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Original research

Continuing versus discontinuing antiplatelet drugs, vasodilators, and/or cerebral ameliorators on perioperative total blood loss in total knee arthroplasty without pneumatic tourniquet

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ABSTRACT

Background: Although studies have supported the utility of perioperative continuation of antiplatelet drugs, vasodilators, and cerebral ameliorators in most procedures, no study compared total volume of blood loss after total knee arthroplasty (TKA) in patients continuing and discontinuing these drugs.
Methods: We retrospectively reviewed 266 consecutive patients undergoing TKA, and included 67 patients (25.2%) taking antiplatelet drugs, vasodilators, or cerebral ameliorators in this study. All TKAs were performed without a pneumatic tourniquet. The primary outcome was perioperative total blood loss calculated from blood volume and change in hemoglobin. As subgroup analysis, we compared perioperative total blood loss in patients taking antiplatelet drugs.
Results: There was no significant difference between the continuing group ($n = 38$) and discontinuing group ($n = 29$) in terms of the perioperative total blood loss (1025 ± 364 vs 1151 ± 327 mL, respectively; mean difference 126 mL; 95% confidence interval −45 to 298 mL; $P = .15$). No major bleeding or thrombotic events occurred in either group until postoperative 3-month follow-up. In patients taking antiplatelet drugs ($n = 51$), no significant difference was observed in the total blood loss between the continuing group ($n = 30$) and discontinuing group ($n = 21$) (1056 ± 287 vs 1151 ± 305 mL, respectively; mean difference 95 mL; 95% confidence interval −75 to 264 mL; $P = .27$).
Conclusions: No significant differences in terms of perioperative total blood loss were observed between patients continuing and discontinuing study drugs. Continuing these drugs may be preferable in the perioperative period of TKA.
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Introduction

Antiplatelet drugs, vasodilators, or cerebral ameliorators are commonly used in elderly patients in clinical settings [1,2]. Although preoperative discontinuation of these drugs has been recommended to reduce perioperative blood loss, concerns have recently been raised because discontinuation would increase perioperative medical complications [3,4]. A recent review including a number of randomized controlled trials recommended that these drugs should be continued for most procedures except in patients at low risk of cardiovascular events undergoing major surgery and those undergoing high-risk procedures, such as intracranial surgery [5]. Orthopedic surgery is recognized as having intermediate cardiac risk [6], and it remains controversial whether these drugs should be continued or discontinued during the perioperative period for such procedures.

As the number of elderly patients undergoing total knee arthroplasty (TKA) has continued to increase [7], the numbers of patients on antiplatelet drugs, vasodilators, or cerebral ameliorators are also increasing. Blood loss in the perioperative period remains an important concern in TKA [8]. Although the rate of major bleeding events after surgery has been investigated [9], we aware of that there are no studies comparing the volume of perioperative total blood loss after TKA between patients continuing and discontinuing these drugs.

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We investigated whether there were differences in terms of perioperative total blood loss and major bleeding events among patients continuing antiplatelet drugs, vasodilators, or cerebral ameliorators and patients discontinuing these drugs in TKA. The hypothesis of the study was that the volume of perioperative total blood loss would not be different between patients continuing and discontinuing these study drugs.

Materials and methods

This retrospective comparative study was conducted at a single orthopaedic clinic. The study protocol and publication were approved by the ethics committee.

Consecutive patients undergoing TKA between May 2013 and April 2015 were identified based on a review of our institutional database. All medical records of patients undergoing TKA were reviewed and patients taking antiplatelet drugs, vasodilators, or cerebral ameliorators were identified. During the study period, when patients taking antiplatelet drugs, vasodilators, or cerebral ameliorators were scheduled to undergo TKA, we routinely consulted the primary physician of internal medicine who prescribed the drug regarding whether the drug could be discontinued preoperatively. When discontinuation was allowed, the drug was discontinued preoperatively and restarted 1 day after TKA. We instructed the patients in the period of drug discontinuation as summarized in Table 1. The drugs were continued in cases where continuation was recommended by the primary physician of internal medicine.

The inclusion criteria were patients undergoing TKA and taking antiplatelet drugs, vasodilators, and/or cerebral ameliorators. Patients taking anticoagulating drugs were excluded because they received heparin bridging therapy. Patients taking antiplatelet drugs, vasodilators, and/or cerebral ameliorators who were recommended by the primary physician of internal medicine to receive heparin bridging therapy were also excluded. In addition, patients with severe deformity of the knee joint, for example, due to a history of osteomyelitis or severe trauma, were excluded. Patients who could not be followed up for 3 months were excluded because a follow-up period of more than 1 month would be required to assess major bleeding or thrombotic events [6,10,11].

Outcomes

Primary outcome

The primary outcome of this study is the perioperative total blood loss in TKA. We calculated the total volume of blood using the calculated blood volume and change in hemoglobin from preoperative to postoperative day 4 [12].

Table 1
Days of study drug discontinuation prior to total knee arthroplasty.

Agent	Days of discontinuation
Antiplatelet drug	
Aspirin	7
Clopidogrel	10
Ticlopidine	7
Cilostazol	3
Ethyl icosapentate	7
Beraprost	1
Sarpogrelate	1
Vasodilator	
Limaprost alfadex	1
Kallidinogenase	2
Dipyridamole	2
Cerebral ameliorator	
Nicergoline	2
Ifenprodil	2
Ibudilast	2

First, the blood volume of the patient in liters was calculated using the formula of Nadler et al [13] as follows:

$$\text{Blood volume} = \left(k1 \times \text{height } [\text{m}]^3\right) + (k2 \times \text{body weight } [\text{kg}]) + k3$$

where k1 = 0.3669 for male patients and 0.3561 for female patients; k2 = 0.03219 for male patients and 0.03308 for female patients; and k3 = 0.6041 for male patients and 0.1833 for female patients.

Second, the loss of hemoglobin was estimated according to the following formula:

$$\text{Hb}_{\text{loss}} = \text{blood volume} \times (\text{Hb}_{\text{i}} - \text{Hb}_{\text{e}}) \times 0.001 + \text{Hb}_{\text{t}}$$

Hb_{loss} (g) is the amount of hemoglobin lost up to day 4 after surgery; Hb_i (g/L) is the hemoglobin concentration before surgery; Hb_e (g/L) is the hemoglobin concentration on day 4 after surgery; and Hb_t (g/L) is the amount of hemoglobin transfused.

Finally, the total blood loss was calculated as follows [12]:

$$\text{Total blood loss}(\text{mL}) = 1000 \times \text{Hb}_{\text{loss}}/\text{Hb}_{\text{i}}$$

Secondary outcomes

Secondary outcomes of the study were intraoperative blood loss, rate of blood transfusion, major bleeding events, and major thrombotic events.

Intraoperative blood loss was calculated as the sum of the blood aspirated into the suction canisters and weighing gauzes.

Major bleeding events were defined as (1) cerebral hemorrhage, (2) intra- or retroperitoneal hemorrhage documented by computed tomography scan, (3) bleeding requiring an intervention (ie, surgical reoperation, endovascular embolization, or endoscopic intervention), and (4) bleeding requiring 3 U of red blood cells [11]. Major thrombotic events were defined as (1) stroke, (2) transient ischemic attack, (3) acute coronary syndrome, (4) peripheral arterial ischemia, (5) mesenteric arterial ischemia, (6) deep proximal and distal venous thrombosis based on clinical symptoms, and (7) pulmonary embolism [11].

Subgroup analyses

We planned subgroup analyses for patients taking antiplatelet drugs. In patients taking antiplatelet drugs, we compared the volumes of perioperative total blood loss and intraoperative blood loss, the rate of blood transfusion, major bleeding events, and major thrombotic events.

Surgery and postoperative treatment

All surgeries were performed by one of the 2 surgeons (S.T. and M.W.). Neither a pneumatic tourniquet nor drain was used in any of the patients undergoing TKA during the study period. A subvastus approach was used in all surgeries except in patients with valgus knees, for whom a lateral approach was used. All patients received a cemented, posterior stabilized prosthesis (Scorpio NRG; Stryker Orthopaedics, Mahwah, NJ).

We administered 1 g of tranexamic acid intravenously (Transamin; Daiichi Sankyo, Tokyo, Japan) just prior to skin incision and again at 6 hours after the first administration.

We subcutaneously administered 1.5 or 2.5 mg of fondaparinux (Arixtra; GlaxoSmithKline, Tokyo, Japan) for thromboprophylaxis once every evening for 10 days, starting from postoperative day 1. The dosage was determined based on the renal function and body weight.

For postoperative pain control, intraoperative periarticular injection including ropivacaine, morphine, epinephrine, ketoprofen, and/

or corticosteroid was performed [14,15]. From the day after surgery, oral nonsteroidal anti-inflammatory drug (60 mg of loxoprofen, Surinofen; Aska, Tokyo, Japan) was administered 3 times a day.

An intravenous cefazolin (Cefamezin; Astellas, Tokyo, Japan) was administered perioperatively and every 8 hours for the first 48 hours after surgery.

Sample size

We considered that a 350-mL decrease in perioperative total blood loss would be clinically meaningful with regard to discontinuation of the drugs. We calculated that with a sample of 56 patients (28 patients per treatment group), the study would have 90% power to detect a 350-mL mean decrease in perioperative total blood loss, at a type I error of 5%. For power analysis, we used a standard deviation of 400 mL in the perioperative total blood loss for the preliminary data in postoperative unilateral TKA patients [14].

Statistical analyses

For the primary outcome, the differences in mean perioperative total blood loss and 95% confidence intervals were calculated with Student's *t* test. A 2-sided $P < .05$ was considered statistically significant. To clarify whether there was difference between 2 surgeons, the mean perioperative total blood loss was also compared between 4 groups (continuing group operated by S.T., discontinuing group operated by S.T., continuing group operated by M.W., and discontinuing group operated by M.W.) by one-way analysis of variance.

The differences in mean intraoperative blood loss and 95% confidence intervals were also compared with Student's *t* test. Outcomes and baseline demographic were compared using Student's *t* test for continuous variables and the chi-squared test for categorical variables, respectively.

All statistical analyses were performed with R (The R Foundation for Statistical Computing) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [16].

Results

A total of 266 TKAs were screened for eligibility. After excluding 199 TKAs, the remaining 67 TKAs were included in the study (Fig. 1). A total of 189 patients taking no antiplatelet drugs, vasodilators, cerebral ameliorators, or anticoagulant drugs; 8 patients taking anticoagulant drugs, 1 patient who underwent heparin bridging therapy after discontinuing antiplatelet drug; and 1 patient with a history of osteomyelitis around the knee joint were excluded. All 67 TKAs were followed up over 3 months.

Thirty-eight TKAs were performed with continuation of drugs, and drugs were discontinued in the remaining 29 TKAs. Table 2 summarizes the demographic characteristics of the patients in the 2 groups. The duration of the operation was significantly longer in the continuing group compared with the discontinuing group (90.7 ± 10.6 vs 83.8 ± 9.1 minutes, respectively, $P = .0065$).

In the continuing group, study drugs were prescribed for cerebrovascular ischemia in 20 patients, ischemic heart disease in 8 patients, atrial fibrillation in 5 patients, lower limb peripheral vascular disease in 4 patients, and lumbar spinal canal stenosis in 1 patient. In the discontinuing group, study drugs were prescribed for

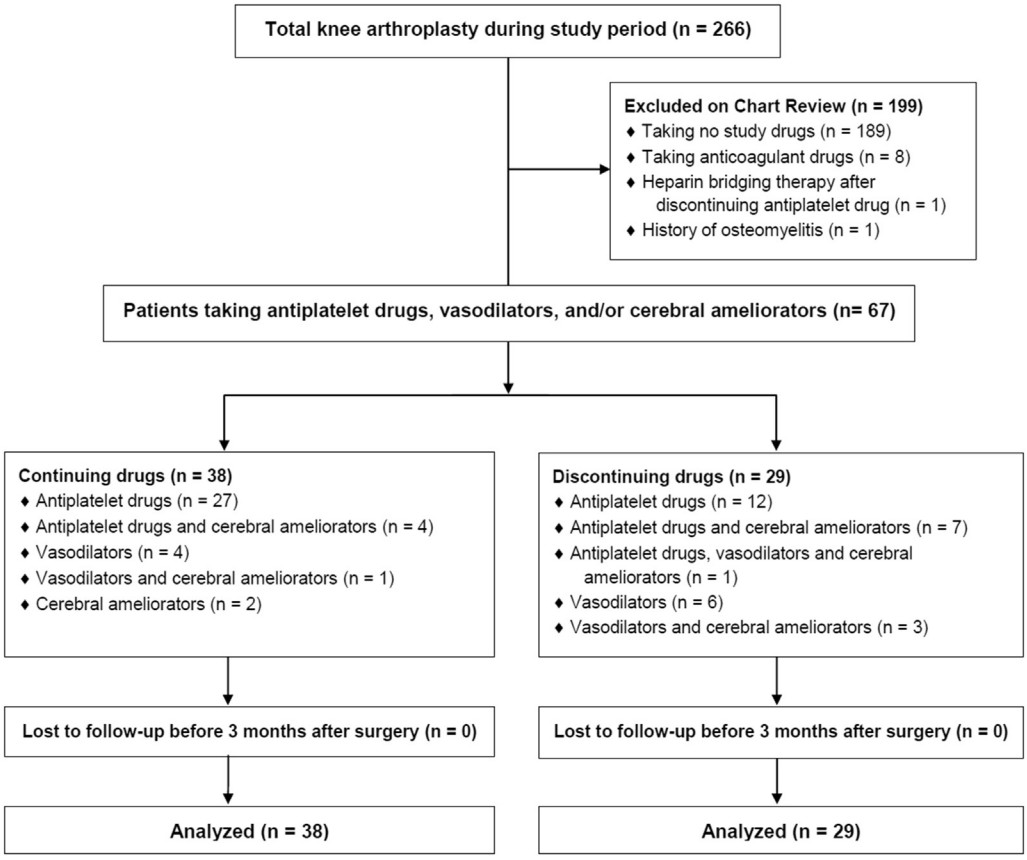

Figure 1. Participant flow chart.

Table 2
Patient demographic and baseline clinical characteristics.

Variable	Continuing group ($n = 38$)	Discontinuing group ($n = 29$)	P value
Age (y)	78.3 ± 6.9	78.0 ± 6.5	.86[a]
Sex (female/male)	29/9	27/2	.07[b]
Height (cm)	149.6 ± 8.2	149.0 ± 5.6	.72[a]
Weight (kg)	60.3 ± 11.4	58.3 ± 8.2	.42[a]
Body mass index (kg/m^2)	26.9 ± 4.3	26.3 ± 3.2	.50[a]
Preoperative diagnosis (OA/RA/AVN)	37/0/1	26/2/1	.25[b]
History of diabetes mellitus (yes/no)	12/26	7/22	.50[b]
Preoperative hemoglobin (g/mL)	12.9 ± 1.5	12.6 ± 1.3	.43[a]
Surgical approach (subvastus/lateral)	38/1	29/0	.25[b]
Duration of operation (min)	90.7 ± 10.6	83.8 ± 9.1	.0065[a]

AVN, avascular necrosis; OA, osteoarthritis; RA, rheumatoid arthritis.
Results are expressed as means ± standard deviation, unless otherwise stated.
[a] P-values were determined with Student's t test.
[b] P-values were determined with χ^2 test.

Table 3
Demographic and baseline clinical characteristics of patients taking antiplatelet drugs.

Variable	Continuing group ($n = 31$)	Discontinuing group ($n = 20$)	P value
Age (y)	77.7 ± 6.9	79.0 ± 6.6	.52[a]
Sex (female/male)	23/8	19/1	.057[b]
Height (cm)	150.1 ± 7.3	149.9 ± 5.8	.92[a]
Weight (kg)	61.4 ± 10.9	57.6 ± 8.9	.21[a]
Body mass index (kg/m^2)	27.2 ± 4.6	25.6 ± 3.0	.15[a]
Preoperative diagnosis (OA/RA/AVN)	31/0/0	17/2/1	.085[b]
History of diabetes mellitus (yes/no)	11/20	6/14	.69[b]
Preoperative hemoglobin (g/mL)	12.7 ± 1.7	12.4 ± 1.5	.65[a]
Surgical approach (subvastus/lateral)	30/1	20/0	.42[b]
Duration of operation (min)	91.8 ± 10.8	84.7 ± 9.7	.020[a]

AVN, avascular necrosis; OA, osteoarthritis; RA, rheumatoid arthritis.
Results are expressed as means ± standard deviation, unless otherwise stated.
[a] P-values were determined with Student's t test.
[b] P-values were determined with χ^2 test.

cerebrovascular ischemia in 15 patients, ischemic heart disease in 5 patients, lower limb peripheral vascular disease in 8 patients, and lumbar spinal canal stenosis in 1 patient.

Primary outcome

The perioperative total blood loss was 1024.5 ± 363.8 mL in the continuing group versus 1150.6 ± 326.6 mL in the discontinuing group. There was no significant difference between the 2 groups in primary outcome of this study (mean difference 126.1 mL; 95% confidence interval −45.4 to 297.6 mL; $P = .15$).

There were no differences between 2 surgeons in the comparison between 4 groups: the amount of perioperative total blood loss in the continuing group operated by S.T., discontinuing group operated by S.T., continuing group operated by M.W., and discontinuing group operated by M.W. was 1050.0 ± 349.3, 1156.0 ± 390.3, 1020.3 ± 275.0, and 1068.4 ± 360.0 mL, respectively ($P = .76$).

Secondary outcome

In terms of intraoperative blood loss, there was no difference between the continuing group and discontinuing group (210.4 ± 134.8 vs 235.7 ± 138.3 mL, respectively; mean difference 25.3; 95% confidence interval −41.8 to 92.5 mL; $P = .45$).

No patients in the continuing group and 2 patients (7.1%) in the discontinuing group had blood transfusion ($P = .09$).

Neither major bleeding events nor major thrombotic events occurred in either group.

In the continuing group, 1 patient experienced superficial infection and 1 patient experienced delayed healing of the surgical site.

Subgroup analysis

A total of 51 TKAs were identified for subgroup analyses for patients taking antiplatelet drugs. Thirty-one TKAs were performed with continuation of antiplatelet drugs, and 20 TKAs with discontinuation of antiplatelet drugs. Table 3 summarizes the demographic characteristics of the patients in the 2 groups.

The perioperative total blood loss was 1056.4 ± 287.2 mL in the continuing group versus 1151.1 ± 305.2 mL in the discontinuing group. No significant difference was observed between the 2 groups (mean difference 94.7 mL; 95% confidence interval −74.9 to 264.4 mL; $P = .27$).

The intraoperative blood loss was 211.6 ± 111.4 mL in the continuing group versus 211.3 ± 125.4 mL in the discontinuing group. There was no significant difference between the groups (mean difference 0.4 mL; 95% confidence interval −67.1 to 67.8 mL; $P = .99$).

Discussion

The differences in the volume of perioperative blood loss between continuation and discontinuation of antiplatelet drugs, vasodilators, or cerebral ameliorators have not been investigated in the perioperative period of TKA. Our study showed that there were no differences in terms of perioperative total blood loss among patients continuing antiplatelet drugs, vasodilators, and/or cerebral ameliorators and those discontinuing these drugs. In addition, subgroup analyses excluding patients taking only vasodilators or cerebral ameliorators showed similar results.

Our study had a number of limitations. In this study, patients continuing study drugs were those who were instructed to continue the drugs by the primary physician of internal medicine. Thus, patients in the continuing group may have been at higher risk than those in the discontinuing group. Comparison of the volume of blood loss was reasonable in our study; however, comparison of the rates of major bleeding events and major thrombotic events would be biased.

Different drugs were included in this study, and the distribution of drugs was not completely the same between the continuing and discontinuing groups. We should note that more restricted allocation was optimal to conclude the research question of this study more rigidly.

The surgeon was not blinded to the groups due to the retrospective nature of this study. Information regarding continuation of study drugs could provide a warning to the surgeon. The lack of blinding design can lead to exaggerated estimates of treatment effect [17]. However, the surgeons recognize continuation or discontinuation of the study drugs in practice, and the greater similarity to standard clinical practice could make the results more easily applicable in routine medical care [18]. We believe that our study would provide useful information despite the lack of blinding.

The setting of our study was a specialized clinic for knee and hip surgery. The study included only 2 surgeons. Therefore, care should be taken in generalizing our results to other clinical settings.

We routinely used tranexamic acid during the study period. Although no studies have confirmed that the use of tranexamic acid increases thrombotic events, it should be noted that a few studies have investigated thrombotic risk in high-risk patients for cardiac events [19,20].

Major bleeding events are among the most important concerns regarding continuation of study drugs. Our study fulfilled the sample size for primary outcome, but not for major bleeding events due to the low frequency. Two randomized controlled trials investigated perioperative bleeding complications. Oscarsson et al [6] compared the effects of 75 mg of aspirin with placebo in high-risk patients undergoing noncardiac surgery, and concluded that perioperative aspirin reduced the risk of major adverse cardiac events without increasing bleeding complications. Mantz et al [11] compared the effects of perioperative treatment with discontinuation of 75 mg of aspirin starting 10 days before surgery with placebo, and concluded that there were no differences in terms of the occurrence of major thrombotic or bleeding events. These findings supported the results of our study.

Previous studies revealed that withdrawal of study drugs, especially antiplatelet drugs, could represent a risk for occurrence of complications [1,3]. We believe that continuing antiplatelet drugs, vasodilators, and/or cerebral ameliorators may be preferable in the perioperative period of TKA because this study showed that continuation of these drugs had no influence on perioperative blood loss in TKA.

Conclusions

In a nonrandomized comparative study, total blood loss did not differ significantly among patients continuing and discontinuing antiplatelet drugs, vasodilators, and/or cerebral ameliorators in the perioperative period of TKA without pneumatic tourniquet.

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