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Perioperative antiplatelet therapy and cardiovascular outcomes in patients undergoing joint and spine surgery☆

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Abstract

Study objective—Perioperative thrombotic complications after orthopedic surgery are associated with significant morbidity and mortality. The use of aspirin to reduce perioperative cardiovascular complications in certain high-risk cohorts remains controversial. Few studies have addressed aspirin use, bleeding, and cardiovascular outcomes among high-risk patients undergoing joint and spine surgery.

Design/setting/patients—We performed a retrospective comparison of adults undergoing knee, hip, or spine surgery at a tertiary care center during 2 periods between November 2008 and December 2009 (reference period) and between April 2013 and December 2013 (contemporary period).

Measurements—Patient demographics, comorbidities, management, and outcomes were ascertained using hospital datasets.

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Main results—A total of 5690 participants underwent 3075 joint and spine surgeries in the reference period and 2791 surgeries in the contemporary period. Mean age was 61 ± 13 years, and 59% were female. In the overall population, incidence of myocardial injury (3.1% vs 5.8%, $P < .0001$), hemorrhage (0.2% vs 0.8%, $P = .0009$), and red blood cell transfusion (17.2% vs 24.8%, $P < .001$) were lower in the contemporary period. Among 614 participants with a preoperative diagnosis of coronary artery disease (CAD), in-hospital aspirin use was significantly higher in the contemporary period (66% vs 30.7%, $P < .0001$); numerically, fewer participants developed myocardial injury (13.5% vs 19.3%, $P = .05$), had hemorrhage (0.3% vs 2.1%, $P = .0009$), and had red blood cell transfusion (37.2% vs 44.2%, $P < .001$) in the contemporary vs reference period.

Conclusions—In a large tertiary care center, the incidence of perioperative bleeding and cardiovascular events decreased over time. In participants with CAD, perioperative aspirin use increased and appears to be safe.

Keywords

Orthopedic surgery; Aspirin; Antiplatelet; Perioperative; Cardiovascular; Myocardial infarction; Myocardial injury; Coronary artery disease; Bleeding; Transfusion

1. Introduction

More than 1.5 million hip, knee, and spine orthopedic surgeries are performed in the United States each year [1]. Case volumes have risen steadily during the past decade, particularly among older adults with the highest cardiovascular risks [1,2]. Perioperative cardiovascular complications are a major concern because they impart significant postoperative morbidity and mortality. Perioperative myocardial infarction (MI) occurs in up to 5% of participants within 30 days of noncardiac surgery and is associated with increased short-term mortality [3–5]. Myocardial injury without definite MI is also independently associated with increased postoperative mortality [6–10]. Perioperative thrombotic complications are often attributed to enhanced platelet activation after surgery [11,12]. Aspirin, a potent inhibitor of platelet aggregation, can reduce risks of thrombotic complications and major vascular events but with the competing risk of bleeding [13,14]. The net benefit of perioperative aspirin to reduce rates of thrombotic complications for individuals at risk for cardiovascular complications remains uncertain. In a recent large randomized study of patients with cardiovascular risk factors undergoing noncardiac surgery, routine perioperative aspirin increased rates of major bleeding without a reduction in death or MI at 30 days, although the study enrolled few high-risk patients [15].

Despite increased awareness of perioperative cardiovascular thrombotic risks, wide variation in clinical practice remains [16]. The impact of perioperative antiplatelet administration and strategies on bleeding and cardiovascular outcomes in the highest risk groups also requires further investigation [17]. We compared participants undergoing joint and spine surgery during 2 periods at a large academic medical center to determine trends in perioperative antiplatelet administration and its association with postoperative MI, myocardial injury, hemorrhage, red blood cell transfusion (RBCT), and mortality.

2. Methods

2.1. Study design

We performed a retrospective cohort analysis of consecutive adults undergoing knee, hip, or spine surgery at a tertiary care center between November 1, 2008, and December 31, 2009 (reference period) and between April 3, 2013 and December 31, 2013 (contemporary period). The time frame of the contemporary period was abridged to coincide with the release of an update to the institutional recommendations regarding perioperative aspirin use. Complete methods have been described previously [14]. Clinical data were obtained from hospital administrative, laboratory and blood bank databases, and retrospective review of the medical record. The study was approved by the New York University School of Medicine Institutional Review Board (New York, NY) with a waiver of informed consent.

2.2. Patients and outcomes

International Classification of Diseases, Ninth Revision (*ICD-9*) procedure codes were used to identify surgical spinal fusion (81.0x), refusion of spine (81.3x), joint replacement of lower extremity (81.5x), and other procedures on spine (81.6x). Patient demographics and preoperative cardiovascular comorbidities were abstracted from an administrative dataset. In-hospital antiplatelet therapy among participants with coronary artery disease (CAD) was obtained from a hospital dataset and retrospective record review. Myocardial injury was defined by a rise in serum troponin above the 99% upper reference limit of the laboratory. Plasma cardiac troponin I (cTnI) was measured using the VITROS cTnI ES assay (Ortho-Clinical Diagnostics, Rochester, NY) or the ST AIA-PACK 2nd generation cTnI assay (Tosoh Bioscience, Tokyo, Japan). Myocardial infarction was defined by *ICD-9* diagnosis code 410.x, not present on admission. Postoperative hemorrhage was defined by *ICD-9* diagnosis code 998.11 and retrospective record review. The RBCTs during admission were determined from a hospital blood bank dataset.

2.3. Statistical analysis

Normally distributed continuous variables were displayed as mean (SD) and were compared using the unpaired Student *t* test. Categorical variables were displayed as frequencies and percentages and were compared by χ^2 and Fisher exact tests. Logistic regression models were used to identify the effect of the reference and contemporary periods on thrombotic, bleeding, and transfusion outcomes for the unmatched study population. Models were adjusted for age, sex, diabetes, CAD, heart failure, prior stroke/transient ischemic attack (TIA), kidney disease, and urgent surgery, with final model covariates selected via a stepwise approach when $P < .1$. Statistics were calculated using SPSS 20 (IBM SPSS Statistics, Armonk, NY). Two-tailed $P < .05$ was considered to be statistically significant for all tests.

3. Results

A total of 5690 participants underwent 5866 orthopedic surgeries of the spine (38.0%), hip (31.0%), and knee (31.0%), with 3075 procedures in the reference period and 2791 procedures in the contemporary period. Overall, the mean age was 61.0 ± 13.1 years, 58.7%

were female, and 65.5% of participants were white. Preoperative cardiovascular risk factors and procedural characteristics in the 2 periods are displayed in Table 1. Baseline demographics were similar between groups. Individuals undergoing surgery in the contemporary period were more likely to have a history of stroke (3.4% vs 0.6%, $P < .0001$) and less likely to have a history of heart failure (1.4% vs 2.8%, $P < .0001$) than those undergoing surgery in the reference period.

The frequencies of myocardial injury, MI, postoperative hemorrhage, and RBCT in the reference and contemporary periods are depicted in Table 2. Perioperative troponin measurement was performed in 1917 participants and was less frequent in the contemporary period (30.7% vs 34.5%, $P = .002$). Perioperative myocardial injury was detected in 266 participants (4.5% of all participants and 13.9% among participants with troponin measured). Among participants with 1 or more perioperative troponin measurements, myocardial injury was less common in the contemporary period (10.2% vs 16.9%, $P < .0001$). Myocardial infarction was infrequent (0.89%) and not significantly different between groups. Coded perioperative hemorrhage and RBCT were significantly less common in the contemporary period in comparison with the reference period, as shown in Table 2. In-hospital and 30-day mortality were infrequent and similar in both periods (0.16% vs 0.07%, $P = .31$).

3.1. Participants with CAD

A preoperative diagnosis of CAD was established in 614 (10.5%) cases. Baseline characteristics of participants with CAD are shown in Table 3. Individuals with CAD in the contemporary period were more likely to have a history of stroke/TIA (10.1% vs 1.5%, $P < .0001$) and less likely to have kidney disease at baseline (17.7% vs 24.5%, $P = .04$). Similar proportions of participants with CAD in the 2 periods underwent coronary revascularization before surgery, although participants in the contemporary period were more likely to have a history of coronary artery bypass graft (30.6% vs 19.0%, $P < .001$).

Among participants with a preoperative diagnosis of CAD, in-hospital perioperative aspirin use was significantly higher in the contemporary period than in the reference period (66.0% vs 30.7%, $P < .0001$), largely because of less frequent discontinuation of outpatient aspirin therapy (Table 4). There was no difference in perioperative clopidogrel use between the 2 periods (10.1% vs 10.1%, $P = .92$).

Data on thrombotic and bleeding outcomes in the reference and contemporary periods are shown in Table 2. Postoperative troponin measurement was performed in most participants with CAD (n = 556, 90.6%), with no difference between the 2 periods (89.9% vs 90.8%, $P = .82$). Myocardial injury occurred in 13.5% in the contemporary period and 19.3% in the reference period ($P = .05$). No difference in rates of MI was observed. Despite increased use of aspirin, coded hemorrhage was uncommon in both groups, and there was a trend toward less RBCT in the contemporary period (37.5% vs 44.5%, $P = .08$) in comparison with the reference period. In-hospital and 30-day mortality were similar in the contemporary and reference periods (0.61% vs 0.35%, $P = .99$).

4. Discussion

In this retrospective observational study of individuals who underwent major joint and spine surgery, we report that the incidence of postoperative cardiovascular events decreased over time. Among participants with CAD, there was a trend toward fewer episodes of perioperative myocardial injury in the contemporary period. Despite increased use of aspirin in participants with CAD, no concomitant increase in perioperative RBCTs or postoperative hemorrhage was observed.

Significant reductions in the frequency of perioperative myocardial injury were also identified in the contemporary period among participants without established CAD. Even after multivariable adjustment, the contemporary period was significantly associated with reduced perioperative myocardial injury. The mechanism of reduced myocardial injury in the overall cohort undergoing orthopedic surgery remains uncertain. Potential explanations for the observed trends may include improved patient selection, perioperative aspirin or statin use, appropriate β-blocker use after incorporation of the 2008 Perioperative Ischemic Evaluation trial (POISE) findings into clinical practice [18], enhanced surgical techniques, improved pain management, mitigation of surgical bleeding, minimizing RBCT, and/or improved management of perioperative hypotension. Further investigation is necessary to determine the etiology of these encouraging perioperative trends.

A clear rationale exists to reduce rates of perioperative MI and myocardial injury in patients undergoing noncardiac surgery. In the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation study, a large international prospective cohort of 15 133 patients 45 years and older, postoperative elevated troponins were identified in 8% of patients, and peak measurements were independently correlated with short-term 30-day mortality in multivariable analyses [9]. Similar findings were observed in a single-center cohort of 2232 intermediate- and high-risk patients 60 years and older undergoing noncardiac surgery, with a 2.5-fold relative risk of 30-day mortality associated with minor troponin elevations (≤0.59 μg/L) and a 4-fold relative risk associated with more significant troponin elevations (>0.60 μg/L) [8]. Stratified values of troponin are also independent predictors of mortality at 1 year in patients at the highest cardiovascular risks undergoing vascular surgery [19]. Although orthopedic procedures have historically been classified as intermediate-risk surgery, data on postoperative cardiovascular outcomes are limited [20]. Myocardial injury has been reported to occur in 5.8% to 17% of patients in single-center studies and correlates with long-term mortality [14,30]. In a small series of patients undergoing hip surgery, postoperative positive troponins were associated with a 10-fold increase in the incidence of major cardiac events at 1 year [21]. Similarly, patients older than 60 years undergoing emergency orthopedic surgery with elevated troponins in the postoperative period had a 12-fold odd of mortality at 1 year in multivariable analyses [22]. Thus, prevention of myocardial injury and MI represents an opportunity to reduce postoperative cardiovascular events.

Although antiplatelet use in high-risk patient subsets undergoing orthopedic surgery appears to be safe and may provide some perioperative cardiovascular risk reduction based on the findings of the present study, strategies of perioperative aspirin administration failed to yield benefits in large randomized controlled trials. The Pulmonary Embolism Prevention trial

randomized 13 356 patients undergoing hip surgery to aspirin or placebo. In this trial, perioperative aspirin therapy reduced rates of venous thromboembolism but was not associated with reductions in postoperative MI or death [23]. In the second POISE trial (POISE-2), 10 010 patients at risk for vascular complications and undergoing noncardiac surgery were randomized to perioperative aspirin or placebo [15]. At 30 days, there was no difference in the primary outcome of death or nonfatal MI, but aspirin was associated with an increased incidence of major bleeding [24]. Effects of aspirin were similar regardless of Revised Cardiac Risk Index (RCRI) score or whether patients took aspirin before randomization [15]. However, only 39% of patients underwent orthopedic surgery, and less than a quarter had a history of CAD. Subgroup analyses from POISE-2 of patients with a preoperative diagnosis of CAD are not yet available. Smaller, randomized trials have yielded conflicting results [25]. An observational study of patients undergoing elective pancreatic surgery also demonstrated that aspirin continuation in the perioperative period was not associated with increased rates of bleeding, transfusions or procedural complications, corroborating the findings of the present study and demonstrating the safety of aspirin in other surgical procedures [26]. A small study of patients with CAD and prior stents undergoing spine surgery also reported that perioperative aspirin administration appears to be safe [27].

At present, the use of perioperative aspirin in patients with CAD without coronary stents is controversial. Current American College Of Cardiology/American Heart Association guidelines recommend that perioperative antiplatelet therapy should be determined by a consensus of the surgeon, anesthesiologist, cardiologist, and the patient [28]. It remains reasonable to continue aspirin when the risks of thrombotic events outweigh those of increased bleeding. Still, refined approaches to risk stratification for patients undergoing noncardiac surgery are warranted. The utility of preoperative platelet reactivity testing to assess thrombotic or bleeding risks of antiplatelet therapy has not been studied. Risk prediction algorithms to determine the net clinical benefit of perioperative aspirin warrant further investigation.

There are limitations to this retrospective, observational study of perioperative outcomes. First, serum troponin assays were performed at the discretion of the surgical team without a standardized collection schedule in the postoperative period. Troponin measurements were largely confined to patients with the greatest burden of cardiovascular risk factors and the highest pretest probability of perioperative myocardial injury. Although some occult myocardial injury may have been missed, this is unlikely to have substantially affected the study results. Second, aspirin continuation or initiation was performed at the discretion of the surgeon and cardiologist based on the perceived risks of bleeding and thrombosis. No standardized clinical risk assessment tools were used. The clinical rationale for initiation, continuation, or discontinuation of aspirin was not available. Associations between in-hospital aspirin use and clinical outcomes are confounded by the clinical indication for use, and causality cannot be inferred. Use and discontinuation of nonsteroidal anti-inflammatory drugs that may have contributed to bleeding and thrombotic end points were not recorded. Third, data on aspirin administration during the surgical hospitalization were only available for participants with a history of CAD and were not available for the full cohort undergoing orthopedic surgery. Fourth, improvements in medical and surgical perioperative management

between 2008 and 2013 may represent significant unmeasured confounders, including more stringent RBCT thresholds and increased rates of high-potency statin use in the perioperative period. Fifth, newer generations of drug-eluting stents were likely more common in individuals with a history of percutaneous coronary intervention undergoing surgery in the contemporary period. Second-generation drug-eluting stents have been associated with the lowest rates of stent thrombosis [29]. Data on stent characteristics or location were not available for this analysis. Sixth, the results of POISE-1 may have altered management of perioperative β-blocker use during the study period. POISE-2 results were not yet available at the time orthopedic and spine surgeries were performed and therefore did not impact the observed rates of antiplatelet use in this analysis. Finally, the study was conducted at a single center, which may limit the generalizability of the findings.

5. Conclusion

In a large tertiary care center, the incidence of perioperative bleeding and cardiovascular events decreased over time. In patients with CAD, perioperative aspirin use appears to be safe and may reduce the incidence of postoperative thrombotic outcomes. Additional studies are necessary to determine optimal strategies for perioperative cardiovascular risk reduction.

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Table 1

Preoperative cardiovascular risk factors and procedural characteristics

	Reference period (n = 3075)	Contemporary period (n = 2791)	*P*
Age, mean (+/− SD) (y)	60.7 ± 13.3.15	61.2 ± 12.8	.15
Female sex	1816 (59.1%)	1629 (58.4%)	.49
Body mass index	29.6 ± 6.6	29.7 ± 6.6	.56
RCRI			
0 Risk factors	2341 (76.1%)	2110 (75.6%)	.58
1 Risk factors	597 (19.4%)	545 (19.5%)	
2 Risk factors	118 (3.8%)	110 (3.9%)	
3+ Risk factors	19 (0.6%)	26 (0.9%)	
RCRI ≥1	734 (23.9%)	681 (24.4%)	.65
CAD	326 (10.6%)	288 (10.3%)	.72
Prior MI	89 (2.9%)	88 (3.2%)	.62
Heart failure	86 (2.8%)	40 (1.4%)	<.0001
Stroke/TIA	18 (0.6)	96 (3.4%)	<.0001
Creatinine >2 mg/dL	15 (0.5%)	14 (0.5%)	.92
Diabetes mellitus	446 (14.5%)	408 (14.6%)	.92
Urgent surgery	180 (5.9%)	112 (4.0%)	.001
Procedure type			
Spine	1161 (37.8%)	1067 (38.2%)	.03
Knee	996 (32.4%)	822 (29.5%)	
Hip	918 (29.9%)	902 (32.3%)	

Abbreviations: CAD: Coronary artery disease, MI: myocardial infarction, RCRI: Revised cardiac risk index, TIA: transient ischemic attack.

Table 2

Frequency of myocardial injury, MI, bleeding, and RBCT among participants undergoing orthopedic surgery in the reference and contemporary periods

	All	Reference period	Contemporary period	*P*	Adjusted odds ratio
Overall (n = 5866)					
Myocardial injury	266 (4.5%)	179 (16.9% [a])	87 (10.2% [a])	<.0001	0.59 (0.44–0.79)[a]
MI	49 (0.8%)	20 (0.7%)	29 (1.0%)	.14	1.73 (0.95–3.14)
RBCT	1242 (21.2%)	762 (24.8)	480 (17.2%)	<.0001	0.63 (0.56–0.73)
Hemorrhage	31 (0.5%)	26 (0.8%)	5 (0.2%)	.0009	0.24 (0.09–0.63)
Patients with CAD (n = 614)					
Myocardial injury	102 (16.6%)	63 (19.3%)	39 (13.5%)	.05	0.70 (0.43–1.13)
MI	14 (2.3%)	7 (2.1%)	7 (2.4%)	.81	1.05 (0.35–3.23)
RBCT	251 (40.9%)	144 (44.2%)	107 (37.2%)	.08	0.76 (0.55–1.07)
Hemorrhage	8 (1.3%)	7 (2.1%)	1 (0.3%)	.07	0.17 (0.02–1.44)

Abbreviations: CAD: Coronary artery disease, MI: Myocardial infarction, RBCT: Red blood cell transfusion.

[a]Among patients with a troponin measured in the perioperative period.

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Table 3

Preoperative cardiovascular risk factors and procedural characteristics in patients with established CAD

	Reference period (n = 326)	Contemporary period (n = 288)	*P*
Age, mean (+/− SD) (y)	70.3 ± 10.3	69.8 ± 10.4	.53
Female sex	198 (60.7%)	168 (58.7%)	.62
Body mass index	30.4 ± 6.6	30.1 ± 5.9	.62
RCRI			
1 Risk factors	207 (63.5%)	174 (60.4%)	.37
2 Risk factors	100 (30.7%)	89 (30.9%)	
3+ Risk factors	19 (5.8%)	25 (8.7%)	
Prior MI	89 (27.3%)	88 (30.6%)	.42
Coronary revascularization	166 (50.9%)	163 (56.6%)	.18
Coronary artery bypass graft	62 (19.0%)	88 (30.6%)	.001
Percutaneous coronary intervention	120 (36.8%)	113 (39.2%)	.54
Heart failure	38 (11.7%)	28 (9.8%)	.46
Stroke/TIA	5 (1.5%)	29 (10.1%)	<.0001
Kidney disease (GFR <60)	80 (24.5%)	51 (17.7%)	.04
Creatinine >2 mg/dL	4 (1.2%)	6 (2.1%)	.4
Diabetes mellitus	93 (28.5%)	79 (27.4%)	.76
Peripheral arterial disease	7 (2.1%)	10 (3.5%)	.32
Urgent surgery	36 (11.0%)	23 (8.0%)	.32
Procedure type			
Spine	100 (30.7%)	99 (34.4%)	
Knee	106 (32.5%)	85 (29.5%)	.57
Hip	120 (36.8%)	104 (36.1%)	

Abbreviation: GFR, glomerular filtration rate; MI, Myocardial Infarction; RCRI, Revised Cardiac Risk Index; TIA, Transient Ischemic Attack.

Table 4

Perioperative aspirin administration and clinical outcomes in the reference and contemporary periods among patients with CAD

	All (n = 614)	Reference period (n = 326)	Contemporary period (n = 288)	*P*
Perioperative aspirin use	290 (47.2%)	100 (30.7%)	190 (66.0%)	<.0001
Aspirin initiation	44 (7.2%)	26 (8%)	18 (6.3%)	.50
Aspirin continuation	246 (40.1%)	74 (22.7%)	172 (59.7%)	<.0001
No perioperative aspirin	324 (52.8%)	226 (69.3%)	98 (34.0%)	<.0001
Aspirin discontinuation	136 (22.1%)	99 (30.4%)	37 (12.8%)	<.0001
Perioperative clopidogrel use	62 (10.1%)	33 (10.1%)	29 (10.1%)	.92
Perioperative statin use	444 (72.3%)	225 (69.0%)	219 (76.0%)	.06