Postoperative Anaemia Is a Risk Factor for Bleeding-Related Event in Thromboprophylaxis Using Fondaparinux Sodium Injection after Total Knee or Hip Arthroplasty

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INTRODUCTION

Venous thromboembolism is a frequent, life-threatening postoperative complication of total knee arthroplasty (TKA) and total hip arthroplasty (THA). 1,2 Without thromboprophylaxis, the prevalence rate is 40–84% for venographically verified postoperative deep-vein thrombosis and 2–7% for pulmonary embolism. 3,4 Thromboprophylaxis with fondaparinux sodium (FPX) injection is effective in TKA and THA, with a lower incidence of venous thromboembolism (4.0 and 12.5%, respectively) than that associated with enoxaparin injection (9.0 and 27.8%, respectively). 3,4

FPX is a selective inhibitor of activated factor X (Xa). 5–7 Although several studies have suggested that the effectiveness of FPX is superior to that of low-molecular-weight heparin, 8,12 bleeding associated with FPX has been reported. 3,13

Clinical trials have reported that the incidence of bleeding-related event (a decrease in haemoglobin ≥2.0 g/dL compared to post-operative value) in thromboprophylaxis with FPX after TKA or THA was 11.8–55.5%. 14 Therefore, bleeding as a life-threatening side effect of thromboprophylaxis with FPX should be prevented. Therefore, bleeding-related event would be a criterion as withdrawal of thromboprophylaxis with FPX in clinical setting. However, the risk factor for bleeding-related event following administration of FPX has not been fully elucidated. The purpose of this study is therefore to assess the risk factor for bleeding-related event following thromboprophylaxis with FPX in patients who have undergone TKA or THA.

PATIENTS AND METHODS

Patient Selection Between September 2007 and December 2010, 246 consecutive adult patients who underwent TKA or THA with auto-transfusion and thromboprophylaxis with FPX injection (Arixtra® injection, GlaxoSmithKline K.K., Tokyo, Japan) 1.5 or 2.5 mg per day in the Department of Orthopedic Surgery, Mie University Hospital were enrolled. Twenty out of 246 patients were excluded from the analysis because of i) discontinuation of FPX treatment for reasons other than postoperative bleeding, ii) renal impairment (creatinine clearance <30 mL/min) and iii) antiphospholipid antibody syndrome patient; a total of 226 patients were therefore selected for analysis (Fig. 1). This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the ethics committee of Mie University Graduate School of Medicine and Faculty of Medicine (approval no.: 1622).
Thromboprophylaxis after TKA or THA  

Thromboprophylaxis with FPX was performed from postoperative day (POD) 1 to 14 after TKA or THA. The FPX dose was 2.5 mg/d (September 2007 to December 2008) or 1.5 mg/d (January 2009 to December 2010). Laboratory test values including haemoglobin levels were assessed on admission and at POD1, 4, 7, 10 and 14. Bleeding-related event was defined as a decrease in haemoglobin level of more than 2 g/dL from the POD1 level during FPX administration.16–19)

**Propensity Score-Adjusted Multivariate Logistic Analysis**  
Risk factors for bleeding-related event were evaluated using multivariate logistic analyses with adjusted propensity score. This analysis identified 12 risk factors for bleeding in general surgery: anaemia and thrombocytopenia on admission and at POD1; activated partial thromboplastin time (aPTT) > upper limit of normal (ULN) and prothrombin time – international normalized ratio (PT-INR) > ULN on POD1; surgical type (TKA); concomitant use of antiplatelet medications; FPX dose of 2.5 mg/d; body weight < 50 kg; age > 75 years; and creatinine clearance < 50 mL/min.20–22)

Anaemia and thrombocytopenia on admission and at POD1 were defined as haemoglobin < lower limit of normal (LLN) (male: 13.2 g/dL; female: 10.8 g/dL) and platelet count < LLN (130 000/µL), respectively. The ULN for aPTT and PT-INR were defined as 40 s and 1.2, respectively. Propensity scores for target variables were calculated with a multivariate logistic model using the 11 other variables.

**Pair-Matching Methods**  
To guarantee the validity of this retrospective analysis, propensity score-matching analysis was conducted between patients with and without the risk factor identified through multivariate logistic analyses. Propensity scores were calculated using logistic regression on the following variables: surgical type (TKA of THA); FPX dose (1.5 mg/d or 2.5 mg/d); age; male; body weight; creatinine clearance > 50 mL/min; aPTT > upper limits of normal and PT-INR > upper limits of normal at POD1; haemoglobin and platelets on admission and at POD1 were defined as haemoglobin < lower limit of normal (LLN) (male: 13.2 g/dL; female: 10.8 g/dL) and platelet count < LLN (130 000/µL), respectively. The ULN for aPTT and PT-INR was defined as 40 s and 1.2, respectively. Propensity scores for target variables were calculated with a multivariate logistic model using the 11 other variables.

**Haemoglobin Reduction by TKA or THA in Patients with and without Bleeding-Related Event**  
All patients were classified into one of two groups (with and without bleeding-related event or with and without anaemia at POD1),
and ΔHb (obtained by subtracting the haemoglobin level at POD1 from the haemoglobin level on admission) was compared between the groups.

Statistical Analysis Statistical analysis of the clinical data was performed using JMP version 7.0.1 (SAS Institute, Cary, NC, U.S.A.) and GraphPad Prism 5.03 (GraphPad Software, Inc., San Diego, CA, U.S.A.). Propensity score-matching analysis was performed using R software version 3.2.2 (The R Foundation). Quantitative variables were expressed as the median with range or interquartile range. Differences between two groups were statistically compared using Fisher’s exact test or the Mann–Whitney U-test. Survival analyses to investigate the difference in cumulative frequency of bleeding between two groups were performed using the Gehan-Breslow-Wilcoxon test and the log-rank test. Significance was established at a p value of <0.05.

RESULTS

Patients Patient characteristics are shown in Table 1. Of 226 patients, 62 underwent TKA and 164 underwent THA. Twenty-eight patients (12.4%) were diagnosed as having a bleeding-related event. Haemoglobin levels of all patients which diagnosed with be bleeding-related event improved by discontinuing FPX administration. There was not patient which received transfusion after TKA or THA.

Propensity Score-Adjusted Multivariate Logistic Analysis Propensity score-adjusted multivariate logistic analysis showed that only anaemia on POD1 was associated with the risk of bleeding-related event (odds ratio (OR) 3.75, 95% confidential interval (CI): 1.02–24.5, p = 0.04) (Table 2). The survival analysis showed that the frequency of bleeding-related event in patients with anaemia on POD1 was higher than that in patients without anaemia on POD1 (Fig. 2, p = 0.059, Gehan-Breslow-Wilcoxon test; p = 0.060, log-rank test).

Pair-Matching Method Eighty (40 patients in each group) of 226 patients were selected using a propensity score-matching method between the patient groups with and without anaemia on POD1. Twelve (15.0%) of 80 patients were diagnosed as having a bleeding-related event. Propensity scores were calculated using logistic regression on the following variables: surgical type; FPX dose; age; male; body weight; creatinine clearance; aPTT > ULN, PT-INR > ULN, platelets at POD1; concomitant use of antiplatelet medications. The patient characteristics of each group are shown in Table 3. The ASDs of each variables were less than 0.2. Survival analysis after propensity score matching showed that the rate of bleeding was significantly higher in the anaemia group than in the group with no anaemia (Fig. 3, p = 0.0015, Gehan–Breslow–Wilcoxon test; p = 0.0016, log-rank test).

Comparison of Haemoglobin Reduction by TKA or THA between Patients with and without Bleeding The median ΔHb in patients with bleeding-related event was

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Odds ratio (95% confidential interval)</th>
<th>C Statistics</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia on POD1</td>
<td>3.75 (1.02–24.5)</td>
<td>0.70</td>
<td>0.04</td>
</tr>
<tr>
<td>Anaemia on admission</td>
<td>1.81 (0.77–4.57)</td>
<td>0.69</td>
<td>0.25</td>
</tr>
<tr>
<td>Thrombocytopenia on POD1</td>
<td>1.75 (0.68–4.39)</td>
<td>0.80</td>
<td>0.36</td>
</tr>
<tr>
<td>Thrombocytopenia on admission</td>
<td>0.52 (0.01–11.2)</td>
<td>0.99</td>
<td>0.69</td>
</tr>
<tr>
<td>aPTT (POD1) &gt; ULN</td>
<td>4.47 (0.17–72.5)</td>
<td>0.95</td>
<td>0.31</td>
</tr>
<tr>
<td>PT-INR (POD 1) &gt; ULN</td>
<td>2.23 (0.56–7.59)</td>
<td>0.82</td>
<td>0.24</td>
</tr>
<tr>
<td>Total knee arthroplasty</td>
<td>1.74 (0.58–5.03)</td>
<td>0.86</td>
<td>0.31</td>
</tr>
<tr>
<td>Concomitant antiplatelet drug</td>
<td>1.45 (0.35–4.84)</td>
<td>0.82</td>
<td>0.58</td>
</tr>
<tr>
<td>Fondaparinux dosage 2.5 mg/d</td>
<td>1.41 (0.58–3.41)</td>
<td>0.74</td>
<td>0.44</td>
</tr>
<tr>
<td>Body weight &lt;50kg</td>
<td>1.24 (0.46–3.19)</td>
<td>0.78</td>
<td>0.66</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>0.93 (0.29–2.59)</td>
<td>0.80</td>
<td>0.90</td>
</tr>
<tr>
<td>Creatinine clearance &lt;50 mL/min</td>
<td>0.58 (0.10–2.69)</td>
<td>0.92</td>
<td>0.51</td>
</tr>
</tbody>
</table>

PT-INR, prothrombin time-international normalized ratio; POD, postoperative day; ULN, upper limit of normal; aPTT, activated partial thromboplastin time.
1.6 (−0.4–4.0) g/dL, which tended to be higher than that in patients without bleeding-related event (1.0 [−1.8–3.6] g/dL) (Fig. 4a, \( p = 0.10 \)). The median ΔHb in patients with anaemia on POD1 was 1.2 (−1.1–5.4) g/dL, which was significantly higher than that in patients without anaemia on POD1 (0.3 [−1.8–2.4] g/dL) (Fig. 4b, \( p < 0.0001 \)).

**DISCUSSION**

Bleeding is the primary complication of thromboprophylaxis with FPX. It has previously been reported that postoperative bleeding increases hospital costs and the length of the patient’s hospital stay.\(^{24}\) Bleeding-related event might be a criterion as withdrawal of thromboprophylaxis with FPX in clinical setting. Despite the significant consequences of bleeding-related event, there is a lack of information about risk factors for bleeding-related event by thromboprophylaxis with FPX after TKA or THA. To the best of our knowledge, this study is the first to report that anaemia on POD1 is an independent risk factor for bleeding-related event following thromboprophylaxis with FPX after TKA or THA. The product information for FPX injection indicates that the risk of bleeding is increased by renal dysfunction (creatinine clearance <50 mL/min), age >75 years and body weight <50 kg, probably because decreased renal clearance of FPX.\(^{25}\) However, in this study, creatinine clearance <50 mL/min, age >75 years and body weight <50 kg were not identified as independent risk factors for bleeding-related event by multivariate logistic regression analysis. Zufferey \textit{et al.} reported that risk factors of bleeding following major orthopaedic surgery

![Fig. 4. Comparison of Haemoglobin Reduction by TKA or THA between Patients with and without Bleeding (a) and between Patients with and without Anaemia on POD1 (b)](image)

Graph shows median (interquartile range) of ΔHb. ΔHb was calculated by subtracting the haemoglobin level at POD1 from that of the baseline level at admission. Bleeding-related event and control indicates groups of patients with and without bleeding-related event (a), respectively. Anaemia and No anaemia indicates groups of patients with and without anaemia on POD1 (b), respectively.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Anaemia on POD1 (n = 40)</th>
<th>No anaemia (n = 40)</th>
<th>( p ) Value</th>
<th>ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip arthroplasty</td>
<td>28 (70.0)</td>
<td>28 (70.0)</td>
<td>1.00</td>
<td>0.000</td>
</tr>
<tr>
<td>Total knee arthroplasty</td>
<td>12 (30.0)</td>
<td>12 (30.0)</td>
<td></td>
<td></td>
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<tr>
<td>Fondaparinux dose (mg/d)</td>
<td></td>
<td></td>
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<tr>
<td>1.5 mg/d</td>
<td>22 (55.0)</td>
<td>24 (60.0)</td>
<td>0.82</td>
<td>0.005</td>
</tr>
<tr>
<td>2.5 mg/d</td>
<td>18 (45.0)</td>
<td>16 (40.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>66 [39–86]</td>
<td>65 [37–81]</td>
<td>0.86</td>
<td>0.044</td>
</tr>
<tr>
<td>Male</td>
<td>2 (5.0)</td>
<td>2 (5.0)</td>
<td>1.00</td>
<td>0.000</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58.9 [39.5–81.6]</td>
<td>59.1 [39.2–90.6]</td>
<td>0.92</td>
<td>0.024</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min) (^a)</td>
<td>83.8 [33.5–157.4]</td>
<td>88.9 [44.5–153.9]</td>
<td>0.61</td>
<td>0.174</td>
</tr>
<tr>
<td>aPTT &gt; ULN</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.00</td>
<td>0.000</td>
</tr>
<tr>
<td>PT-INR &gt; ULN</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.00</td>
<td>0.000</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>10.2 [7.4–13.1]</td>
<td>12.2 [11.6–14.6]</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
<tr>
<td>Platelet (10(^3)/µL)</td>
<td>191 [110–271]</td>
<td>192 [123–302]</td>
<td>0.85</td>
<td>0.017</td>
</tr>
<tr>
<td>Concomitant of antiplatelet</td>
<td>3 (7.5)</td>
<td>3 (7.5)</td>
<td>1.00</td>
<td>0.000</td>
</tr>
</tbody>
</table>

\(^a\) Creatinine clearance was calculated by Cockcroft–Gault equation. ASD, absolute standardized difference; aPTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio.
with fondaparinux thromboprophylaxis is dosage of FPX.\(^{26}\)
However, the study doesn’t perform analysis including haemoglobin and coagulation factor as confounding factors. On the other hand, it has been reported that elevated anti-Xa activity by FPX was observed in patients with renal impairment but not in patients with body weight <50 kg or age ≥ 75 years.\(^{27}\)
However, no significant correlation between anti-Xa activity and the occurrence of postoperative bleeding was observed following thromboprophylaxis with FPX.\(^{28}\) Therefore, together with the results of this study, bleeding following thromboprophylaxis after TKA or THA might not be related to the renal clearance of FPX. To determine whether an association exists between anti-Xa activity and bleeding events in patients with thromboprophylaxis with FPX, further investigations are necessary.

The main cause of anaemia on POD1 might be intraoperative and postoperative blood loss. In this study, a high tendency for reduced haemoglobin level was observed in patients with bleeding compared with those without bleeding (Fig. 4a). Although we could not obtain data of blood loss from electric medical record in this study population during the TKA or THA, the reduction in haemoglobin levels among patients with anaemia on POD1 was significantly greater than that among patients without anaemia (Fig. 4b). Therefore, we speculated that a relationship might exist between intraoperative and postoperative blood loss and bleeding-related event following thromboprophylaxis with FPX.

The present study has some limitations that need to be considered. First, it was difficult to exclude the potential effects of unknown confounders other than those employed in the present study. Second, in propensity score matching analysis, only ASD of creatinine clearance did not reach a value less than 0.1. Because the ASD of creatinine clearance was less than 0.2, it is speculated that there is less than 15% of non-overlap in the two distribution. Third, the findings cannot precisely explain why anaemia on POD1 is a risk factor for bleeding-related event. Additionally, this was a small, historical cohort study in a single centre. Therefore, to validate our result, a controlled prospective observational study will be required.

There are some selective factor Xa inhibitors for thromboprophylaxis after TKA or THA. Bleeding is a life-threatening side effect of thromboprophylaxis with these inhibitors similarly to FPX. The results of this study might be adapted to thromboprophylaxis with these inhibitors. Therefore, further studies would be needed to confirm whether anaemia on POD1 is a risk factor for bleeding-related event by thromboprophylaxis with other factor Xa inhibitors.

**CONCLUSION**

The present study suggests that anaemia on POD1 is an independent risk factor for bleeding-related event following thromboprophylaxis with FPX after TKA or THA. Therefore, in patients with anaemia on POD1, stringent haemoglobin monitoring is recommended for early identification of bleeding following thromboprophylaxis with FPX.

**Conflict of Interest** The authors declare no conflict of interest.

**REFERENCES**

12. Bauer KA. New anticoagulants: anti IIa and anti-Xa activities and the occurrence of postoperative bleeding was observed following thromboprophylaxis with FPX.


