Perioperative complications following preoperative cessation of antithrombotic agents for total knee arthroplasty

A retrospective study

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Abstract

The number of elderly patients undergoing total knee arthroplasty (TKA) has steadily increased. Elderly patients undergoing TKA usually have underlying diseases, and some of them take antithrombotic agents for the prevention or treatment of these co-morbidities, including cardiovascular, cerebrovascular, or thromboembolic diseases. When these patients are scheduled to undergo TKA, preoperative cessation of antithrombotic agents is considered on the basis of its risks and benefits. This study was aimed to evaluate the impact of discontinuing antithrombotic agents for primary total knee arthroplasty (TKA) on perioperative complications.

Patients who underwent primary TKA between 2008 and 2012 were identified, and classified into two groups: group A, in whom antithrombotic agents were ceased preoperatively, and group B, in which patients did not receive antithrombotic therapy. Patient characteristics, history of antithrombotic therapy, intraoperative blood loss, perioperative blood transfusion, postoperative 30-day complications, and postoperative hospital stay were recorded.

Of 885 patients undergoing primary TKA, 218 (24.6%) patients were included in group A, and 667 (75.4%) in group B. Group A received transfusion more frequently than group B ($P < 0.001$). However, there was no difference between the two groups in terms of intraoperative blood loss, postoperative 30-day complications, and postoperative hospital stay.

Patients who discontinued antithrombotic drugs before primary TKA do not have a higher incidence of postoperative 30-day complications, including cardiovascular, cerebrovascular, or thromboembolic events. Moreover, the estimated intraoperative blood loss was not different compared with patients not receiving antithrombotic agents preoperatively. Larger prospective studies of this issue are required.

Abbreviations: ASA = American Society of Anesthesiologists, BMI = body mass index, CI = confidence interval, IPTW = inverse probability of treatment weighting, OR = odds ratio, SD = standard deviation, TKA = total knee arthroplasty.

Keywords: Antithrombotic agents, Cessation, Perioperative complications, Total knee arthroplasty

1. Introduction

As the elderly population has grown, the number of patients undergoing total knee arthroplasty (TKA) has steadily increased.[1] Elderly patients undergoing TKA usually have underlying diseases, and some of them take antithrombotic agents for the prevention or treatment of these co-morbidities, including cardiovascular, cerebrovascular, or thromboembolic diseases. When these patients are scheduled to undergo TKA, preoperative cessation of antithrombotic agents is considered on the basis of risks and benefits to the patient.

Perioperative antithrombotic therapy can be associated with bleeding-related complications. Furthermore, neuraxial anesthesia is often preferred to general anesthesia in patients undergoing TKA because major morbidity and mortality have been reported to be lower with neuraxial anesthesia than with general anesthesia.[2] Neuraxial anesthesia while on antithrombotic therapy carries the risk of spinal epidural hematoma; thus, administration of most anticoagulants or antiplatelet agents should be stopped before neuraxial anesthesia. Preoperative cessation of antithrombotic agents can reduce perioperative bleeding and affect the type of anesthesia administered. However, cessation can exacerbate the underlying comorbidity for the patient taking the medication. Additionally, withholding antithrombotic agents carry the risk of rebound hypercoagulability, and since surgery itself is associated with hypercoagulability, this renders the patient potentially susceptible to thromboembolic events.[3,4]

Currently, the effect of preoperative cessation of antithrombotic agents for TKA on perioperative complication rates is unclear. Thus, we retrospectively evaluated the impact of

discontinuing antithrombotic agents for primary TKA on perioperative complication rates.

2. Methods

After obtaining the approval of the Institutional Review Board of SMG-SNU (Seoul Metropolitan Government Seoul National University) Boramae Medical Center (No. 26–2013–64), patients who underwent elective TKA from January 2008 to December 2012 were retrospectively identified using the electronic medical records from our hospital. Patients with an incomplete medical record were excluded.

Baseline characteristics included age, American Society of Anesthesiologists (ASA) physical status, co-morbidities, history of antithrombotic medication, and type of anesthesia. The following procedure subtypes were also recorded: unilateral TKA, staged bilateral TKA (different operations during the same hospitalization), and simultaneous bilateral TKA (operation on the same day). Perioperative data included intraoperative estimated blood loss, blood transfusion, cardiovascular events (angina, arrhythmia, and myocardial infarction), cerebrovascular events (transient ischemic attack and stroke), thromboembolic events (deep vein thrombosis and pulmonary embolism), and postoperative hospital stay. Postoperative 30-day complications included postoperative bleeding, cardiovascular events (angina, arrhythmia, and myocardial infarction), cerebrovascular events (transient ischemic attack and stroke), thromboembolic events (deep vein thrombosis and pulmonary embolism), respiratory events (pneumonia and pulmonary aspiration), and gastrointestinal events (ileus). The patients were classified into two groups: group A, in whom antithrombotic agents were ceased preoperatively, and group B, wherein patients who had not taken antithrombotic agents according to their recent medical history.

The standard practice for the management of antithrombotic therapy in patients scheduled for TKA at our institution was to cease aspirin or clopidogrel 7 days preoperatively, cilostazol 2 days preoperatively, warfarin or triflusal 5 days preoperatively, limaprost or sarpogrelate 1 day preoperatively, and ticlopidine 10 days preoperatively. For patients who received antiplatelet agents for cardiovascular reasons, such as a history of percutaneous coronary intervention, the cessation of antiplatelet agents was under supervision of cardiologists. Antithrombotic therapy was restarted 2 days after surgery in patients who stopped antithrombotic therapy preoperatively.

The primary outcome was the incidence of postoperative 30-day complications. Secondary outcome included intraoperative estimated blood loss, perioperative blood transfusion, and postoperative hospital stay. Continuous data are expressed as means ± standard deviation (SD), and categorical data as frequencies (%).

Statistical analyses were performed using R, version 3.1.0 (Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/). Categorical variables were analyzed using the chi-square or Fisher exact test, and continuous variables using Student t-test. To reduce the impact of selection bias and potential confounders in an observational study, rigorous adjustment for significant differences in patient characteristics was performed using a multivariable model with the inverse probability of treatment weighting (IPTW).[5] With this method, weights for patients who did not receive antithrombotic agents preoperatively were the inverse of (1 − propensity score) and weights for patients who stopped antithrombotic medication preoperatively were the inverse of the propensity score. Multiple logistic

regression analysis was performed to derive the propensity scores. The following variables were included in the propensity score model: sex, age, body mass index (BMI), presence of underlying diseases (hypertension, diabetes, cardiovascular disease, cerebrovascular disease, renal disease, and others), and procedure subtype. The discrimination of propensity score model was assessed by means of the concordance index. In addition, for more rigorous adjustment to avoid selection bias and confounding effects, the multiple linear or logistic regression analysis was performed with IPTW as the weights and included covariates such as preoperative antithrombotic medication, American Society of Anesthesiologists (ASA) physical status, type of anesthesia, and all pre-specified covariates. A P value less than 0.05 was considered statistically significant.

3. Results

In total, 914 patients underwent primary TKA from January 2008 to December 2012. Twenty-nine patients were excluded owing to an incomplete medical record. Of 885 patients who underwent primary TKA, 218 (24.6%) patients discontinued antithrombotic agents preoperatively (group A), and 667 (75.4%) patients did not receive antithrombotic therapy preoperatively (group B). No patients underwent TKA while maintaining antithrombotic therapy.

Baseline patient data are presented in Table 1. Patients in group A were older ($P < 0.001$), had higher incidences of hypertension ($P < 0.001$), cardiovascular diseases ($P < 0.001$), and cerebrovascular diseases ($P < 0.001$), and presented with higher ASA physical status ($P < 0.001$) than patients in group B. After adjustment by IPTW, there was no significant difference between the two groups with the exception of ASA physical status ($P < 0.001$). The antithrombotic agents used preoperatively are shown in Table 2.

The incidences of postoperative 30-day complications are presented in Table 3. Postoperative cardiovascular complications occurred more frequently in group A compared with group B ($P = 0.035$). However, after adjustment by IPTW, there was no significant difference in the incidence of postoperative cardiovascular complications ($P = 0.083$). Furthermore, the overall incidence of postoperative 30-day complications was not different between the two groups ($P = 0.671$). One patient in group B died postoperatively owing to a gastrointestinal problem.

Clinical outcomes related to the preoperative use of antithrombotic agents are presented in Table 4. Intraoperative estimated blood loss was similar between the two groups ($P = 0.101$); however, patients in group A received transfusions more frequently than patients in group B did ($P = 0.003$). Postoperative hospital stay was similar between the two groups (group A vs. Group B, 21.1 ± 7.8 days vs. 20.9 ± 7.5 days; $P = 0.654$). Additionally, multiple logistic regression analysis with propensity score was performed to adjust for potential confounders including ASA physical status and type of anesthesia in a separate model. Patients in group A received transfusion more frequently (odds ratio [OR], 1.567; 95% confidence interval [CI], 1.227–2.002; $P < 0.001$), while there was no difference between the two groups in the overall likelihood of postoperative 30-day complications (OR, 0.940; 95% CI, 0.532–1.662; $P = 0.831$). Similarly, multiple linear regression analyses with adjustment for all covariates and IPTW as a weight were performed to examine the effect between the two groups. However, the use of preoperative antithrombotic agents did not affect intraoperative blood loss, or postoperative hospital stay.

Table 1

Baseline characteristics of the patients.

	Group A (n=218)	Group B (n=667)	P	Adjusted by IPTW P value
Gender (male/female)	27 (12.39%)	79 (11.84%)	0.831	0.182
Age, y	72.32±6.85	69.89±7.67	<0.001	0.790
Height, cm	152.66±7.75	152.74±7.26	0.886	0.663
Weight, kg	63.12±10.42	61.32±9.99	0.022	0.916
BMI (kg/cm^2)	27.04±3.74	26.24±3.63	0.005	0.681
Hypertension: yes	187 (85.78%)	409 (61.32%)	<0.001	0.306
Diabetes: yes	57 (26.15%)	128 (19.19%)	0.028	0.798
Cardiovascular disease	38 (17.43%)	29 (4.35%)	<0.001	0.863
Peripheral vascular disease	0 (0%)	2 (0.30%)	1.000	0.106
Cerebrovascular disease	31 (14.22%)	34 (5.10%)	<0.001	0.839
Renal disease	5 (2.29%)	7 (1.05%)	0.181	0.385
Others	26 (11.93%)	88 (13.19%)	0.628	0.890
ASA physical status			<0.001	<0.001
1	3 (1.38%)	157 (23.54%)		
2	205 (94.04%)	504 (75.56%)		
3	10 (4.59%)	6 (0.90%)		
Type of anesthesia			0.138	0.051
Spinal	174 (79.82%)	562 (84.26%)		
Spinal-epidural	2 (0.92%)	12 (1.80%)		
General	42 (19.27%)	93 (13.94%)		
Procedure subtypes			0.210	0.688
Unilateral	106 (48.62%)	331 (49.63%)		
Staged bilateral	79 (36.24%)	264 (39.58%)		
Simultaneous bilateral	33 (15.14%)	72 (10.79%)		

Data are expressed as means±SD or numbers of patients (%).

ASA = American Society of Anesthesiologists, BMI = body mass index, Group A = patients who discontinued antithrombotic agents preoperatively, Group B = patients who were not receiving antithrombotic agents preoperatively, IPTW = inverse probability of treatment weighting.

Table 2

Antithrombotic agents used preoperatively.

	Patients (n)
Aspirin	135
Clopidogrel	20
Aspirin + clopidogrel	12
Warfarin	12
Aspirin + warfarin	2
Ticlopidine	1
Triflusal	13
Cilostazol	10
Aspirin + cilostazol	2
Sarpogrelate	8
Aspirin + sarpogrelate	1
Limaprost	2

4. Discussion

The present study shows that patients who discontinued antithrombotic agents before primary TKA do not have a higher incidence of postoperative 30-day complications, including cardiovascular, cerebrovascular, or thromboembolic events, compared with those who were not receiving any antithrombotic agents preoperatively. Intraoperative estimated blood loss was similar in patients who stopped antithrombotic agents preoperatively and those who were not receiving antithrombotic therapy preoperatively. However, the incidence of perioperative transfusion was higher in patients who stopped taking antithrombotic agents preoperatively.

Owing to its significant benefits, TKA utilization has increased over the last 2 to 3 decades.[1,6] Furthermore, as life expectancy increases, the TKA utilization rate is expected to increase continuously.[7] TKA is most commonly performed for

Table 3

Postoperative 30-day complications.

	Group A (n=218)	Group B (n=667)	P	Adjusted by IPTW P value
Cardiovascular	4 (1.83%)	2 (0.30%)	0.035	0.083
Cerebrovascular (TIA/stroke)	3 (1.38%)	2 (0.30%)	0.099	0.090
Thromboembolic (DVT/PE)	3 (1.38%)	8 (1.20%)	0.737	0.499
Respiratory	1 (0.46%)	3 (0.45%)	1.000	0.286
Postoperative bleeding	0 (0%)	0 (0%)	—	—
Gastrointestinal problem	0 (0%)	2 (0.30%)	1.000	0.094
Total	11 (5.05%)	17 (2.55%)	0.067	0.671

DVT = deep vein thrombosis, Group A = patients who discontinued antithrombotic agents preoperatively, Group B = patients who were not receiving antithrombotic agents preoperatively, IPTW = inverse probability of treatment weighting, PE = pulmonary embolism, TIA = transient ischemic attack.

Table 4

Clinical outcomes according to the preoperative use of antithrombotic agents.

| | Group A vs. Group B | | | | |
| | Adjusted by IPTW | | | Adjusted by IPTW and covariates | |
Response variable	Estimate (95% CI)	P		Estimate (95% CI)	P
Postoperative 30-day complication[*]	1.043 (0.615, 1.769)	0.877		0.940 (0.532, 1.662)	0.831
Intraoperative EBL[†]	20.740 (−4.086, 45.566)	0.101		21.838 (−1.126, 44.803)	0.062
Perioperative transfusion[*]	1.359 (1.110, 1.666)	0.003		1.567 (1.227, 2.002)	<0.001
Postoperative hospital day[†]	−0.228 (−1.224, 0.769)	0.654		−0.158 (−1.074, 0.758)	0.735

CI = confidence interval, EBL = estimated blood loss, Group A = patients who discontinued antithrombotic agents preoperatively, Group B = patients who were not receiving antithrombotic agents preoperatively, IPTW = inverse probability of treatment weighting.

[*] Estimate was odds ratio from the logistic regression.

[†] Estimate was coefficient from the linear regression.

osteoarthritis, and for other knee diseases such as rheumatoid arthritis and psoriatic arthritis. Thus, many elderly patients undergo TKA, some of whom receive antithrombotic therapy related to co-morbidities. In the present study, 218 of the 885 (24.6%) patients who underwent primary TKA received antithrombotic agents for co-morbidities. When patients receiving antithrombotic therapy are scheduled for TKA, several factors must be considered, such as the risks associated with cessation or continuation of antithrombotic agents and its effect on the type of anesthesia administered. Neuraxial anesthesia is associated with a lower incidence of perioperative complications, blood transfusion, and mortality rate.[2,8,9] In our institution, TKA is routinely performed as an elective surgery under neuraxial anestheia, unless contraindications for neuraxial anesthesia are present, such as coagulopathy or patient refusal. Thus, 750 of the 885 (84.7%) patients underwent TKA under neuraxial anesthesia. To perform neuraxial anesthesia, cessation of most of the available antithrombotic agents is mandatory to prevent spinal epidural hematoma.[10] Moreover, perioperative antithrombotic therapy can increase perioperative bleeding and transfusion rates.[11,12] However, preoperative cessation of antithrombotic therapy can cause exacerbation of underlying diseases, resulting in thrombosis.[13–15] Currently, no clear guidelines exist regarding the perioperative use of antithrombotic agents. As shown in our data, patients receive antithrombotic agents owing to various diseases. Thus, decision-making regarding preoperative cessation of antithrombotic therapy requires careful consideration of the risks and benefits. Many elderly patients have multiple co-morbidities; therefore, assessment of the risks and benefits in such individuals is more challenging.

Our findings suggest that cessation of antithrombotic agents before TKA may not alter the risk of perioperative complications compared with the normal population. In principle, evaluating the perioperative complications related to the cessation of antithrombotic therapy requires inclusion of patients who maintain perioperative antithrombotic therapy. However, in our institution, TKA is routinely performed as an elective surgery under neuraxial anesthesia after cessation of antithrombotic therapy. Thus, it was not possible to compare perioperative complication rates in patients who discontinued antithrombotic agents preoperatively and those who did not. Thus, we compared patients who stopped antithrombotic medications with those who did not receive antithrombotic agents, specifically with regards to perioperative complications, and performed a statistical adjustment to reduce the effect of selection bias and confounding variables.

Several studies evaluated the perioperative complications according to whether antithrombotic agents were maintained during the procedure. Jacob et al[16] retrospectively investigated the effect of continuing clopidogrel during elective total hip and knee arthroplasty on perioperative complications, and showed that patients who continued clopidogrel were more likely to receive a blood transfusion postoperatively. However, the incidence of 30-day adverse cardiac events was not significantly different compared with patients who discontinued clopidogrel preoperatively. Manaqibwala et al[17] reported that patients on clopidogrel who underwent hip fracture surgery were likely to have significantly longer hospital stays; however, they had a similar rate of bleeding complications compared with patients who stopped clopidogrel preoperatively. In these two studies, considerably fewer patients were on clopidogrel compared with those who stopped clopidogrel preoperatively; however, no statistical adjustment was performed. Furthermore, the type of anesthesia that could also affect postoperative complications was not described. The type of anesthesia used may differ depending on whether clopidogrel was continued.

Guidelines regarding the perioperative management of antithrombotic therapy recommend cessation schedules or bridging therapy owing to the risk of thromboembolism.[18–20] The American Heart Association and American College of Cardiology recommend cessation timing of antiplatelet agents related to the risk of adverse cardiac events. Premature discontinuation of dual antiplatelet therapy is associated with stent thrombosis, myocardial infarction, and mortality in patients with coronary stents. Thus, for patients with coronary stents, elective surgery should be postponed for 4 to 6 weeks (bare-metal stents) or 1 year (drug-eluting stents) if dual antiplatelet therapy must be discontinued.[18] When TKA is planned in patients at high risk of thromboembolism or adverse cardiac events, bridging therapy can be initiated.[19,20] TKA is generally performed as an elective surgery and, as such, scheduling is flexible. The procedure can be postponed until completion of stent endothelialization in patients with coronary stents. In our study, the patients undergoing TKA were in a stable cardiac condition. Thus, preoperative cessation of antithrombotic agents may not have resulted in an increased incidence of perioperative complications compared with the normal population.

In the present study, the incidence of perioperative blood transfusion was higher in patients who stopped antithrombotic agents than in those with no history of antithrombotic therapy, although the estimated intraoperative blood loss was similar. This higher perioperative transfusion rate may be related to the postoperative resumption of antithrombotic therapy.

This study has several limitations. First, data were collected from a single center; hence, the results can not be generalized for other institutions. Furthermore, this study was of a retrospective design, which has inherent weaknesses. Larger prospective studies based on multicenter data are required. Additionally, there was no transfusion protocol to ensure the consistency of decision-making regarding blood transfusion. Thus, surgeons decided the transfusion requirements of the patients on a case-by-case basis. Finally, as only a few patients were receiving each antithrombotic agent, with the exception of aspirin, no subgroup analysis according to the type of antithrombotic agents was performed. Perioperative outcomes following discontinuation of each type of antithrombotic agent should be further evaluated.

In conclusion, patients who discontinued antithrombotic drugs before primary TKA do not have a higher incidence of postoperative 30-day complications, including cardiovascular, cerebrovascular, or thromboembolic events. Moreover, the estimated intraoperative blood loss was not different compared with patients not receiving antithrombotic agents preoperatively. However, larger prospective studies of this issue are required.

Acknowledgments

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