Clinical Assessment of Postoperative Anemia Associated with Edoxaban in Patients Undergoing Total Knee Arthroplasty Compared to Fondaparinux

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Abstract

Edoxaban, an oral direct factor Xa inhibitor, was developed and approved for anticoagulant thromboprophylaxis after total knee arthroplasty (TKA). We retrospectively investigated the postoperative anemia by oral administration of edoxaban 30 mg compared with fondaparinux 2.5 mg in TKA patients. Two hundred twenty-nine patients who underwent TKA in National Hospital Organization Okayama Medical Center from July 2010 to June 2012 were divided into two groups; pre- and post-approval of edoxaban: fondaparinux-group (F-group) and edoxaban-group (E-group). As the primary endpoint, the frequency of postoperative anemia was evaluated. Blood coagulation values and relations between these parameters and postoperative anemia were also investigated. The frequency of postoperative anemia was significantly higher in E-group than F-group patients (52.7% vs. 37.8%; p < 0.05). Hemoglobin (Hgb) levels were decreased with the peak at postoperative day (POD) 3 in both groups, and the change of Hgb values from POD1 (ΔHgb) was significantly increased in the E-group (p = 0.04). At each POD, prothrombin time (PT) and international normalized ratio of PT (PT-INR) prolonged from the preoperative day in E-group were significantly higher than F-group. Additionally, PT and PT-INR in the E-group at POD3 were significantly prolonged in patients with postoperative anemia and the sensitivity of cut-off values to predict postoperative anemia was superior to the activated partial thromboplastin time (aPTT). Thus, as the frequency of postoperative anemia tended to be higher in E-group, edoxaban 30 mg might require vigilance, and prolonged PT and PT-INR could potentially predict edoxaban-associated postoperative anemia after TKA.

Key words edoxaban; total knee arthroplasty; postoperative anemia; prothrombin time

Total knee arthroplasty (TKA) is one of the most frequently performed joint replacement surgeries for patients with gonarthrosis and rheumatoid arthritis and is increasingly performed in aging populations. TKA is associated with a high risk of postoperative venous thromboembolism (VTE), which is manifested as both asymptomatic deep vein thrombosis (DVT) and symptomatic pulmonary embolism (PE). DVT has the potential to induce PE, which has a high incidence of sudden death. Without thromboprophylaxis after TKA, DVT occurs in approximately 40–80% of patients. Since VTE is serious life-threatening complication after TKA, aggressive prophylaxis with anticoagulant thromboprophylaxis is recommended after TKA. However, anticoagulant thromboprophylaxis after TKA might place the patients at risk of potentially serious postoperative anemia. Thus, the considerable vigilance for postoperative anemia might be required during anticoagulant thromboprophylaxis after TKA.

Conventionally, anticoagulant thromboprophylaxis has been performed using unfractionated heparin, warfarin, low molecular weight heparins, or an indirect factor Xa (FXa) inhibitor (fondaparinux, a synthetic pentasaccharide). However, these drugs have several clinical limitations such as the requirement for continuous peripheral intravenous injections, the need to constantly monitor coagulation because of inter-individual and individual variability including differences in response, drug-food or drug–drug interactions and slow pharmacokinetics, administration of daily injections, heparin-induced thrombocytopenia, etc. A non-vitamin K antagonist oral anticoagulant, edoxaban (LIXIANA®), which is an oral direct factor Xa (FXa) inhibitor, was developed and approved for pharmacological thromboprophylaxis to prevent VTE after TKA beginning July 2011 in Japan. Edoxaban has overcome the above-described clinical limitations by allowing a once-daily oral administration and no requirement to monitor coagulation.

In 2001, Bauer et al. reported that major bleeding by treatment with fondaparinux 2.5 mg once daily occurred significantly higher than enoxaparin 30 mg twice daily in patients undergoing elective major knee surgery, but there were no significant difference between these groups in the incidence of bleeding leading to death or reoperation or occurring in a critical organ. On the other hand, the patients treated with fondaparinux was significantly more effective in preventing DVT than enoxaparin. Generally, fondaparinux is also frequently used as traditional anticoagulant thromboprophylaxis after TKA. However, only one report has retrospectively
compared edoxaban with fondaparinux in patients undergoing TKA.\textsuperscript{11)}

The purpose of this retrospective study was the clinical assessment of edoxaban through the evaluation of postoperative anemia of oral edoxaban administration at the usual dose of 30 mg once daily compared with subcutaneous fondaparinux at 2.5 mg once daily in patients undergoing TKA. The primary endpoint was assessed by the frequency of postoperative anemia defined as the presence of excessive reduction of hemoglobin (Hgb) level or provision of irradiated red blood cell (RBC) concentrates transfusion. Furthermore, we examined whether values for blood coagulation parameters could be a predictor of postoperative anemia during anticoagulant thromboprophylaxis with edoxaban after TKA.

PATIENTS AND METHODS

Patient Criteria This study was approved by Clinical Study Review Committee, National Hospital Organization Okayama Medical Center (Reference number: H24-Clinical Study-05). Since this was a retrospective study where patient-identifying information was fully anonymized and was not be included in final analysis, study specific written informed consent for our clinical records to be used in this study was waived. Data on patients undergoing TKA at the Department of Orthopaedic Surgery in our hospital from July 2010 to June 2012 were extracted and divided according to whether data were recorded before or after approval of edoxaban. Patients who received a subcutaneous injection of fondaparinux 2.5 mg once daily after TKA in the year before edoxaban approval (July 2010 to June 2011) were eligible for enrollment as the fondaparinux-group (F-group) and those who received oral administration of edoxaban 30 mg once daily after TKA in the year after edoxaban approval (July 2011 to June 2012) were eligible for enrollment as the edoxaban-group (E-group). Exclusion criteria were (1) discontinuation of these drugs within 1 d after TKA, (2) transfusion of autologous blood during thromboprophylaxis because of medical treatment insurance, (3) administration of anticoagulant drugs other than study drugs, (4) administration of a different dosage of study drugs, (5) renal failure requiring dialysis, (6) history of bleeding, and (7) postoperative complications (Fig. 1).

During this retrospective study, surgical methods, procedures for anesthesia, and criteria for awakening from anesthesia for patients undergoing TKA were unified. According to the DVT prophylaxis protocol, early postoperative ambulation and physical rehabilitation were enforced for all patients to prevent the onset of DVT in parallel with anticoagulant thromboprophylaxis by edoxaban or fondaparinux.

Evaluation To monitor postoperative complications including side effects of drug administration and blood transfusion, blood tests were respectively performed before TKA, as well as 1, 3, 7, 10, and 14 d after TKA. Postoperative anticoagulant thromboprophylaxis was performed from day 1 to day 14 after TKA. All data on patients from the day the patient underwent the preoperative examination (preoperative day) to postoperative day (POD) 14 or those from the time of discontinuation of drugs were extracted from medical records and the Anesthesia Information Management System under close supervision.

Prognostic Assessments after Anticoagulant Thromboprophylaxis The frequency of postoperative anemia was assessed by the presence of any of the following two items: frequency of patients with a reduction in Hgb level of at least 2 g/dL or administration of transfusion of at least 2 units of irradiated RBC concentrates in reference to a previous report.\textsuperscript{12)} The frequency of postoperative anemia was counted as postoperative anemia (+) if at least one item was
applicable of these two items. Additionally, edoxaban tablets and fondaparinux injection have been recommended to take into account reducing dose for patients with 30 mL/min ≤ Cr (creatinine clearance)<50 mL/min for avoiding a side effect including bleeding. Edoxaban tablets have been also recommended to take into account reducing dose for patients with coadministration of P-glycoprotein inhibitors as the bleeding risk criteria. Therefore, we also investigated the possible effect of these respective bleeding risk criteria on the frequency of postoperative anemia.

Changes in Hgb in both the E- and F-group were serially evaluated on the preoperative day and POD 1, 3, 7, 10, and 14, respectively. Reduction in the Hgb level (ΔHgb) was determined by a decrease from POD 1, as referred to in a report from Sasaki et al.11) Transfusion of irradiated RBC concentrates was given to patients whose Hgb had decreased to ≤7.5 g/dL or to those with symptomatic anemia diagnosed to require RBC transfusion by a doctor.

Coagulability after anticoagulant thromboprophylaxis was evaluated by the following coagulation parameters: activated partial thromboplastin time (APTT), prothrombin time (PT), and international normalized ratio of prothrombin time (PT-INR) on the preoperative day and POD 1, 3, 7, 10, and 14, respectively. Plasma samples for APTT value was analyzed with the STA® PT-A 5 reagent (Diagnostica Stago, Inc., Parsippany, NJ, U.S.A.) on a measured using STA® R® evolution (Diagnostica Stago, Inc.). Measurement of PT and PT-INR values were performed using the STA® NEOPLASTINE Cl Plus 10 (Diagnostica Stago, Inc.) on a STA-R® evolution. The quality control of these coagulation analyses were performed every day in each lot of test reagent. These reagents and instruments used for coagulation analyses were unified during this retrospective study.

Statistical Analyses Continuous variables are represented as the mean±standard deviation (S.D.) or median. Comparisons were performed using the Kruskal–Wallis test followed by the Mann–Whitney’s U-test or ANOVA following Turkey’s multiple comparison test for continuous variables and Fisher’s Exact Test for categorical variables, as appropriate. Optimal cut-off points of APTT, PT, and PT-INR were calculated for optimization of sensitivity and specificity. The receiver-operating characteristic (ROC) curves were plotted and the area under the ROC curves were calculated to represent their performance to predict postoperative anemia. Statistical significance was set at p<0.05 and p<0.01. All statistical analyses described above were performed with GraphPad Prism6 software (GraphPad Software, San Diego, CA, U.S.A.).

RESULTS

The 281 patients who underwent TKA at our institution from July 2010 to June 2012 were divided into two groups according to whether they received TKA in the year before (July 2010 to June 2011) or after (July 2011 to June 2012) approval of edoxaban (Fig. 1). A total of 52 patients were subsequently excluded, and 229 patients (E-group, 110 patients; F-group, 119 patients) were enrolled and studied (Fig. 1). Table 1 shows the baseline characteristics of patients in these two groups. There were no significant differences between the E- and F-group except for Hgb and PT-INR (p<0.01).

After the start of anticoagulant thromboprophylaxis, the frequency of patients who discontinued the drug because of a hemorrhage-related event have no significant differences (data not shown). In addition, the frequency of patients who discontinued the drug for other reasons, including hospital discharge and switching to another anticoagulant drug, also did not differ between the two groups (data not shown).

To evaluate postoperative anemia of the anticoagulant thromboprophylaxis employed, we assessed the frequency of patients with a reduction in Hgb level of at least 2 g/dL or administration of RBC transfusion. The frequency of patients with a reduced Hgb level of at least 2 g/dL in the E-group was significantly greater than in the F-group (Table 2). Although the frequency of patients who received RBC transfusion was no significant difference between these groups, those of E-group was also higher than F-group (Table 2). In summary, the E-group had a significantly higher frequency of postoperative anemia (52.7%) compared with the F-group (37.8%) during anticoagulant thromboprophylaxis (Table 2).

Figure 2 shows serial changes in Hgb level and ΔHgb values in the E- and F-group after TKA. The decrease in Hgb peaked at POD 3 and gradually recovered until POD 14 in both

Table 1. Baseline Characteristics of Patients on the Day of the Preoperative Examination

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Edoxaban (n=110)</th>
<th>Fondaparinux (n=119)</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>21/89</td>
<td>16/103</td>
<td>0.28</td>
</tr>
<tr>
<td>Age (year)</td>
<td>75.2±7.4</td>
<td>76.4±7.3</td>
<td>0.22</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151.8±7.8 (n=108)</td>
<td>150±7 (n=118)</td>
<td>0.29</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.7±10.8</td>
<td>57.2±11.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>12.6±1.5</td>
<td>12.0±1.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>D-Dimer (µg/mL)</td>
<td>1.3±1.0 (n=24)</td>
<td>1.6±1.6 (n=32)</td>
<td>0.57</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>35.5±3.9</td>
<td>36.2±4.6</td>
<td>0.23</td>
</tr>
<tr>
<td>PT (s)</td>
<td>13.3±1.1</td>
<td>13.4±1.2</td>
<td>0.13</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.02±0.12</td>
<td>1.05±0.12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Scr (mg/dL)</td>
<td>0.74±0.21</td>
<td>0.70±0.18</td>
<td>0.23</td>
</tr>
<tr>
<td>Intraoperative hemorrhage volume (mL/kg)</td>
<td>3.4±2.3 (n=100)</td>
<td>2.8±1.9 (n=112)</td>
<td>0.09</td>
</tr>
<tr>
<td>History of VTE (+/−/unknown)</td>
<td>2/108/0</td>
<td>2/117/0</td>
<td>1.00</td>
</tr>
<tr>
<td>Combined antithrombogenic drugs (+/−/unknown)</td>
<td>25/85/0</td>
<td>36/89/0</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Data are expressed as the mean±S.D. or number. *p-Values are determined by Mann–Whitney’s U-test or Fisher’s exact test, as appropriate. †Patient was excluded if data were lacking. ‡Patient with D-dimer concentration of less than 0.5µg/mL or more than 30µg/mL was excluded. Hgb, hemoglobin; APTT, activated partial thromboplastin time; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; Scr, serum creatinine; VTE, venous thromboembolism.
groups. At POD1 and 14, the Hgb level in the E-group was significantly higher than that in the F-group. At POD3, although Hgb levels did not differ significantly between groups, ΔHgb values from the Hgb level at POD1, which was normalized to 0, was significantly increased in the E-group compared with the F-group ($p=0.04$) (Fig. 2).

Figure 3 shows serial changes in coagulation parameters, including APTT, PT, and PT-INR, during anticoagulant thromboprophylaxis. At the preoperative day, there was no significance between E- and F-group in APTT, PT, and PT-INR. On the other hand, PT-INR was significantly prolonged in the F-group compared with the E-group (Cox regressor test). This contradiction is thought to be due to the difference of statistic analysis (Mann–Whitney’s $U$-test vs. Turkey’s multiple comparison test). Although the median APTT was significantly prolonged at each postoperative day point compared with preoperative day in both groups, the median APTT did not significantly differ between E- and F-group. On the other hand, in E-group, PT and PT-INR were also significantly prolonged at POD3, and higher level of PT and PT-INR were kept from POD3 to POD14 in both groups. However, in F-group, although PT and PT-INR were significantly prolonged at POD3, these values were significantly lower than those in E-group. In addition, prolonged PT and PT-INR values at POD3 were reduced to same level as preoperative day in F-group, except for PT at POD10 (Fig. 3).

Next, the relation between coagulation parameters and postoperative anemia was assessed in patients under edoxaban or fondaparinux treatment at preoperative day and POD3. Each values of APTT, PT, and PT-INR were not significantly different between postoperative anemia and postoperative anemia (−) group at preoperative day point in both E- and F-group. On the other hand, prolonged PT and PT-INR values were significantly higher in patients with postoperative anemia than

<table>
<thead>
<tr>
<th>Events</th>
<th>Edoxaban ($n=110$)</th>
<th>Fondaparinux ($n=119$)</th>
<th>$p$-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in Hgb of at least 2 g/dL (+/−)</td>
<td>36/74 (32.7%)</td>
<td>22/97 (18.5%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Administration of RBC transfusion (+/−)</td>
<td>33/77 (30.0%)</td>
<td>25/94 (21.0%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Postoperative anemia (+/−)</td>
<td>58/52 (52.7%)</td>
<td>45/74 (37.8%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are expressed as numbers. *$p$-Values are determined by Fisher’s exact test. Hgb, hemoglobin; RBC, red blood cell.
in those with postoperative anemia (−) at POD3, but APTT was not in E-group. Thus, PT and PT-INR were certainly prolonged at POD3 in patients with postoperative anemia by edoxaban treatment after TKA (Table 3). However, in F-group, prolonged APTT, PT, and PT-INR has no significant difference at POD3 (Table 3). Then, to reveal the potential of these coagulation parameters at POD3 as predictors of postoperative anemia in those treated with edoxaban, ROC analysis was performed to assess the performance of cut-off values to predict postoperative anemia. As a result, the cut-off values for
PT and PT-INR in the E-group at POD3 were calculated as 15.3 s \( \{ \text{AUC} 0.615 (95\% \text{ confidence interval: 0.506 to 0.724), sensitivity 60.0\%, specificity 66.1\%, } p = 0.043 \} \) and 1.22 \( \{ \text{AUC} 0.617 (95\% \text{ confidence interval: 0.508 to 0.726), sensitivity 58.0\%, specificity 69.6\%, } p = 0.038 \} \), respectively (Figs. 4b, c). However, the cut-off value for APTT was calculated as 47.2 s \( \{ \text{AUC} 0.607 (95\% \text{ confidence interval: 0.498 to 0.715), sensitivity 62.0\%, specificity 64.3\%, } p = 0.059 \} \) (Fig. 4a). The \text{AUC} value of PT and PT-INR were superior to those of APTT by ROC analysis.

**DISCUSSION**

In this retrospective study, the postoperative anemia by the administration of usual dose of 30 mg of edoxaban compared with subcutaneous fondaparinux 2.5 mg were assessed in patients undergoing TKA. The frequency of postoperative anemia was significantly increased in patients treated with edoxaban 30 mg compared to those treated with fondaparinux 2.5 mg. We defined the postoperative anemia by a reduced Hgb level by at least 2 g/dL or provision of RBC transfusion (Table 2). Schulman et al. has defined that the major bleeding by clinically overt bleeding was accompanied by a decrease in Hgb of \( \geq 20 \text{ g/L} \).\(^{12}\) We added the provision of RBC transfusion to the Schulman’s definition of Hgb reduction to evaluate postoperative anemia more objectively. In Table 2, the frequency of patients who received RBC transfusions was increased in E-group, but did not differ significantly between the E- and F-group. This might be because even though a patient had a Hgb level \( \leq 7.5 \text{ g/dL} \), the decision to transfuse was made by the doctor or based on the patient’s condition.

To our knowledge, this is the first retrospective study to assess the postoperative anemia by administration of the usual recommended dose of oral edoxaban 30 mg once daily compared with that of subcutaneous fondaparinux 2.5 mg once daily. Sasaki et al. reported that the reduction in Hgb level and the incidence of DVT in patients treated with edoxaban 15 mg were lower than in those treated with fondaparinux 1.5 mg. However, there was no significant difference between these groups.\(^{11}\) In terms of evaluation of postoperative anemia, their study indicated that reduction of Hgb during the administration of edoxaban at a dose lower than usual was not inferior to a less than usual recommended dose of fondaparinux. On the other hand, our present study indicated that the postoperative anemia were higher in patients treated with the usual recommended dose of edoxaban compared to those treated with fondaparinux (Table 2).

We additionally evaluated the possible effect of each respective bleeding risk criteria, reduced renal function (Ccr < 50 mL/min) on our data. As a result, the ratio of the patients with Ccr < 50 mL/min had no significant difference between E- and F-group (Supplementary Table 1). We also evaluated the influence of another bleeding risk criteria, the patients with P-glycoprotein inhibitors coadministration in E-group. Five patients in E-group were removed because they had coadministration of P-glycoprotein inhibitors with edoxaban. However, the frequency of postoperative anemia in E-group was still significantly higher than F-group, as well as the result from Table 2 (Supplementary Table 2). Thus, it was thought to have little influence on the frequency of postoperative anemia after TKA in our data population. To prevent VTE occurrence, usual dose of edoxaban 30 mg or fondaparinux 2.5 mg have been positively administered to the patients whose overall life state is determined to be stable after TKA even if the patients have corresponded to take into account reducing dose criteria in Department of Orthopaedic Surgery in our hospital.

Compared with subcutaneous fondaparinux, which has 100% bioavailability, the pharmacokinetic features of edoxaban, such as bioavailability, including the ratio of absorption
from the gastrointestinal tract and metabolism, might vary greatly among individuals. The half-life of edoxaban at usual dose is about 8 to 10 h and is shorter than that of fondaparinux (about 17 h).\(^{9,13}\) Additionally, pharmacologic effect of both FXa inhibitor is also different, whether directly binding or indirectly binding through the antithrombin III. These differences might enhance sensitivity to individual differences and require vigilance regarding the frequency of VTE and postoperative anemia after TKA. Thus, the vigilance for postoperative anemia might be required during anticoagulant thromboprophylaxis with edoxaban compared to that with fondaparinux after TKA.

Several researchers have already reported the need for and effectiveness of monitoring these non-vitamin K antagonist oral anticoagulants FXa inhibitors including rivaroxaban (Xarelto\(^6\)) and apixaban (Eliquis\(^6\)) from the point of managing bleeding complications, compliance, thromboembolic events, renal or hepatic impairment.\(^{14,15}\) Rivaroxaban prolonged PT more sensitively than the APTT, and apixaban also prolonged PT dose-dependently.\(^{16,17}\) Thus, measuring PT could predict the approximate anticoagulant activity of these FXa inhibitors.\(^{16,17}\) Edoxaban also might have a stronger effect in prolonging PT than prolonging APTT in plasma concentration dependent manner.\(^{6,8,10}\) Such change of coagulation biomarkers levels reflected specific inhibition of FXa, including prolongation of PT and anti-FXa activity, which may be due to interaction with FXa as well as with the prothrombinase complex.\(^7\) Taken together, the monitoring of FXa inhibitors might be desirable for predicting anticoagulant effect and bleeding risk. Standard laboratory coagulation tests for PT might be useful for this purpose at present stage.

Here, we also investigated the relation of anticoagulation parameters in patients treated with edoxaban or fondaparinux. At each postoperative day point, APTT, PT, and PT-INR were significantly prolonged from preoperative day in both groups, and prolonged PT and PT-INR value were significantly higher in patients treated with edoxaban than those with fondaparinux (Figs. 3a–c). Thus, treatment with edoxaban has the strong possibility for a prolonged PT and PT-INR. Considering the absolute value of PT in detail, the PT value generally has variations among the coagulation assay reagents and instruments. Then, the reagents and instruments used for coagulation analyses were unified during this study. The PT values were measured by our employed coagulation assay reagent, STA\(^6\) NEOPLASTINE CI Plus 10 reagent, which have lower variation for plasma sample.\(^{39}\) Therefore, the data for the variation of PT and PT-INR absolute values would not be due to interday variation caused by used coagulation assay reagent.

Additionally, to our knowledge there are currently no reports of the relationship between PT or PT-INR prolongation and the frequency of postoperative anemia after TKA. Therefore, we examined whether PT or PT-INR could become a predictor of postoperative anemia during edoxaban treatment. Amazingly, PT, and PT-INR were significantly prolonged in patients with postoperative anemia treated with edoxaban (Table 3). However, the APTT did not differ significantly between patients with and without postoperative anemia. In contrast, prolonged APTT, PT, and PT-INR has no significant difference in F-group (Table 3). Thus, these results suggested that the over prolongation of PT and PT-INR might be a predictor of postoperative anemia in patients treated with edoxaban undergoing TKA. We also analyzed the potential of a cut-off value for PT, PT-INR, and APTT at POD3 as a predictor of postoperative anemia. As a result, PT 15.3 s and PT-INR of 1.22 at POD3 were significant and more specific cut-off values than the APTT value of 47.2 s as a predictor of postoperative anemia during edoxaban treatment after TKA (Fig. 4). These data also showed the clinical features of edoxaban and suggested that the PT and PT-INR might be useful to predict postoperative anemia during edoxaban treatment after TKA.

Our study had several limitations. This retrospective study design did not allow randomization. Patients treated with fondaparinux had a lower Hgb level and higher PT-INR compared to those administered edoxaban, which indicated a possible increase in postoperative anemia in the F-group, as previously reported.\(^{20}\) However, the patients treated with edoxaban had a higher incidence of postoperative anemia during anticoagulant thromboprophylaxis than those treated with fondaparinux.

In conclusion, we showed that the clinical assessment of oral administration of edoxaban 30 mg once daily were associated with a tendency toward higher incidences of postoperative anemia compared with subcutaneous administration of fondaparinux 2.5 mg once daily in this study. Thus, vigilance is needed with regard to postoperative anemia after TKA when edoxaban 30 mg is used. Furthermore, the prolongation of PT and PT-INR in patients with postoperative anemia has the potential to predict edoxaban-associated postoperative anemia after TKA.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

REFERENCES


