Intraoperative blood loss, mL	400 (200-800)	150 (50-300)	.033
Chest tube output post-rCABG, mL			
First 24 hours	900 (700-1340)	735 (490-980)	.002
25-48 hours	315 (130-410)	260 (116-465)	.550
49-72 hours	110 (0-300)	80 (0-200)	.623
73-96 hours	0 (0-120)	0 (0-25)	.388
Hemoglobin, g/dL			
Postoperative day 0	11.5 ± 1.6	11.8 ± 1.6	.292
Postoperative day 1	10.9 ± 1.6	11.5 ± 1.6	.042
Postoperative day 2	10.6 ± 1.5	11.1 ± 1.4	.061
Postoperative day 3	10.3 ± 1.4	11 ± 1.5	.008
Intraoperative transfusions, n (%)			
Red blood cells	17 (43.6)	25 (25.8)	.064
Fresh frozen plasma	9 (23.1)	9 (9.3)	.048
Platelets	8 (20.5)	7 (7.2)	.035
Cryoprecipitate	4 (10.3)	5 (5.2)	.277

Abbreviations: IQR, interquartile range; rCABG, robotic-assisted coronary artery bypass graft.