Perioperative Clopidogrel and Postoperative Events after Hip and Knee Arthroplasties

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Abstract

Background Hip and knee arthroplasties are widely performed and vascular disease among patients having these procedures is common. Clopidogrel is a platelet inhibitor that decreases the likelihood of thrombosis. It may cause intraoperative and postoperative bleeding, but its discontinuation increases the risk of vascular events. There is currently no consensus regarding the best perioperative clopidogrel regimen that balances these concerns.

Questions/purposes We determined (1) the relationship between time of perioperative clopidogrel administration and postoperative bleeding-related events after hip and knee arthroplasties and (2) patient characteristics or surgical factors that may predict these events.

Methods We retrospectively queried our inpatient pharmacy database for patients who received clopidogrel from

2007 to 2009 and identified 116 patients who underwent hip or knee arthroplasty. We recorded the time of perioperative clopidogrel administration, bleeding-related postoperative events, patient characteristics, and surgical factors.

Results Patients who withheld clopidogrel 5 or more days before hip or knee arthroplasty had lower rates of reoperation for infection and antibiotics prescribed for the surgical wound. Postoperative events did not vary with timing of clopidogrel resumption after surgery. Advanced age, an American Society of Anesthesiologists (ASA) score of 4, and revision surgery predicted increased readmission, reoperation for hematoma or infection, antibiotic use, and death.

Conclusions Holding clopidogrel for at least 5 days before hip or knee arthroplasty may lower the rate of bleeding-related events. We found no increase in events when patients resumed clopidogrel immediately after surgery. Advanced age, ASA score of 4, and revision surgery may be risk factors for bleeding-related events.

Level of Evidence Level IV, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Introduction

Arthroplasty of the hip and knee are widely performed in the United States, and the frequency of arthroplasty is projected to increase in the coming years [8–11]. Similarly, cardiovascular, cerebrovascular, and peripheral vascular diseases are prevalent among the age groups of patients that have hip and knee arthroplasties and are among the leading causes of morbidity and mortality in the United States [14, 20].

Clopidogrel is a platelet inhibitor indicated for use in patients with acute coronary syndrome, stroke, or peripheral

arterial disease. Adenosine diphosphate released by damaged tissues activates platelet aggregation by binding to two G-protein-coupled receptors, one of which is the P2Y₁₂ receptor. Clopidogrel inhibits platelet aggregation by irreversibly binding to the P2Y₁₂ receptor. Once administered, the effect of clopidogrel persists for the remaining duration of the platelet lifespan, approximately 7 to 10 days. The half-life of a single 75-mg oral dose of clopidogrel is 6 hours. After 5 days, 96% of this dose is excreted [1].

Based on these pharmacology and pharmacokinetics, the manufacturer's prescribing guidelines recommend clopidogrel be discontinued 5 days before elective surgery to avoid bleeding complications [1]. Excessive bleeding during hip and knee arthroplasties may result in the need for intraoperative and postoperative blood transfusions, which has the potential for multisystem morbidity [7, 17]. Other potential sequelae include wound complications requiring antibiotics, reoperation for hematoma or infection, readmission, and death. However, if clopidogrel is withheld for an extended time in an effort to avoid the aforementioned events, the risk of life-threatening cardiovascular events may increase [2]. Balancing these competing concerns in patients undergoing hip and knee arthroplasties who take clopidogrel is difficult. In the event that a patient discontinues clopidogrel before arthroplasty, the optimal length of time before surgery that the drug should be withheld and the earliest that it can be safely resumed are currently unknown. The existing literature lends little insight into this dilemma. In fact, it has not been established whether concern for bleeding secondary to clopidogrel even demands discontinuation before surgery. In one study of 970 patients undergoing hip and knee arthroplasties who received clopidogrel, aspirin, dipyridamole, low-molecular-weight heparin, or warfarin for deep vein thrombosis (DVT) prophylaxis, clopidogrel was not associated with hematoma or gastrointestinal bleeding [3]. Patients receiving clopidogrel reportedly had a mean postoperative hemoglobin level similar to that of patients not receiving clopidogrel after operative treatment for hip fracture [5]. Another recent study reported no increase in

the rate of complications or transfusions among patients receiving clopidogrel requiring nonelective orthopaedic surgery [16]. A couple studies suggest there is no consensus among orthopaedic surgeons regarding the best perioperative clopidogrel regimen [6, 12].

We therefore determined (1) the relationship between time of perioperative clopidogrel administration and postoperative bleeding-related events after hip and knee arthroplasties and (2) patient characteristics or surgical factors that may predict these events.

Patients and Methods

We queried the inpatient pharmacy database at our institution for all patients who received clopidogrel as an inpatient from 2007 to 2009 for peripheral vascular disease, cerebrovascular disease, or after cardiac stent placement. Of the 417 patient files retrieved, 116 patients underwent 126 primary or revision hip or knee arthroplasties. Patients undergoing either unicompartamental or total joint arthroplasty were included in this sample. We reviewed the charts of these 116 patients for the data described below using a uniform protocol. Data regarding timing of clopidogrel administration were available for 114 of the 126 arthroplasties performed. These arthroplasties were divided into three groups according to length of time clopidogrel was withheld before surgery: 0 days ($n = 8$), 1 to 4 days ($n = 17$), and 5 + days ($n = 89$). The institutional review board at our institution approved this retrospective review.

To compare whether clinical characteristics differed between groups, Fisher's exact test was performed for categorical variables (eg, American Society of Anesthesiologists [ASA] score, type of surgery) and the Mann-Whitney U test for continuous variables (eg, age). There were no differences among the groups in demographics or incidence of cardiovascular disease (Table 1).

All patient data were collected through review of inpatient hospital records up to 30 days after surgery. We did not have access to any outpatient records or postdischarge

Table 1. Characteristics of the study population ($n = 114$ arthroplasties) categorized by number of days clopidogrel was held before surgery.

Variable	Number of days clopidogrel was held before surgery			p value
	0 ($n = 8$, 7%)	1–4 ($n = 17$, 15%)	5+ ($n = 89$, 78%)	
Age (years)*	75.6 (13.1)	70.0 (8.6)	69.9 (9.8)	0.290
Sex (female)	2 (25%)	5 (29.4%)	29 (32.6%)	1.000
Race (white)	7 (100%)	17 (100%)	83 (95.4%)	1.000
Cardiovascular disease (yes) [†]	5 (62.5%)	13 (76.5%)	64 (71.9%)	0.861
Elective procedure (yes)	7 (100%)	16 (94.1%)	84 (96.6%)	0.628

* Values are expressed as mean, with SD in parentheses; the remaining values are expressed as number of arthroplasties, with percentage in parentheses; [†]congestive heart failure and myocardial infarction.

records from outside institutions. We recorded each patient's date of last preoperative dose of clopidogrel, date of surgery, and date of first postoperative dose of clopidogrel. The events recorded for each patient were antibiotics prescribed as an inpatient at the discretion of the surgeon for operative-site cellulitis or wound drainage; reoperation for operative-site infection diagnosed using serum inflammatory markers (CBC, erythrocyte sedimentation rate, C-reactive protein) in addition to joint aspirate leukocyte count and culture, reoperation for operative site hematoma, 30-day readmission, and in-hospital death. Age and ASA score [4] were recorded for each patient. We presumed these characteristics would have the strongest relationship with postoperative bleeding-related events among patients receiving clopidogrel. Type of surgery (unicompartmental knee arthroplasty, primary/revision THA, or primary/revision TKA) was recorded. This was the surgical factor we believed would have the strongest relationship with postoperative bleeding-related events among patients on clopidogrel.

Mean and SD were calculated for continuous variables; frequency and proportion were calculated for categorical variables. In testing the association between time of perioperative clopidogrel administration and 30-day readmission, reoperation for hematoma or infection, antibiotics prescribed for the operative site, and in-hospital death, logistic regression analysis was performed. All analyses were performed using SAS® software (Version 9.2; SAS Institute Inc, Cary, NC, USA). Patients with missing data points were excluded from relevant analyses.

Results

Bleeding-related postoperative events were less frequent in patients who withheld clopidogrel 5 or more days before surgery (Table 2) and did not vary with the number of days after surgery clopidogrel was resumed (Table 3). Patients who withheld clopidogrel for 5 or more days before surgery had lower rates of reoperation for infection

($p = 0.014$) and antibiotics prescribed for cellulitis or wound drainage ($p = 0.001$) (Table 2). Of the patients who did not discontinue clopidogrel before surgery, 25% had reoperation for infection and 38% were prescribed antibiotics for the operative site (data not shown). No association was found between the number of days clopidogrel was withheld before surgery and rates of 30-day readmission, reoperation for hematoma, or death.

Increased age, ASA score of 4, and revision surgery were associated with increased rates of bleeding-related postoperative events in patients receiving clopidogrel (Table 4). Among patients undergoing hip and knee arthroplasties who were taking clopidogrel, older patients were more likely to undergo reoperation for infection ($p = 0.033$), be prescribed antibiotics for the operative site ($p = 0.042$), and die during their hospital course ($p = 0.037$). A greater percentage (50%) of patients with an ASA score of 4 as compared with patients with a lower ASA score underwent reoperation for hematoma ($p = 0.005$). Revision surgery was associated with an increased rate of postoperative events: 22% of patients needing revision surgery were readmitted within 30 days ($p = 0.001$), 17% underwent reoperation for hematoma ($p = 0.009$), 28% were prescribed antibiotics for the operative site ($p < 0.0001$), and 11% died as an inpatient ($p = 0.019$).

Discussion

Clopidogrel is a platelet inhibitor widely prescribed for vascular disease to decrease the likelihood of thrombosis. Although effective in this regard, clopidogrel has the potential to cause intraoperative and postoperative bleeding in patients undergoing arthroplasty [19]. The decision to discontinue clopidogrel is complicated by the resultant increased risk of vascular events [2]. There is a paucity of literature on the outcome of perioperative clopidogrel administration in patients undergoing nonelective orthopaedic surgery and no evidence-based guidelines for perioperative clopidogrel management in hip and knee

Table 2. Relationship between number of days clopidogrel was held before surgery and outcomes.

Binary outcome*	Number of days clopidogrel was held before surgery						
	0 (n = 8, 7%)	1–4 (n = 17, 15%)			5 + (n = 89, 78%)		
	Odds ratio (reference)	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
30-day readmission	1	0.44	0.02–8.04	0.578	0.24	0.02–2.67	0.248
Reoperation for hematoma	1	0.47 [†]	0.01–∞	1.000	0.34 [†]	0.03–∞	1.000
Reoperation for infection	1	0.19	0.01–2.47	0.203	0.07	0.01–0.58	0.014
Antibiotics for operative site	1	0.10	0.01–1.24	0.083	0.04	0.01–0.28	0.001
In-hospital death	1	0.47 [†]	0–18.35	0.640	0.08	0.004–1.41	0.085

* Logistic regression analysis for binary outcomes; [†]a median unbiased estimate from exact test.

Table 3. Relationship between number of days after surgery clopidogrel was restarted and outcomes.

Binary outcome*	Number of days after surgery clopidogrel was restarted			p value
	0 (n = 6, 5%)	1 (n = 88, 75%)	>1 (n = 24, 20%)	
30-day readmission				0.680
Yes	0	5 (6%)	0	
No	6 (100%)	83 (94%)	24 (100%)	
Reoperation for hematoma				1.000
Yes	0	2 (2%)	0	
No	6 (100%)	86 (98%)	24 (100%)	
Reoperation for infection				0.680
Yes	0	5 (6%)	0	
No	6 (100%)	83 (94%)	24 (100%)	
Antibiotics for operative site				1.000
Yes	0	3 (3%)	0	
No	6 (100%)	85 (97%)	24 (100%)	

* Fisher's exact test for binary outcomes.

arthroplasties [5, 6, 12, 16]. It also is unknown which patients are particularly susceptible to the potentially deleterious effects of clopidogrel. As a result, we determined (1) the relationship between time of perioperative clopidogrel administration and postoperative bleeding-related events after hip and knee arthroplasties and (2) patient characteristics or surgical factors that may predict these events.

Although our exploratory study may provide some seed information helpful in this difficult clinical situation, we understand our work has limitations. First, although our findings were statistically significant, there exists the potential for Type I error. The generalizability of our findings may be limited by characteristics unique to our study population. Second, because observational studies are vulnerable to confounding factors, we were able to observe only correlations, not determine causal relationships. A multivariate model may have helped eliminate some confounders, but owing to the low number of observed postoperative events, we did not have the power to adjust for other variables. Third, the retrospective design of our study may represent an inherent source of error as we were limited by the accuracy of the patient records available. Fourth, we did not have access to postdischarge records from outside institutions, so the patient data we collected may be incomplete.

Our data suggest patients who do not discontinue clopidogrel at least 5 days before surgery may have a higher incidence of reoperation for infection and antibiotics prescribed for operative-site cellulitis and/or wound drainage. The timing of postoperative clopidogrel resumption did not influence the rate of postoperative events. One study reported no bleeding events in a patient undergoing hip and knee arthroplasties who was given clopidogrel for

postoperative DVT prophylaxis [3]. However, only one patient receiving clopidogrel was studied, thus precluding any conclusions.

We found increased age, ASA score of 4, and revision surgery were associated with increased rates of postoperative events in patients receiving clopidogrel undergoing hip or knee arthroplasty. These risk factors are associated with increased postoperative complications in the population receiving hip and knee arthroplasties [13, 15, 18, 21]. However, in our cohort of patients taking clopidogrel, the rate of complications was severalfold greater than that previously observed in the population receiving arthroplasty as a whole. For example, as compared with published rates of complications after revision arthroplasty, patients taking clopidogrel who underwent revision had a four- to 13-fold higher rate of mortality, six- to 24-fold higher rate of infection, and twofold higher rate of readmission [13, 21] (Table 5). Although this observation may be unique to the population at our institution or a function of our sample size, the possibility exists that the deleterious effects of age, comorbidities, and revision surgery are magnified in patients taking clopidogrel. Consideration should be given to preoperative platelet administration, meticulous surgical technique, and close postoperative monitoring in at-risk patients undergoing hip and knee arthroplasties taking clopidogrel.

A larger retrospective or prospective investigation may further reinforce and expand our findings. A prospective study would allow for more sensitive detection of smaller hematomas and bleeding secondary to clopidogrel administration that may result in prolonged recovery or joint stiffness. Future work also may examine reversal of the effects of clopidogrel with platelet infusion, particularly in emergent (eg, sepsis) circumstances.

Table 4. Univariate test of the relationship between each predictor and outcome.

Binary outcome	Number of arthroplasties	Age Mean (SD) (years)	ASA score			Type of surgery								
			p value*	Odds ratio (95% CI)	2	3	4	p value [†]	Odds ratio (95% CI)	Primary	Revision	p value [†]	Odds ratio (95% CI)	
Total population	126	70 (9.7)			20 (16%)	102 (81%)	4 (3%)			108 (86%)	18 (14%)			
30-day readmission			0.43	1.05 (0.95–1.15)					0.11	2.33 (0.22–24.4)			< 0.01	0.03 (0.003–0.31)
Yes	5 (4%)	74.0 (11.1)				1 (5%)	3 (3%)	1 (25%)			1 (1%)	4 (22%)		
No	121 (96%)	69.8 (9.6)				19 (95%)	99 (97%)	3 (75%)			107 (99%)	14 (78%)		
Reoperation for hematoma			0.14	1.09 (0.97–1.23)					0.01	50.8 (4.67–552)			0.01	0.05 (0.005–0.48)
Yes	4 (3%)	77.3 (11.5)				0	2 (2%)	2 (50%)			1 (1%)	3 (17%)		
No	122 (97%)	69.7 (9.6)				20 (100%)	100 (98%)	2 (50%)			107 (99%)	15 (83%)		
Reoperation for infection			0.03	1.14 (1.01–1.29)					1.00	0.67 (0.09–4.95)			0.54	0.65 (0.07–6.21)
Yes	5 (4%)	80 (11.7)				1 (5%)	4 (4%)	0			4 (4%)	1 (6%)		
No	121 (96%)	69.6 (9.4)				19 (95%)	98 (96%)	4 (100%)			104 (96%)	17 (94%)		
Antibiotics for operative site			0.04	1.12 (1.01–1.24)					0.22	2.34 (0.27–20.3)			< 0.0001	0.02 (0.003–0.22)
Yes	6 (5%)	78.5 (10.8)				1 (5%)	4 (4%)	1 (25%)			1 (1%)	5 (28%)		
No	120 (95%)	69.6 (9.4)				19 (95%)	98 (96%)	3 (75%)			107 (99%)	13 (72%)		
In-hospital death			0.04	1.28 (0.98–1.68)					0.09	34.3 (1.77–665)			0.02	NA
Yes	2 (2%)	85 (2.8)				0	1 (1%)	1 (25%)			0	2 (11%)		
No	124 (98%)	69.7 (9.5)				20 (100%)	101 (99%)	3 (75%)			108 (100%)	16 (89%)		

* Mann-Whitney U test; † Fisher's exact test; ASA = American Society of Anesthesiologists; NA = not applicable.

Table 5. Rates of complications after revision arthroplasty.

Study	Readmission	Infection	Mortality
All patients			
Mahomed et al. [13]	10%	0.95%	2.6%
Zhan et al. [21]	8.48%	0.25%	0.84%
Patients taking clopidogrel			
Current study	22%	6%	11%

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