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A Strategy of Continued Antiplatelet Agents, Vitamin K Antagonists, and Direct Oral Anticoagulants Throughout the Perioperative Period of Total Knee Arthroplasty in Patients Receiving Chronic Antithrombotic Therapy

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Background: Although continuing antithrombotic therapy is desirable to prevent perioperative cardiovascular and cerebrovascular diseases, perioperative blood loss remains a concern in patients undergoing total knee arthroplasty. The purpose of this study was to assess the impact of continuing chronic antithrombotic therapy on blood loss and major bleeding events.

Methods: We classified 201 consecutive patients undergoing total knee arthroplasty into 2 groups: (1) patients taking antiplatelet agents, vitamin K antagonists, and/or direct oral anticoagulants, referred to as the continuing antithrombotic therapy group (n = 32); and (2) patients not receiving these agents, referred to as the no antithrombotic therapy group (n = 169). During the study period, antithrombotic agents were continued perioperatively in all patients receiving antithrombotic therapy. Surgical procedures were performed without the use of a pneumatic tourniquet or drain. Screening for deep vein thrombosis was routinely performed before and after total knee arthroplasty. The total perioperative blood loss was calculated from blood volume and change in hemoglobin from preoperatively to postoperative days 1, 3, and 7.

Results: The perioperative blood loss after total knee arthroplasty did not differ significantly between the continuing antithrombotic therapy group and the no antithrombotic therapy group at 1 day postoperatively (448 ± 213 compared with 495 ± 345 mL [95% confidence interval (CI) of the difference, −172 to 77 mL]; p = 0.45), 3 days postoperatively (841 ± 308 compared with 826 ± 328 mL [95% CI, −108 to 139 mL]; p = 0.81), and 7 days postoperatively (855 ± 313 compared with 861 ± 245 mL [95% CI, −122 to 108 mL]; p = 0.91). No patients in the continuing antithrombotic therapy group and 2 patients (1.2%) in the no antithrombotic therapy group had allogeneic blood transfusion (p = 1). No major bleeding events occurred in the continuing antithrombotic therapy group.

Conclusions: Perioperative blood loss in patients continuing chronic antithrombotic therapy during total knee arthroplasty was not significantly different from that in patients receiving no chronic antithrombotic therapy.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

The management of chronic antithrombotic therapy using antiplatelet agents, vitamin K antagonists, or direct oral anticoagulants in the perioperative setting is a common problem in total knee arthroplasty[1,2]. Chronic antithrombotic therapy is essential for some patients with cardiovascular and cerebrovascular diseases[3]. However, balancing the risk of excessive bleeding due to continued treatment and thrombotic risk when discontinued remains an important concern[1].

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A systematic review and meta-analysis supported continuing antiplatelet agents in surgical procedures with low bleeding risk[4]. However, the bleeding risk due to continuing antiplatelet agents remains controversial during the perioperative period for total knee arthroplasty[5-7]. There has been a paucity of studies investigating the impact of continuing vitamin K antagonists and direct oral anticoagulants. Bridging therapy with heparin had been recommended for patients undergoing a surgical procedure[1,8]. However, in some types of surgical procedures, a strategy of continuing anticoagulants was associated with preferable postoperative results[9-11].

A strategy of continuing chronic antithrombotic therapy has been used for patients undergoing total knee arthroplasty in our department. This current study was performed to assess the impact of continuing chronic antithrombotic therapy on perioperative total blood loss and bleeding complications in total knee arthroplasty.

Materials and Methods

The study was performed at the Adult Knee Reconstruction Division of a single general hospital (Hokusuikai Kinen Hospital). The study protocol and publication were approved by the local ethics committee.

We reviewed patients recruited by 1 treating surgeon to undergo total knee arthroplasty between January 2015 and December 2017 in our department. Antithrombotic agents, including antiplatelet agents, vitamin K antagonists, and direct oral anticoagulants, were continued perioperatively in all patients receiving such agents during the study period.

Patients undergoing primary total knee arthroplasty were included in this study. The exclusion criteria were patients undergoing staged bilateral total knee arthroplasty with an interval of <6 months between the knees for a staged bilateral surgical procedure, patients undergoing a single-anesthetic bilateral total knee arthroplasty, and patients undergoing single-anesthetic total knee arthroplasty and total hip arthroplasty.

The 201 included patients were classified into 2 groups: (1) patients receiving chronic antithrombotic therapy with antithrombotic agents, including antiplatelet agents, vitamin K antagonists, and/or direct oral anticoagulants, referred to as the continuing antithrombotic therapy group (n = 32); and (2) patients not taking such agents, referred to as the no antithrombotic therapy group (n = 169).

Perioperative Medication

Chronic antithrombotic therapy with antithrombotic agents, including antiplatelet agents, vitamin K antagonists, and direct oral anticoagulants, was continued during the perioperative period, including the day of the surgical procedure.

Antibiotic prophylaxis with 1 g of Cefamezin (cefazolin; Astellas) was administered intravenously perioperatively.

For both the continuing antithrombotic therapy group and the no antithrombotic therapy group, 1 g of Transamin (tranexamic acid; Daiichi-Sankyo) was administered intravenously just prior to skin incision.

We performed the intraoperative periarticular injection with a solution consisting of 300 mg of ropivacaine, 8 mg of morphine, 40 mg of methylprednisolone, 50 mg of ketoprofen, and 0.3 mg of epinephrine[12].

All patients received 4 mg of the oral nonsteroidal anti-inflammatory drug, Lorcam (lornoxicam; Taisho Toyama), 3 times a day.

No thromboprophylaxis was routinely used to prevent venous thromboembolism.

Anesthesia and Surgical Procedure

All patients were managed with general anesthesia by board-certified anesthesiologists. Anesthesia was induced using the short-acting volatile anesthetic, Sevofrane (sevoflurane; Maruishi), and the intravenous anesthetic, Diprivan (propofol; AstraZeneca), and was maintained with sevoflurane and a continuous infusion of the short-acting opioid, Ultiva (remifentanil; Janssen)[12]. Intravenous fentanyl citrate was used as supplementation when required[12]. Although a clear target threshold of intraoperative blood pressure was not determined, anesthesiologists controlled intraoperative blood pressure for each patient to balance intraoperative bleeding risk with high blood pressure and ischemic risk with low blood pressure.

All total knee arthroplasties were performed or were supervised by 1 surgeon using a cemented, posterior-stabilized prosthesis. No pneumatic tourniquet was used during the study period. No drain was placed for any of the patients.

Blood Management Strategies

We did not use any predeposited autologous transfusion or intraoperative blood salvage techniques for the patients included in the study. We planned additional allogeneic blood transfusion for patients who had a hemoglobin level of <7.0 g/dL and were asymptomatic or patients who had a hemoglobin level of <10.0 g/dL and had symptoms related to anemia[13].

Preoperative and Postoperative Screening for Deep Vein Thrombosis

As routine preoperative laboratory testing, the plasma D-dimer level was measured in all patients scheduled for total knee arthroplasty. Patients with a plasma D-dimer level of >0.5 μg/mL were routinely tested for deep vein thrombosis by skilled clinical laboratory technicians using ultrasonography.

At 1 day after total knee arthroplasty, all patients were screened for the presence of deep vein thrombosis by ultrasonography. At 7 days after the total knee arthroplasty, patients were screened using the clinical model of Wells et al.[14], and those with a score of ≥3 were again tested by ultrasonography. These measurements were performed during hospitalization because the current Japanese universal health insurance system allows >7 days of hospitalization for patients undergoing total knee arthroplasty.

Primary Outcome

The primary outcome was the volume of perioperative blood loss, which was measured using the calculated blood

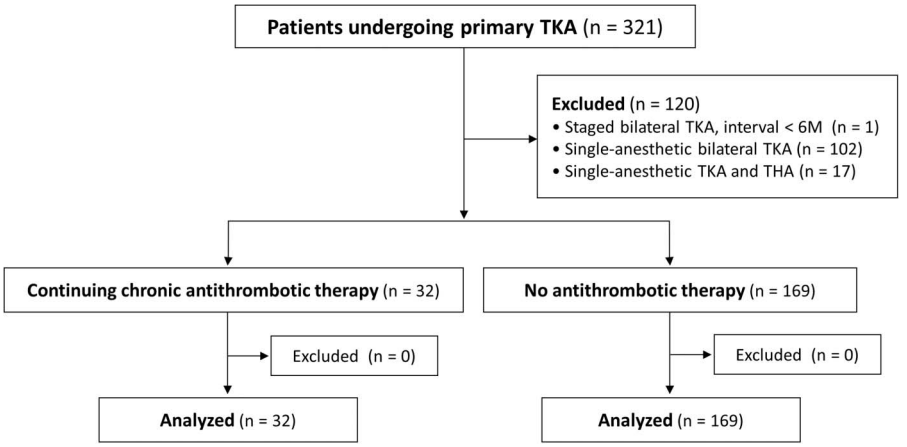

Fig. 1

Participant flowchart. Antithrombotic therapy was not interrupted during the study period in patients receiving chronic antithrombotic therapy with antiplatelet agents, vitamin K antagonists, and/or direct oral anticoagulants. TKA = total knee arthroplasty, M = months, and THA = total hip arthroplasty.

volume and change in hemoglobin from preoperatively to postoperative days 1, 3, and 7[15,16]. The blood volume of each patient was calculated using the formula reported by Nadler et al.[16].

Secondary Outcomes

Intraoperative blood loss was compared between the continuing antithrombotic therapy group and the no antithrombotic therapy group. The number of patients requiring allogeneic blood

TABLE I Patient Demographic and Baseline Clinical Characteristics

Characteristics	Continuing Antithrombotic Therapy (N = 32)	No Antithrombotic Therapy (N = 169)	P Value
Age* *(yr)*	80 ± 6	74 ± 9	<0.001†
Sex‡			0.51§
Female	22	127	
Male	10	42	
Height* *(cm)*	153 ± 7	153 ± 9	0.96†
Weight* *(kg)*	60.8 ± 9.5	61.0 ± 11.9	0.92†
Body mass index* *(kg/m^2)*	26.0 ± 3.4	26.1 ± 4.4	0.88†
Preoperative diagnosis‡			0.43§
Osteoarthritis	30	147	
Rheumatoid arthritis	0	11	
Osteonecrosis	2	11	
History of diabetes mellitus‡			0.18§
Yes	8	24	
No	24	145	
Preoperative hemoglobin* *(g/dL)*	13.1 ± 1.0	12.9 ± 1.3	0.24†
Preoperative knee flexion angle* *(deg)*	123 ± 12	119 ± 17	0.27†
Preoperative knee extension angle* *(deg)*	−10 ± 5	−11 ± 8	0.83†
Duration of operation* *(min)*	100 ± 16	100 ± 14	0.88†
Deep vein thrombosis detected by preoperative screening‡			0.58§
Yes	1	4	
No	31	165	

*The values are given as the mean and the standard deviation. †Student t test. ‡The values are given as the number of patients. §Chi-square test.

TABLE II Medication Used for Antithrombotic Therapy

1. Antiplatelets (n = 22)
   1A. Single agent for antiplatelet therapy (n = 18)
      Aspirin (n = 9)
      Cilostazol (n = 4)
      Clopidogrel (n = 2)
      Ethyl icosapentate (n = 2)
      Beraprost (n = 1)
   1B. Combination antiplatelet therapy (n = 4)
      Aspirin and cilostazol (n = 1)
      Aspirin and ticlopidine hydrochloride (n = 1)
      Cilostazol and clopidogrel (n = 1)
      Clopidogrel and sarpogrelate (n = 1)
2. Vitamin K antagonist (n = 3)
   Warfarin (n = 3)
3. Direct oral anticoagulants (n = 6)
   Dabigatran (n = 3)
   Rivaroxaban (n = 2)
   Apixaban (n = 1)
4. Antiplatelet and direct oral anticoagulant (n = 1)
   Rivaroxaban and cilostazol (n = 1)

transfusion was recorded. Bleeding and thrombotic events up to 3 months after total knee arthroplasty were also investigated with special reference to deep vein thrombosis.

Sample Size Calculation and Statistical Analysis

We used the following parameters to calculate the sample size: an overall 2-sided significance level of 0.05, 80% power, a between-group difference for the change in the mean perioperative calculated blood loss score of 200 mL, and a within-group standard deviation of 287 mL. Using these parameters, we estimated that 33 patients would be needed per group. As the minimum unit of allogeneic transfusion was made from 200 mL of whole blood in Japan, we considered a 200-mL difference to be a reasonable estimate of the minimal clinically important difference with respect to perioperative blood loss. The standard deviation of 287 was based on estimates of variability from our prior work in which the perioperative calculated blood loss was compared between patients with and without antiplatelet agents, in whom total knee arthroplasty was performed under lumbar anesthesia without the use of a pneumatic tourniquet[6].

The differences in the mean value and the 95% confidence interval (CI) were analyzed with the unpaired Student t test for comparison of perioperative total blood loss between groups. Although we planned to exclude participants with missing data with regard to the primary outcome from the analysis, the primary outcome data were available for all participants included in this study.

The unpaired Student t test was used to assess continuous variables, and the chi-square test was used to compare categorical variables.

All statistical tests were performed at a 2-sided 5% significance level.

Results

A total of 321 patients were screened for eligibility. We excluded 1 patient who underwent staged bilateral total knee arthroplasty with a 3-month interval, 102 patients who underwent single-anesthetic bilateral total knee arthroplasty, and 17 patients who underwent single-anesthetic total knee arthroplasty and total hip arthroplasty. The remaining 201 patients were included in the study (Fig. 1). Data with regard to the primary outcome were available for all 201 patients, and these patients were followed for >3 months.

Of the 201 patients, 32 (15.9%) received chronic antithrombotic therapy, and 169 did not. Table I summarizes the demographic characteristics of the patients in the 2 groups. The agents administered to the 32 patients receiving chronic antithrombotic therapy are shown in Table II.

The calculated perioperative total blood loss is shown in Table III. There were no significant differences in perioperative total blood loss between the 2 groups.

The intraoperative blood loss (and standard deviation) was 178 ± 127 mL in the continuing antithrombotic therapy group and 172 ± 103 mL in the no antithrombotic therapy group. The difference between the groups was not significant (95% CI, −35 to 47 mL; p = 0.78).

No patients in the continuing antithrombotic therapy group and 2 patients (1.2%) in the no antithrombotic therapy group required blood transfusion (p = 1).

Postoperative deep vein thrombosis screening using a pulse-wave Doppler ultrasound system indicated that 1 patient

TABLE III Perioperative Total Blood Loss Calculated from Blood Volume and Change in Hemoglobin

	Continuing Antithrombotic Therapy* (N = 32)	No Antithrombotic Therapy* (N = 169)	95% CI of the Difference *(mL)*	P Value
Postoperative day 1	448 ± 213	495 ± 345	−172 to 77	0.45†
Postoperative day 3	841 ± 308	826 ± 328	−108 to 139	0.81†
Postoperative day 7	855 ± 313	861 ± 245	−122 to 108	0.91†

*The values are given as the mean and the standard deviation in milliliters. †Student t test.

(3.1%) in the continuing antithrombotic therapy group and 17 patients (10.1%) in the no antithrombotic therapy group had deep vein thrombosis (p = 0.32). No symptomatic pulmonary embolism was observed.

With regard to major bleeding complications, 1 patient in the no antithrombotic therapy group had subarachnoid hemorrhage at 4 weeks after the total knee arthroplasty. This was the only bleeding complication in either group.

Discussion

A strategy of continuing antiplatelet agents, vitamin K antagonists, and direct oral anticoagulants during total knee arthroplasty was not associated with increasing perioperative blood loss in patients receiving chronic antithrombotic therapy. Moreover, the rate of required allogeneic blood transfusion did not differ between patients continuing chronic antithrombotic therapy and those with no antithrombotic therapy.

The amount of perioperative blood loss was not significantly different between patients with continuing chronic antithrombotic therapy and patients not receiving antithrombotic therapy in this study. Although postoperative bleeding is one of the most important concerns in the decision whether to continue chronic antithrombotic therapy[1], the amount of blood loss has not been well investigated in total knee arthroplasty. With regard to antiplatelet agents, 2 previous studies measured total blood loss in patients undergoing total knee arthroplasty. These 2 studies included patients taking aspirin and compared perioperative blood loss between patients continuing and discontinuing antiplatelet use. Meier et al. reported that there were no significant differences in perioperative blood loss between 17 patients continuing aspirin and 79 patients discontinuing aspirin[5]. Tsukada and Wakui reported that there was no significant difference in perioperative blood loss between 31 patients continuing several types of antiplatelet agents and 20 patients discontinuing these agents[6]. To our knowledge, there have been no studies quantifying total blood loss after total knee arthroplasty in relation to the continued use of anticoagulants, including vitamin K antagonists and direct oral anticoagulants. Our current study suggested that continuing chronic antithrombotic therapy using anticoagulants would not be associated with blood loss in the setting of individually controlled blood pressure during total knee arthroplasty without pneumatic tourniquet use.

This study had several limitations. We retrospectively reviewed consecutive patients who underwent total knee arthroplasty and classified these patients into 2 groups according to whether they had received chronic antithrombotic therapy. The surgeons and anesthesiologists were aware of whether the study subjects had received chronic antithrombotic therapy. A double-blinded randomized controlled study, in which patients with chronic antithrombotic therapy are allocated to continuing the anticoagulation or receiving a placebo, would be preferable to strictly investigate the impact of continued chronic antithrombotic therapy on perioperative blood loss.

Although this current study fulfilled the sample size required to compare perioperative blood loss between the group continuing chronic antithrombotic therapy and the group with no antithrombotic therapy, the number of patients was too small to assess the impact of continuing chronic antithrombotic therapy on the occurrence of thrombotic events. For example, although the results of our study showed a possibility of a decreased risk of deep vein thrombosis in the continuing antithrombotic therapy group (1 [3.1%] of 32 patients in the continuing antithrombotic therapy group and 17 [10.1%] of 169 patients in the no antithrombotic therapy group), the difference was not significant.

Our study patients did not receive thromboprophylaxis. The lengths of hospital stays in our study were longer than those in North America and Europe, which may delay postoperative ambulation. These are possible reasons for the high rate of deep vein thrombosis in our study, in which 18 (9.0%) of 201 patients developed deep vein thrombosis. One study using the National Inpatient Sample of the United States showed that the rate of patients who developed deep vein thrombosis was 0.45% in 2011[17]. We should note that this current single-center study also had other specific features, including surgical procedures without a pneumatic tourniquet and the routine use of intravenous tranexamic acid, that could affect the amount of perioperative blood loss.

In our study, the continuing antithrombotic therapy group included patients who received different types of anticoagulation treatment such as single antiplatelet therapy, dual antiplatelet therapy, single anticoagulant therapy, and combined antiplatelet and anticoagulant therapy. The anticoagulation mechanism differs between types of anticoagulation treatment. Moreover, types of anticoagulation treatment were determined based on the pathologic condition of each patient. Caution is required in interpretation of the results of our study because these heterogeneities can affect the study results.

Our results suggest that the strategy of continuing chronic antithrombotic therapy may be one option for patients who are receiving chronic antithrombotic therapy and are scheduled for total knee arthroplasty. We believe that this strategy would reduce the risk of thrombotic events compared with the interruption of chronic antithrombotic therapy prior to the surgical procedure.

In conclusion, the calculated perioperative blood loss did not significantly increase in the continuing antithrombotic therapy group compared with the no antithrombotic therapy group in the postoperative period after total knee arthroplasty. A strategy of continuation of antiplatelet agents, vitamin K antagonists, and direct oral anticoagulants may be an alternative for patients receiving chronic antithrombotic therapy during total knee arthroplasty. ■

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