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Original Article

Safety of fondaparinux for prevention of postoperative venous thromboembolism in urological malignancy: A prospective randomized clinical trial

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Abbreviations & Acronyms
ACCP = American College of Chest Physicians
ALT = alanine aminotransferase
AST = aspartate aminotransferase
AUA = American Urological Association
DD = D-dimer
DVT = deep venous thrombosis
eGFR = estimated glomerular filtration rate
FPX = fondaparinux
HIT = heparin induced thrombocytopenia
Lap = laparoscopic
LDUH = low-dose unfractionated heparin
LMWH = low molecular weight heparin
LRP = laparoscopic radical prostatectomy
MDCT = multidetector-row computed tomography
NA = not applicable
NS = not significant
POD = postoperative day
PTE = pulmonary thromboembolism
RRP = radical retropubic prostatectomy
SFMC = soluble fibrin monomer complex
VTE = venous thromboembolism

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Objectives: To prospectively evaluate the safety of postoperative fondaparinux in comparison with low molecular weight heparin in patients undergoing uro-oncological surgery.

Methods: The present study was a prospective, single-blind, non-inferiority randomized trial. A total of 359 patients undergoing surgery for urological malignancy were enrolled from January 2011 to December 2012. A total of 298 of these patients (fondaparinux group, 152; low molecular weight heparin group, 146) were evaluable for the intention-to-treat-analysis. Patients were randomly assigned to low-dose unfractionated heparin, 5000 units twice daily until postoperative day 1 plus either fondaparinux 2.5 mg once daily or low molecular weight heparin 2000 units twice daily until postoperative day 5. The primary end-point was postoperative bleeding as by independent review, and the study was powered to show the non-inferiority of fondaparinux versus low molecular weight heparin. The other adverse events were evaluated. D-dimer and soluble fibrin monomer complex levels were measured perioperatively.

Results: Bleeding occurred in 21 patients (12 in the fondaparinux group and 9 in low molecular weight heparin group, respectively). No significant differences were detected in the incidence of postoperative bleeding and the other adverse events between the two groups. The D-dimer was elevated on postoperative day 1 in one patient (16.6 μg/mL). In another patient, the soluble fibrin monomer complex was elevated (109 μg/mL).

Conclusions: Fondaparinux is non-inferior to low molecular weight heparin with respect to risk of bleeding. The favorable safety profile of fondparinux supports its prophylactic use as an alternative to low molecular weight heparin after surgery for urological malignancy.

Key words: fondaparinux, thromboprophylaxis, urological malignancy, urological surgery, venous thromboembolism.

Introduction

DVT is a serious complication after surgical intervention, potentially resulting in fatal PTE. Recent recognition of the close causality between these two classes of events has led to wider use of the term "VTE" for both DVT and PTE.[1,2]

The AUA advocates prevention of DVT in its best-practice statement for patients undergoing urological surgery. Nevertheless, up to 18.1% of urological oncologists and laparoscopic/robotic surgeons do not routinely use thromboprophylaxis.[3]

As timely detection and treatment of PTE is difficult, thromboprophylaxis can be an effective option for preventing such surgery-related mortality. Cancer surgery seems to have at least twice the risk of postoperative DVT, and more than threefold the risk of fatal PTE than similar procedures in non-cancer patients.[4] The incidence of VTE thus remains an issue, despite mechanical and pharmacological thromboprophylaxis, ranging from 0.5% to 7.2% after radical prostatectomy,[5,6] 4.3% to 24% after radical cystectomy,[5,7] 1.0% to 7.1% after nephrectomy[5,8] and 0% to 11.1% after nephroureterectomy.[9,10]

The use of heparin as thromboprophylaxis has been extensively investigated over the past 30 years.[11–13] The ACCP and the AUA recommend the use of LDUH (grade 1B) or LMWH

(grade 1B) plus mechanical prophylaxis after general or abdominal-pelvic surgery in high-risk cancer patients.[14,15]

FPX is the first of a new class of synthetic antithrombotic agent that is equivalent or more effective than LMWH without introducing additional bleeding risk after general surgery.[16] FPX specifically inhibits factor Xa without directly affecting thrombin (factor IIa).[17] However, only low-level supporting evidence is available because of the paucity of clinical trials related to abdominal-pelvic cancer surgery. FPX is not listed in the AUA recommendations.[15] To the best of our knowledge, there have been no randomized controlled trials directly comparing FPX with LMWH for prophylaxis of VTE after surgery for urological malignancy.

Early detection of VTE is a challenge. Both DD and SFMC have been suggested as blood anticoagulation markers for predicting postoperative VTE.[18–20] DD is a marker of the hypercoagulable state and a stable end product of fibrin degradation, which has been widely used in the screening for VTE. SFMC is produced when thrombin sequentially cleaves fibrinopeptides A and B from the amino termini of Aα- and Bβ-chains of fibrinogen. It provides information about the degree of intravascular coagulation in early-stage thrombosis. Their performance has never been evaluated in surgery for urological malignancy.

The aim of the present study was to prospectively evaluate the safety of postoperative FPX in comparison with LMWH in the prevention of VTE in high- to highest-risk patients undergoing surgery for urological malignancy.

Methods

Patient selection

The present study was planned as a prospective, single-blind, non-inferiority randomized trial. Patients with urological malignancy, aged 40 year or older, scheduled for surgery at Jikei University Hospital from January 2011 to December 2012, considered candidates for open or laparoscopic surgery of >45 min in length and with a life expectancy of at least 6 months after surgery were eligible for participation. Exclusion criteria included bodyweight <40 kg; hypersensitivity to FPX or LMWH; contraindication to anticoagulant therapy; active bleeding; documented bleeding disorder or thrombocytopenia; perioperative VTE within the previous year; severe hepatic dysfunction; severe renal dysfunction (eGFR <30 mL/min/1.73 m^2); concurrent disorder, such as gastrointestinal ulceration or diverticulitis, colitis, bacterial endocarditis, severe diabetes mellitus, severe hypertension or disseminated intravascular coagulation; hemorrhagic stroke; brain, spine or eye surgery within the previous 3 months; HIT; or pregnancy. Patients were assigned to one of two groups (FPX or LMWH), and stratified by risk based on ACCP and AUA guidelines before surgery.[15,21]

A total of 10 surgeons participated in the study; all were blinded to drug allocation until the end of the surgical procedure. If patients were taking anticoagulant or antiplatelet agents before surgery, that use was temporarily suspended and restarted at an appropriate time. The present study was carried out under the Declaration of Helsinki and applicable clinical practice. The institutional ethics committees approved the study protocol, and informed consent was obtained from all patients.

VTE prophylaxis

Mechanical thromboprophylaxis was used in all patients until fully ambulatory. If epidural anesthesia was combined with general anesthesia, the epidural catheter was removed immediately after surgery. Six hours after surgical wound closure and confirmation of no severe bleeding, LDUH (5000 units) was injected subcutaneously; administration was continued every 12 h until the day after surgery. FPX patients received 2.5 mg subcutaneous FPX (Arixtra; Sanofi-Synthelabo, Paris, France) once daily, and LMWH patients received 2000 units LMWH; that is, enoxaparin (Clexane; Aventis Pharma, Bridgewater, NJ, USA) subcutaneously twice daily. Both treatments were administered from POD 2–5. If eGFR ranged from 30 to 50 mL/min/1.73 m^2 and the risk of bleeding was high, FPX and LMWH could be reduced to 1.5 mg and 2000 units daily, respectively, at the discretion of the attending physician.

Evaluation

Blood DD and SFMC levels were measured by latex immunoagglutination assay (LSI Medience Corporation, Tokyo, Japan) before surgery, on PODs 1, 3 and 5, and whenever VTE or other complications were suspected. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4.0 (National Cancer Institute, Bethesda, MD, USA). If preoperative DD was ≥1.5 μg/mL, if clinical symptoms or signs of VTE developed, or if postoperative DD was ≥15 μg/mL, contrast-enhanced 16-row MDCT of the chest to the lower limbs was carried out. Two radiologists evaluated the MDCT images. No SFMC threshold was set for decision-making, because 1 week was required before the results could be obtained (SFMC level of <6.1 μg/mL was considered normal).

Study end-points

The primary objective was to evaluate bleeding of the anticoagulants as safety. Major bleeding was defined as fatal bleeding, bleeding at vital organs, bleeding or hematoma around the surgical beds necessitating reoperation, or bleeding necessitating transfusion of >400 mL red blood cells prepared from whole blood, or >2 g/dL decrease in hemoglobin level within 48 h after bleeding onset.[22] Minor bleeding was defined as clinically abnormal bleeding that could not be described as major. The following specific adverse events were compared: incidence of lymphocele formation, decreased thrombocyte count including HIT, and elevation of AST and ALT. Changes in perioperative blood coagulation markers in relation to VTE events were also investigated.

Statistical analysis

Because there are no data from previous trials to help define the incidence of bleeding events in the urological field, the

estimated incidence was referred to the randomized control study in abdominal surgery that compared bleeding events between LMWH and mechanical thromboprophylaxis.[22] The margin of clinical non-inferiority was fixed at 10%. Assuming 9.2% bleeding events rate in the control group, non-inferiority will be shown within the margin of 10% at a one-sided significance level of 0.05 and a power of 90%, with a sample size of 143 per arm (286 patients in total).[22] We expected a 20% loss to unfit our criteria before the allocation, this would result in a total sample size of 358 patients.

All the analyses were carried out in the intention-to-treat cohort (all randomly assigned patients). For the evaluation of changes in perioperative blood coagulation markers, per-protocol analysis was also carried out (Fig. 1). For non-parametric testing, the χ^2-test was used. For continuous variables, the unpaired *t*-test depending on data normality was carried out. GraphPad PRISM, version 5 (GraphPad Software, San Diego, CA, USA) was used for all statistical analyses. A *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

During the study period, 359 consecutive patients underwent surgery for urological malignancies (Fig. 1). A total of 61 patients were excluded: 39 did not meet the inclusion criteria, two declined to participate and 20 withdrew their consent for various reasons. The remaining 298 patients were evaluated in intention-to-treat analysis (Fig. 1). A total of 16 patients did not receive the assigned treatment after randomization owing to intraoperative or postoperative bleeding, or immediate reoperation. The preoperative characteristics were similar between the two patient groups (Table 1). Based on the AUA Best Practices Statement, 64 and 234 patients were in the high- and highest-risk groups, respectively;[15] by ACCP classification, all patients were high risk.[20] One patient in the FPX group had VTE 3 years previously, which was successfully treated with anticoagulation therapy. Surgical and therapeutic details are summarized in Table 2. In total, 244 radical prostatectomies, 22 radical nephroureterectomies and 32 radical nephrectomies were carried out. Operation time, estimated blood loss, time to ambulation and transfusion rates did not differ significantly between the two groups.

Complications

The FPX group was non-inferior for major and minor postoperative bleeding, compared with the LMWH group; there were one (0.7%) and two (1.3%) major bleeding events in the LMWH and FPX groups, respectively (Table 3). Red blood cell transfusion was required for all the patients who had hematoma in the pelvis. Minor bleeding episodes developed in eight out of 146 LMWH patients (5.5%) and 10/152 FPX patients (6.6%; $P = 0.81$). These included bloody drain discharge ($n = 3$ and 5, respectively), gross hematuria ($n = 1$ in both groups), surgical site hematoma ($n = 1$ and 2, respectively), hemoglobin <2 g/dL ($n = 2$ in both group) and one hematoma of pelvis only in the LMWH group. Lymphocele occurred in three prostatectomies with concomitant pelvic lymphadenectomy irrespective of whether open or

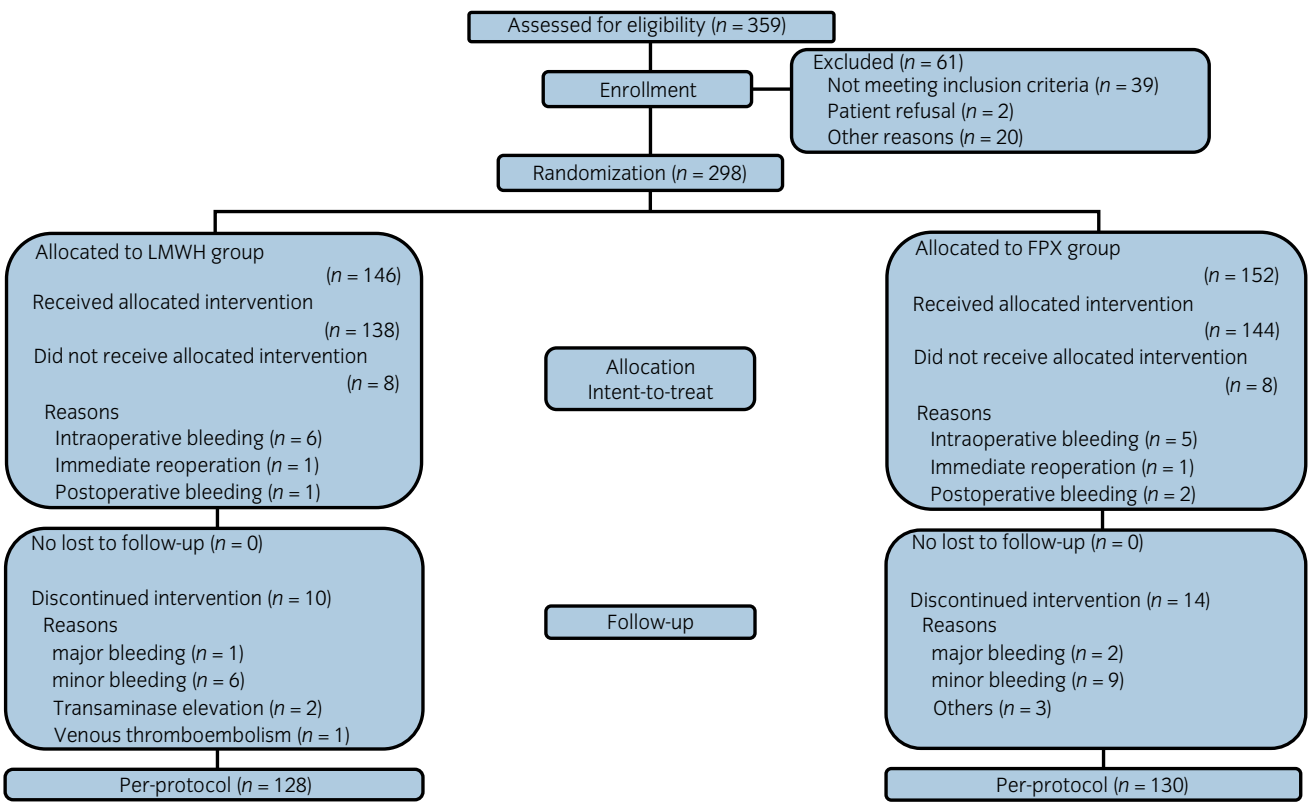

Fig. 1 Flow diagram for treatment.

Table 1 Baseline demographics and clinical characteristics of patients

	LMWH (n = 146)	FPX (n = 152)	P-value
Mean age, years (range)	63.9 ± 7.5 (40–82)	64.7 ± 7.5 (40–86)	0.340
Sex (male/female)	138/8	144/8	0.934
Mean body mass index, kg/m^2 (range)	23.9 ± 2.6 (18.1–32.1)	23.7 ± 2.6 (17.0–31.4)	0.642
Median Brinkman index (range)	430 (0–2700)	327 (0–2000)	0.073
AUA guidelines, no. patients (%)	High 32 (21.9)	High 32 (21.1)	0.856
	Highest 114 (78.1)	Highest 120 (78.9)	
Ninth ACCP guideline, no. patients (%)	High 146 (100)	High 152 (100)	NA
Preoperative drugs, no. patients (%)			
Antiplatelet drugs	12 (8.2)	13 (8.6)	0.951
Anticoagulation drugs	4 (2.7)	4 (2.6)	
Prior VTE, no. patients (%)	0 (0)	1 (0.7)	0.326
Prior congestive heart failure (New York Heart Association grade III or IV), no. patients (%)	0 (0)	0 (0)	NA
Chronic obstructive pulmonary disease, no. patients (%)	4 (2.7)	1 (0.7)	0.162
Inflammatory bowel disease, no. patients (%)	4 (2.7)	3 (2.0)	0.662
Other malignancy, no. patients (%)	8 (5.5)	10 (6.6)	0.690

Table 2 Surgical and therapeutic characteristics of patients

	LMWH (n = 146)	FPX (n = 152)	P-value
Surgical procedures (no. patients)	LRP 106	LRP 106	NA
	RRP 18	RRP 14	
	Lap nephrectomy 12	Lap nephrectomy 17	
	Open nephrectomy 3	Open nephrectomy 0	
	Lap nephroureterectomy 7	Lap nephroureterectomy 14	
	Open nephroureterectomy 0	Open nephroureterectomy 1	
Mean time from skin incision to closure, min (range)	298.0 ± 75.6 (150–617)	290.9 ± 67.3 (115–588)	0.391
Mean estimated blood loss, mL (range)	549.0 ± 590.5 (0–3510)	488.0 ± 535.6 (0–3240)	0.349
Median time to ambulation, day (median)	1.52 ± 0.78 (1)	1.44 ± 0.73 (1)	0.403
Intraoperative or perioperative transfusion, no. patients (%)	18 (12.3)	15 (9.9)	0.499
Concomitant treatment, no. patients (%)			
Graduated compression stockings	146 (100)	152 (100)	NA
Intermittent pneumatic compression	146 (100)	152 (100)	

laparoscopic. There were no VTE events in these cases. One patient in the LMWH group and two patients in the FPX group showed thrombocytes <10.0 × 10^4/μL, but these decreases resolved spontaneously without discontinuation of pharmacological prophylaxis. Transaminase elevation was the most frequently observed adverse event, but the incidence did not differ significantly between the two groups. Grade 1 or 2 AST/ALT elevation was noted in 60 patients in the LMWH group and 47 patients in the FPX group, but those values returned to baseline without further treatment.

Table 3 Safety outcomes during treatment

	LMWH (n = 146) No. patients (%)	FPX (n = 152) No. patients (%)	P-value
Major bleeding	1 (0.7)	2 (1.3)	0.586
Minor bleeding	8 (5.5)	10 (6.6)	0.690
Lymphocele	2 (1.3)	1 (0.7)	0.538
Thrombocytes decrease less than 10.0 × 10^4/μL	1 (0.7)	3 (2.0)	0.334
Elevated AST/ALT	G1 54 (37.0)	G1 47 (30.9)	0.170
	G2 6 (4.1)	G2 0 (0)	

DD and SFMC

A total of 10 LMWH patients and three FPX patients had preoperative DD values >1.5 μg/mL. MDCT, carried out in eight of the LMWH patients and all three FPX patients, showed no preoperative VTEs. A total of 12 LMWH patients and nine FPX patients had preoperative SFMC concentrations above the normal range (<6.1 μg/mL). Overall, DD values were significantly elevated after surgery compared with preoperative baseline values, over 15 μg/mL in four patients (two in each group) on POD 1. No patients showed DD values above 15 μg/mL on POD 3 or 5. No significant difference was noted in these values between groups ($P > 0.05$, Fig. 2). SFMC values in both groups peaked on POD 1 (LMWH group: POD 1 *vs* before surgery, $P = 0.04$; *vs* POD 3, $P = 0.02$; *vs* POD 5, $P < 0.0001$. FPX group: POD 1 *vs* before surgery, $P < 0.0001$; *vs* POD 3, $P < 0.0001$; *vs* POD 5, $P < 0.0001$). No significant difference was observed between groups ($P > 0.05$, Fig. 3). However, in

the per-protocol cohort, DD values on POD 5 had a tendency to be lower in the FPX group than in the LMWH group ($P = 0.0505$, data not shown).

Development of VTE

Three VTEs occurred in two LMWH patients (0.7%). No events occurred in the FPX group. However, there was no statistical difference between the two groups. Proximal DVT accompanied by non-fatal PTE was detected in one patient, who presented with right leg edema 1.5 months after open radical prostatectomy; DD and SFMC levels were 8.5 and 109 μg/mL on POD 1, respectively. The other patient, who had undergone laparoscopic radical prostatectomy, developed dyspnea with elevated DD (16.6 μg/mL), and was diagnosed with non-fatal PTE without DVT on POD 1 while still taking LDUH. Both patients were treated with intravenous unfractionated heparin and oral anticoagulant. An inferior vena cava filter was implanted in the former patient. Both were treated successfully without any sequela.

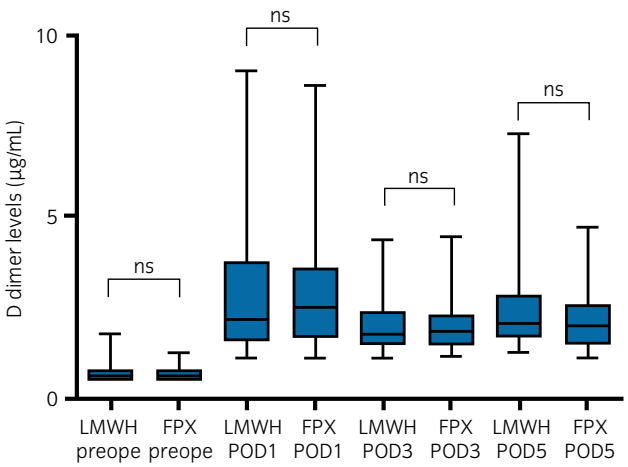

Fig. 2 Changes in perioperative DD levels. Median values are shown by a horizontal line inside the box. The lower and upper edge of the whisker represent the minimum and the maximum of the DD levels, respectively. The lower and upper end of the box represent the 25th and 75th percentiles, respectively.

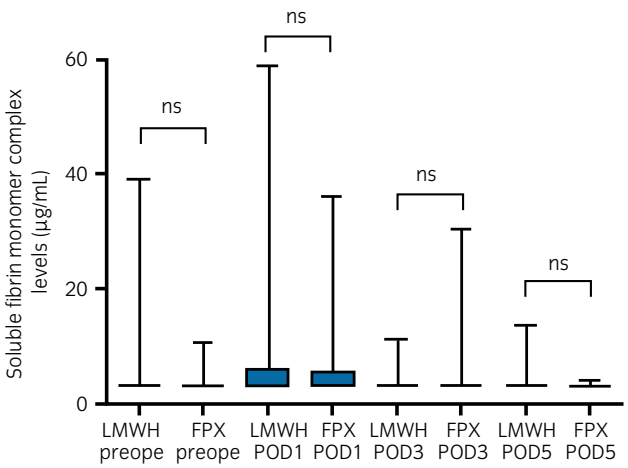

Fig. 3 Changes in perioperative SFMC levels. Median values are shown by a horizontal line inside the box. The lower and upper edge of the whisker represent the minimum and the maximum of the SFMC levels, respectively. The lower and upper end of the box represent the 25th and 75th percentiles, respectively.

Discussion

To the best of our knowledge, this is the first reported study to prospectively compare FPX with LMWH for thromboprophylaxis in patients undergoing surgery for urological malignancy. In our intention-to-treat-analysis, the incidence of major and minor postoperative bleeding of FPX was non-inferior to LMWH as the thromboprophylaxis use for urological malignancy. Though none of these events necessitated surgical intervention, discontinuation of the study drug was considered mandatory in the affected patients.

Postoperative bleeding in the FPX group occurred at a rate similar to that reported by Leonardi *et al.*, in a prospective study of various anticoagulation agents including LMWH and FPX for general, gynecological, thoracic, and urological surgeries.[23] However, pharmacological prophylaxis was discontinued at a higher rate in the present study than in that study (8.1% *vs* 2.0%). Turpie *et al.*, in a meta-analysis of anticoagulant prophylaxis carried out for orthopedic surgeries, showed that FPX did not increase the risk of clinically relevant bleeding compared with LMWH.[24] Anticoagulation agents were discontinued in all patients with bleeding in the present study, even those with minor bleeding, at the discretion of the attending physician. Other adverse events were not serious and resolved spontaneously. No statistically significant differences were found between the groups.

The overall incidence of VTE in the present study was 0.7% ($n = 2$ in the LMWH group), lower than for previous studies without thromboprophylaxis, but comparable with those studies involving the prophylactic use of anticoagulants.[6,8] The meta-analysis by Turpie *et al.* showed no difference in the incidence of VTE between LMWH (0.4%) and FPX (0.6%).[24] Agnelli *et al.* reported similar findings in high-risk abdominal surgery. In the subgroup of patients undergoing surgery for malignancy, FPX reduced the relative risk of VTE by 38.6%.[16] Meanwhile, Benjamin *et al.* suggested that lymphocele was an independent risk factor for VTE, and pharmacological thromboprophylaxis increased the rate of lymphocele formation.[25] Lymphocele was diagnosed in three patients who had undergone prostatectomy with concomitant pelvic lymphadenectomy in the present study. However, there were no VTE events in these cases.

The results of the present study suggest that the safety of FPX was non-inferior to LMWH. Whether FPX performs better than LMWH remains unconfirmed, owing to the limited number of patients. Potential disadvantages in the use of FPX include lack of a reversal agent, long half-life compared with other agents, non-applicability in patients with severe renal dysfunction and temporal restrictions in combination with epidural anesthesia. Nevertheless, FPX should be included among the reasonable thromboprophylactic options for high- to highest-risk patients undergoing urological surgery in safety.

DD and SFMC threshold values have been widely investigated for the detection of VTE after various types of surgery. Those values vary by surgery type and by report, ranging

from 2.0 to 20 μg/mL for DD and 3.6 to 20.8 μg/mL for SFMC.[19,20,26,27] In the present study, we set the postoperative DD threshold at 15 μg/mL. DD exceeded this threshold in four patients (two in each group) on POD 1. However, just one of the two patients who developed VTE showed levels higher than this threshold. The other had DD of 8.5 μg/mL, well below the cut-off, but interestingly his SFMC on POD 1 was high (109 μg/mL). Our DD cut-off threshold might thus not be sufficiently sensitive for the detection of VTE; the combined use of DD and SFMC might be more useful. Yoshioka *et al.* found no difference in DD between patients with or without VTE until POD 3, but patients with VTE had significantly higher DD levels on POD 7.[19] There might have been additional subclinical VTE in the present study, as DD was monitored only up to POD 5.

Several limitations should be considered in the interpretation of our study data. First, the two patient groups were too small for us to determine the true incidence of VTE in similar patients. Second, LDUH was used during the first 24 h before starting FPX and LMWH, as required under the Japanese healthcare system, because neither FPX nor LMWH is approved for use immediately after surgery in Japan. The design of the present study was thus to evaluate LDUH plus either FPX or LMWH. VTE was detected on POD 1, before starting LMWH, in one patient. Finally, though no further cases of symptomatic VTE were noted up to 3 months after surgery, many VTE events could have been overlooked as a result of inappropriate DD cut-off values.

In conclusion, the present study showed that the safety of FPX for preventing postoperative VTE in urological malignancy was non-inferior to LMWH. However, larger studies will be required to confirm these findings.

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Conflict of interest

None declared.

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