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The relationships among hemostatic markers, the withdrawal of fondaparinux due to a reduction in hemoglobin and deep vein thrombosis in Japanese patients undergoing major orthopedic surgery

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ABSTRACT

Background: The relationships among the hemostatic markers, the development of deep vein thrombosis (DVT) and the withdrawal of fondaparinux due to a reduction in the hemoglobin levels were examined.
Methods: Two-hundred twenty-one Japanese patients who underwent major orthopedic surgery and were treated with 1.5 mg of fondaparinux instead of 2.5 mg of fondaparinux were studied. Forty-seven of 221 patients discontinued fondaparinux treatment (withdrawal group) and 37 patients developed DVT.
Results: The age, frequency of total knee arthroplasty (TKA), withdrawal of fondaparinux, reduction of hemoglobin and the plasma levels of soluble fibrin (SF), D-dimer and fibrinogen and fibrin degradation product (FDP) on day 1 after the operation were significantly higher in the patients with DVT. Elevated SF, D-dimer or FDP levels were associated with the risk for DVT. The age, frequency of TKA or DVT, anti-Xa activity and the creatinine, FDP and D-dimer levels were significantly higher in the withdrawal group. An anti-Xa level >0.33 mg/l and an elevated D-dimer or FDP level were associated with the risk of withdrawal.
Conclusion: The age and SF levels, TKA and withdrawal of fondaparinux were related to the risk of DVT, and the anti-Xa activity, creatinine level and DVT were related to the risk of withdrawal of fondaparinux due to a reduction in hemoglobin.

1. Introduction

The chromogenic antifactor Xa assay measures the concentration of anticoagulants that inhibit factor Xa. The assay measures the extent to which exogenous factor Xa is inhibited by complexes of unfractionated heparin (UFH)-antithrombin (AT), low- molecular weight heparin (LMWH)-AT, or fondaparinux-AT in patients being treated with UFH, LMWH, or fondaparinux, respectively [1]. The anti-Xa assay is reported to be correlated with the weight, body mass index (BMI) and renal function in patients treated with fondaparinux [2].

Preventing the development of deep vein thrombosis (DVT) is clinically important, because a pulmonary embolism (PE) caused by DVT is often fatal. Orthopedic surgery is associated with a high rate of postoperative venous thromboembolism (VTE) [3,4]. The incidence of VTE ranges from 42 to 57% after total hip arthroplasty (THA) in the absence of thromboprophylaxis, and 41 to 85% after total knee arthroplasty (TKA) [5]. Multiple studies [6–8] have established the efficacy of LMWH for VTE prophylaxis in orthopedic surgery patients.

Fondaparinux is the first selective factor Xa inhibitor approved for use in thromboprophylaxis after orthopedic surgery [9–11], and studies comparing fondaparinux to LMWH showed that it provided thromboprophylaxis in patients after orthopedic surgery [10,11]. New oral anticoagulants have recently been developed and these drugs have been compared with fondaparinux as the standard drug for prophylaxis of VTE [12,13]. However, there have been a few cases of massive bleeding in patients administered fondaparinux [14,15]. Therefore, fondaparinux is frequently administered at a dose of 1.5 mg instead of 2.5 mg in Japan to avoid serious bleeding. The administration of 1.5 mg fondaparinux instead of 2.5 mg fondaparinux is recommended for patients who have risk factors

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for bleeding in Japan. This is because about 50% of Japanese orthopedic patients weight <60 kg, so the 2.5 mg dose is relatively high. There was no significant difference in the frequency of DVT in our preliminary study. The anti-Xa activity is used, UFH or LMWH activity, to monitor the anticoagulant activity [16,17].

This study evaluated the anti-Xa activity and hemostatic markers in 221 patients who underwent major orthopedic surgery and were treated with fondaparinux for the prophylaxis of deep vein thrombosis (DVT) in order to examine the relationships among the anti-Xa activity, DVT and/or withdrawal of fondaparinux due to a reduction of hemoglobin (Hb).

2. Materials and methods

Two hundred twenty-one orthopedic patients treated with 1.5 mg of fondaparinux (GlaxoSmithKline, Tokyo, Japan) and intermittent pneumatic compression for prophylaxis of DVT from February 1, 2010, to December 31, 2011 were enrolled in this study. These patients received 1.5 mg of fondaparinux by hypodermic injection once a day for 14 days beginning 24 h after extubation of lumbar anesthesia. Of these 221 patients, 47 discontinued prophylaxis (withdrawal group), 44 due to a reduction of the hemoglobin level by >2 g/dl compared with day 1 or to a hemoglobin level <7 g/dl. The other 2 patients who discontinued treatment developed DVT, and one other patient had atrial fibrillation, so all 3 patients were changed to other drugs.

The anti-Xa activity, fibrin and fibrinogen degradation products (FDP), D-dimer, soluble fibrin (SF) and AT activity were measured prospectively in the 221 patients who underwent THA or TKA and on days 1, 4, 8 and 15 of the administration of fondaparinux. The diagnosis of DVT was assessed by a whole-leg compression ultrasound examination using standardized ultrasound criteria for venous non-compressibility, and was assessed before the operation, as well as on days 4 and 14 [18]. The study protocol was approved by the Human Ethics Review Committee of the Mie University School of Medicine and a signed consent form was obtained from each subject. This study was faithfully carried out in accordance with the principles of the Declaration of Helsinki.

The anti-Xa activity was monitored for 3 h after the injection of fondaparinux. The anti-Xa activity of fondaparinux was measured using Testzym®Heparin S (Sekisui Medical Co. Ltd. Tokyo, Japan) and a Coagrex®800 system (Sysmex Co. Ltd. Kobe, Japan). Testzym® Heparin S contains bovine Xa (71 nkat/vial), AT (10 IU/vial), a chromogenic substrate (S-2222: Benz–Ile–Glu–Gly–Arg–pNA·HCl 25 mg), pooled lyophilized normal plasma and a buffer (pH8.4) [2,16]. A standard curve was constructed for lyophilized normal plasma using various concentrations of fondaparinux.

The reagents and objects were loaded into the Coagrex 800 (Sekisui Medical)and the anti-FXa activity of fondaparinux was measured automatically. A 135 μl aliquot of FXa was added to 8 μl of plasma (with diluent solution added in advance), and 75 μl of substrate was added. The released p-NA was measured photometrically at 405 nm. The anti-Xa activity of fondaparinux was then calculated using the standard curve. The plasma levels of FDP, D-dimer and SF were measured by the latex agglutination method using Nanopia FDP, Nanopia D-dimer and Nanopia SF reagents (Sekisui Medical) [19]. The plasma levels of AT were measured using a Testzym S ATIII kit (Sekisui).

2.1. Statistical analysis

The data are expressed as the medians (25%–75% tiles). The differences between the groups were examined using the Mann–Whitney *U*-test. The differences between the groups were examined for significance using the Chi-squared test for independence. Cut-off values for the SF, D-dimer and FDP levels were analyzed by a receiver operating characteristic (ROC) curve. A multiple logistic regression analysis was performed to detect the factors predicting the development of DVT or withdrawal of fondaparinux. A *P*-value ≦ 0.05 was considered to be statistically significant. All statistical analyses were performed using Stat flex, ver 6, software package (Artec Co Ltd).

3. Results

Thirty-seven patients developed DVT, but no patients had a PE. The age was significantly higher in the patients with DVT than in the patients without DVT ($p < 0.001$, Table 1). The frequency of DVT was significantly higher in the patients who underwent TKA than in those who underwent THA ($p < 0.001$). There were no significant differences in the sex, body weight, height, body surface area, creatinine and estimated glomerular filtration rate (eGFR) between the patients with and without DVT. The frequency of withdrawal of fondaparinux and the reduction of hemoglobin were significantly higher in the patients with DVT than in those without DVT ($p < 0.01$, respectively). The plasma levels of SF, D-dimer and FDP were significantly higher in the patients with DVT than in those without DVT on day 1 after the operation (Fig. 1A, B and C). There were no significant differences in the anti-Xa activity in the patients who completed the 14 days of treatment with fondaparinux (Fig. 1D), or the AT levels in the patients with and without DVT. The results of the ROC analysis of the SF, D-dimer and FDP levels on day 1 after surgery for predicting the development of DVT are shown in Table 2. Values higher than 13.9 μg/ml of SF, 6.8 μg/ml of D-dimer or 15.7 μg/ml of FDP were associated with a low risk for DVT. In a multiple logistic regression analysis of the association with DVT, the age, TKA and plasma SF level (day 1) were found to be significant (Table 3).

The age was significantly higher in the fondaparinux withdrawal group than in complete administration (CA; 14 days of treatment) group ($p < 0.01$, Table 4). The frequency of withdrawal of fondaparinux was significantly higher in the patients who underwent TKA than in those who underwent THA ($p < 0.05$). There were no significant differences in the weight, height, body mass index (BMI) or body surface area between the withdrawal group and the CA group (Table 4). The eGFRs were significantly lower ($p < 0.01$) and the creatinine levels were significantly higher ($p < 0.01$) in the withdrawal group than in the CA group. The frequency of DVT was also significantly higher in the withdrawal group than in the CA group ($p < 0.01$).

The anti-Xa activity levels were significantly higher in withdrawal group (0.38 mg/l; 0.31–0.45 mg/l) than CA group (0.26 mg/l; 0.18–0.30 mg/l, $p < 0.001$, Fig. 2). There were no significant differences in the SF and AT between the withdrawal group and CA group. The plasma levels of D-dimer and FDP were significantly higher in the withdrawal group than in the CA group on days 1, 8 and 15 after the operation. The results of the ROC analysis of the anti-Xa activity and the SF, D-dimer and FDP levels for predicting the withdrawal of fondaparinux

Table 1
Orthopedic surgery patients with and without DVT.

	With DVT	Without DVT
Number	37	184
Age	75.0 (68.0–80.0)***	64.0 (57.0–72.0)***
Sex (F:M)	32: 5	143:41
THA:TKA	13:24***	155:29***
Withdrawal of fondaparinux	15 (40.5%)**	31 (16.8%)**
Weight (kg)	58.0 (51.9–64.3)	57.0 (49.9–66.2)
Height (cm)	149 (146–156)	153 (149–158)
Body mass index	25.8 (22.7–28.5)*	24.2 (21.2–26.8)*
Body surface area (cm^2)	1.51 (1.45–1.65)	1.53 (1.44–1.66)
Creatinine	0.68 (0.55–0.81)	0.66 (0.54–0.79)
e-GFR	73.3 (56.9–82.3)	75.4 (60.1–88.9)
Reduction of Hb (g/dl)	1.50 (0.98–2.13)**	1.20 (0.50–1.68)**

Hb; hemoglobin, THA; total hip arthroplasty, TKA; total knee arthroplasty.
* $p < 0.05$.
** $p < 0.001$.
*** $p < 0.001$.