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Original Research

Efficacy and safety of thromboembolism prophylaxis with fondaparinux in Japanese colorectal cancer patients undergoing laparoscopic surgery: A phase II study

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HIGHLIGHTS

- We conducted a trial to evaluate the safety of Fondaparinux (FPNX) after Laparoscopic colorectal cancer surgery (LAC).
- FPNX was effective as venous thromboembolism (VTE) prophylaxis, but this treatment led to an incidence of bleeding events.
- We considered that it is necessary to decide whether to administer VTE prophylaxis after LAC based on the patient status.

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ABSTRACT

Purpose: We aimed to assess the safety and efficacy of fondaparinux (FPNX) for patients undergoing laparoscopic colorectal surgery (LAC).

Methods: Patients scheduled for LAC received once-daily subcutaneous injections of FPNX 1.5–2.5 mg for 4–8 days. The primary endpoint was the incidence of bleeding events. The secondary endpoint was the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Results: Among 128 patients evaluable for efficacy, 119 patients were administered FPNX. Nine patients were excluded owing to intraoperative events, including conversion to open surgery among others. Thirteen patients discontinued treatment owing to anastomotic bleeding (n = 5), anastomotic leakage (n = 3), bleeding at drain insertion site (n = 2), subcutaneous bleeding (n = 1), drug-induced rash (n = 1), and sepsis (n = 1). Among the FPNX discontinuations, there were eight cases of bleeding (6.7%), and two cases of major bleeding (1.7%). In multivariate analysis, operative time >300 min was identified as a risk factor for bleeding events ($p = 0.001$) secondary to FPNX. The incidence rate of DVT was 2.5% (3/119 cases); these patients were asymptomatic.

Conclusion: There were no cases of PE. It is necessary to establish strict criteria for VTE prophylaxis with FPNX after LAC for Japanese patients considering the incidence of bleeding events.

1. Introduction

Patients undergoing general surgery are at a certain risk of postoperative venous thromboembolism (VTE) [1,2]. The observed rates of deep vein thrombosis (DVT) range between 15% and 30%, and the risk of fatal pulmonary embolism (PE) is between 0.2% and 0.9% for high-risk general surgery patients [1].

According to Geert et al., the incidence rates of DVT and PE of abdominal surgery are similar to those of other types of surgery [1]. It was reported that incidence of VTE is 24.3% in patients undergoing abdominal surgery [3]. Further, Usuda et al. reported that the incidence of asymptomatic DVT was 15.1% after colorectal surgery [4].

The American Society of Clinical Oncology (ASCO) published an evidence-based clinical practice guideline on the prophylaxis and treatment of VTE and updated it in 2013 and 2015 [5–7]. In the 2007 guideline, it was recommended that all patients undergoing major surgical interventions for malignant disease should be considered for thromboprophylaxis with low-dose unfractionated heparin, low-molecular weight heparin, or fondaparinux (FPNX)

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starting as early as possible for at least 7–10 days before surgery, unless such treatment was contraindicated [8].

FPNX is a synthetic selective factor Xa inhibitor. It was reported that in patients undergoing elective major knee surgery, postoperative treatment with 2.5 mg of FPNX once daily was significantly more effective in preventing DVT than 30 mg of enoxaparin twice daily (12.5% vs 27.8%, respectively; $P < 0.001$) [9]. Additionally, Eriksson et al. reported that FPNX was more effective than, and as safe as, enoxaparin in preventing VTE (incidence of VTE; 8.3% vs 19.1%, respectively; $P < 0.001$) [10].

In Japan, it was reported that the administration of 2.5/1.5 mg FPNX 24 h after colorectal cancer surgery is safe and effective [11]. Conversely, laparoscopic surgery for colorectal cancer (LAC) has become widespread as a minimally-invasive alternative to open surgery. Regarding the risk of VTE, the incidence of postoperative VTE was lower in LAC than open surgery [12]. However, Cui et al. reported that incidence of postoperative VTE after LAC was similar to that after open surgery [13]. Additionally, Kimura et al. reported that the incidence of asymptomatic VTE after laparoscopic surgery for gastrointestinal cancer was 18.3% (13/71 cases). Therefore, VTE prophylaxis with FPNX may be necessary after LAC [14]. We conducted a phase II trial to evaluate the safety and efficacy of FPNX after LAC in Japanese patients with colorectal cancer (UMIN ID: UMIN000006543).

2. Material and methods

We conducted a single-center prospective study between November 2011 and March 2013. This study was approved by the appropriate institutional review board and undertaken according to the ethical principles stated in the Declaration of Helsinki.

A total of 128 patients were enrolled in this study. Patients were eligible for this study if they were planned to undergo LAC for colorectal malignancy. Patients with any contraindication or precaution stated in the package insert of the anticoagulant; history of lower limb orthopedic surgery, abdominal surgery, or cardiovascular surgery within 3 months of enrollment; use of concomitant drugs that are contraindicated for use within 1 week after FPNX administration; VTE diagnosis before surgery; D-dimer $\geq$ 1 μg before surgery; history of arterial thromboembolism; drug addiction or alcohol abuse; scheduled for another surgery during the study; pregnant women or women who had possibility of pregnancy; and those who were deemed as inadequate for study participation by the investigator were excluded from this study.

Patients scheduled for LAC under general anesthesia received once-daily subcutaneous injections of FPNX 2.5 mg or 1.5 mg for 4–8 days. Treatment with FPNX was reinitiated 24 h after surgery. Patients aged over 80 years, those with creatinine clearance less than 50 ml/min, and those with body weight less than 40 kg were administered a dose of 1.5 mg at the discretion of the attending physician. All patients used elastic compression stockings and received intermitted pneumatic compression until post operation day 1.

The primary endpoint measure was the incidence of bleeding complications requiring discontinuation of FPNX administration. The secondary endpoint measure was a composite of symptomatic and asymptomatic DVT detected by ultrasonography of the lower extremities, symptomatic confirmed DVT, or PE up until postoperative day 10. Bleeding complications requiring discontinuation of FPNX administration were defined as follow: bleeding from the digestive anastomosis, retroperitoneal bleeding, intracranial bleeding, bleeding from any vital organ (adrenal gland, pericardium, and spine, among others), a decrease in the hemoglobin level greater than 2 g/dl from the pre-bleeding event level within 48 h after the onset of bleeding, and bleeding that required transfusion of red blood cells derived from whole blood.

For DVT diagnosis, patients with a D-dimer score greater than 1 μg/ml on day 2 and day 7 postoperatively underwent lower extremity Doppler venous ultrasonography (DUS). The DUS examinations were performed by two technicians with more than 10 years of experience.

2.1. Statistical analysis

The software JMP ver.9 (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analyses. Continuous variables are presented as the mean ± standard deviation (SD). The differences between the two groups were assessed by the chi-square test or the unpaired Student's *t*-test. The Cox regression model (logistic regression analysis) was used for multivariate analysis. In all analyses, $p < 0.05$ indicated statistical significance.

3. Results

Between November 2011 and March 2013, 128 patients were enrolled in this study. Nine patients were excluded from the study for the following reasons: four patients underwent conversion to open surgery; three patients presented massive bleeding during the operation; one patient presented anastomotic bleeding immediately after surgery, and one patient presented myocardial infarction immediately after surgery. A total of 119 patients were administered FPNX. Regarding the dose, 107 patients received 2.5 mg and 12 patients received 1.5 mg. The total median duration of FPNX treatment at a dose of 1.5 mg was 5 (range 2–6) days and at 2.5 mg was 6 (1–10) days.

Table 1 shows preoperative clinical characteristics. The study group consisted of 78 men and 50 women with a median age of 69 (range, 38–86) years. The location of the tumor was as follows: 8 patients, cecum; 17 patients, ascending colon; 7 patients, transverse colon; 3 patients, descending colon; 27 patients, sigmoid colon; 20 patients, rectosigmoid junction (Rs); 15 patients, rectum above the peritoneal reflection (Ra); 26 patients, rectum below the peritoneal reflection (Rb); 4 patients, anal canal (P); and 1 patient, multiple colonic lesions. The median body mass index (BMI) was 22.3 (16–30) kg/m^2. Sixty patients had an ASA score of 1 and 68 patients, a score of 2.

Table 2 summarizes the operative procedure and short-term outcomes after surgery including postoperative complications. All

Table 1
Preoperative clinical characteristics.

Gender (male/female)		78/50
Age (year)		69 (range 38–86)
BMI*(kg/m2)		22.3 (16–30)
Height(cm)		159 (141–177)
Body weight (kg)		54.6 (30.0–81.8)
ASA* score	1(%)	60 (46.9)
	2(%)	68 (53.1)
	3(%)	0 (0)
	4(%)	0 (0)
Tumor location	Cecum	8
	Ascending colon	17
	Transverse colon	7
	Descending colon	3
	Sigmoid colon	27
	Rs	20
	Ra	15
	Rb	26
	P	4
	Multiple colon cancer	1

*BMI, Body Mass Index.
*ASA, American Society of Anesthesiologists.

Table 2
Operative procedure and outcomes after surgery.

Operative procedure		
Ileocecal resection	8	
Right hemicolectomy	22	
Left hemicolectomy	7	
Sigmoidectomy	27	
High anterior resection	10	
Low anterior resection	27	
Super low anterior resection	19	
Internal sphincter resection	3	
Abdomino-perineal resection	3	
HARTMANN operation	1	
Subtotal colectomy	1	
Conversion to open surgery (%)	5 (3.9)	
Operating time (min)	232 (range 118–436)	
Operative blood loss (ml)	77 (0–1174)	
No. of patient with complication (%)	41 (32.0)	discontinuation of FPNX[a]
Superficial SSI	7	
Anastomotic bleeding	6	5
Bowel obstruction	6	
Anastomotic leakage	4	3
Failure of urination	4	
Deep vein thrombosis	3	
Liver dysfunction	3	
Enteriris	2	
Bleeding of drain insertion site	2	2
Acute myocardiac infarctionI	1	
Subcutanneous bleeding	1	1
Sepsis	1	1
Drug-induced rash	1	1
Hospital death (%)	1 (0.8)	

[a] FPNX, fondaparinux.

patients underwent LAC, which was converted to open surgery in five cases (3.9%). The median operating time was 232 (118–436) minutes and median operative blood loss was 77 (0–1174) ml. The incidence of postoperative complications was 32.0% (41/128 cases). Thirteen patients (10.9%) discontinued FPNX treatment because of adverse events, such as anastomotic bleeding (5 cases), anastomotic leakage (3 cases), bleeding at the drain insertion site (2 cases), subcutaneous bleeding (1 case), drug-induced rash (1 case), and sepsis (1 case).

Among those that discontinued FPNX treatment, eight patients (6.7%) presented bleeding events. In the intention-to −treat analysis, nine patients (7.0%) presented bleeding events after operation. Two patients (1.7%) presented major bleeding events. Both cases of major bleeding consisted of complicated anastomotic bleeding. In both cases, the hemoglobin level decreased more than 2 g/dl.

Table 3 shows pre and postoperative blood laboratory data and oxygen saturation levels of patients. Although three patients presented liver dysfunction (aspartate aminotransferase $\geq$ 100 U/L and/or alanine aminotransferase $\geq$ 100U/L), they continued to receive FPNX treatment for 6 days after surgery. The D-dimer score on preoperative day (POD) 1, POD 3 and POD 7 were 0.4 (0.2–10.2), 2.0 (0.5–13.3), and 2.3 (0.8–21.0) μg/ml, respectively. At POD3, 102 patients underwent DUS. Three of 119 patients presented asymptomatic DVT. The D-dimer scores on postoperative day 3 of these three patients were 1.9, 1.1, and 1.9 μg/ml. The location of DVT in one patient was the right peroneal vein, in one was the left soleal vein, and in the other, bilateral soleal veins. All three patients were treated with warfarin. One month after warfarin administration, the DVT had resolved in all three patients. There was no case of complicated PTE in this study.

Tables 4 and 5 show univariate and multivariate analyses of risk factors of bleeding events associate with discontinuation of FPNX. In the Yates Chi square test, risk factors for FPNX discontinuation owing to bleeding events were male sex ($p = 0.049$) and operative time >300 min ($p < 0.001$) (Table 4). In the multivariate analysis, operative time >300 min was found to be the significant risk factor for bleeding ($p = 0.001$) (Table 5).

4. Discussion

In this study, the incidence of bleeding events related to FPNX treatment, which was the primary study endpoint, was 6.7% (Intention-to −treat analysis: 7.0%). The incidence of major bleeding was 1.7% in our cohort of Japanese colorectal cancer patients. Hata et al. reported that the incidences of major and minor bleeding events secondary to FPNX in Japanese colorectal cancer

Table 3
Pre- and post- operative blood laboratory data and Oxygen saturation score.

	Pre operation day 1	Post operartion day 3	Post operartion day 7
SaO2	98 (range 94–100)	97 (94–99)	98 (95–100)
ALT (U/L)	16.5 (5–51)	14 (5–117)	28 (6–277)
AST (U/L)	20 (11–59)	16 (9–41)	22 (10–188)
Platelet ($\times 10^4/\mu L$)	21.7 (8.8–41.8)	19.8 (7.9–40.6)	25.2 (10.5–56.0)
D-dimer (μg/mL)	0.4 (0.2–10.1)	2 (0.5–13.3)	2.3 (0.9–21.0)

Table 4
Univariable analysis of factors of bleeding events associate with withdraw FPNX.

Factor	n	Incidence of bleeding events(%)	p value
Age			
<75	92	5 (5.4)	0.131
≥75	27	4 (14.8)	
Sex			
Male	72	8 (11.1)	0.049
Female	47	1 (2.1)	
BMI (kg/m^2)			
<23	67	4 (6.0)	0.458
≥23	52	5 (9.6)	
Rectal surgery			
yes	52	5 (9.6)	0.458
no	67	4 (6.0)	
Operation time (min)			
<300	99	2 (2.0)	0.001
≥300	20	7 (35.0)	
Operative blood loss volume (ml)			
<100	74	3 (4.0)	0.068
≥100	45	6 (13.3)	
Pre operative D-dimer (μg/ml)			
<0.6	76	8 (10.5)	0.077
≥0.6	43	1 (2.3)	
Pre operative Platelet (×10^4/μl)			
<15	15	2 (13.3)	0.403
≥15	104	7 (6.7)	
Pre operative ALT (U/L)			
<35	113	8 (7.1)	0.446
≥35	6	1 (16.7)	
Pre operative AST (U/L)			
<35	113	8 (7.1)	0.446
≥35	6	1 (16.7)	

patients were 0.81 and 9.5%, respectively, and concluded that the administration of FPNX 24 h after colorectal cancer surgery was safe and effective [11]. In Western countries, Turpie et al. reported that the incidences of major and minor bleeding due to FPNX were 1.6% and 0.8%, respectively [15], and Agnelli et al. reported that the incidence of major bleeding was 3.4% [16]. Although, in our study, there was a limitation to evaluate the incidence of bleeding after surgery because nine patients were excluded from this study for conversion to open surgery, massive intra- operative bleeding and other reasons in order to prevent postoperative bleeding events will increase, when comparing our data of bleeding incidence with the outcomes of past research, our results did not differ greatly from those previously reported. However, in the present study, the multivariate analysis showed that operative time >300 min was a significant risk factor ($p = 0.001$) for bleeding events with FPNX treatment. Although in this study, there is no comparison group with bleeding events with FPNX treatment and the bleeding events might due to other aspect of clinical care such as operative procedure, it is necessary to pay close attention to the administration of FPNX in cases of prolonged LAC.

In our study, the incidence of DVT was 2.5% (3/119 cases), and no patients presented PE. Further, all patients that presented DVT were asymptomatic. However, there was a limitation to detect clinically symptomatic DVT or PE strictly because median follow-up term was only 9 days (7–33 days). Sakon et al. reported that in Japan the incidence of VTE was 24.3% in patients undergoing abdominal surgery [3]. Usuda et al. reported that the incidence of asymptomatic DVT was 15.1% after colorectal surgery [4]. Regarding laparoscopic surgery, Kimura et al. reported that 13 patients (18.3%) developed asymptomatic VTE among 71 patients that underwent laparoscopic surgery for gastrointestinal cancer [14]. Mahdi et al. reported that of the 2219 patients who underwent at least one major laparoscopic surgery for uterine, ovarian, or cervical cancers, 15 patients (0.7%) were diagnosed with VTE within 30 days following surgery [17]. These outcomes suggest that the incidence of DVT after laparoscopic surgery is nearly equal to that of open surgery and that the occurrence of PE is relatively rare.

Taken together, the outcomes of these previous studies together with those of the present study suggest that VTE prophylaxis with FPNX can provide a certain benefit Japanese patients with colorectal cancer. However, considering the incidence of bleeding complications, it is difficult to state that VTE prophylaxis with FPNX is always necessary to prevent of DVT after surgery for Japanese patients with colorectal cancer. Although we have not administered VTE prophylaxis (e.g., Xa inhibitor) to patients with colorectal cancer undergoing laparoscopic surgery from 2014 onward, none of our patients have presented complicated symptomatic DVT and PE thus far (data not shown). From the above, strict criteria should be established for the administration VTE prophylaxis with Xa inhibitor after laparoscopic surgery (i.e., abnormally high BMI score and history of DVT).

In the present study, we used direct venography with DUS for the diagnosis of DVT. However, DUS is limited for the diagnosis of DVT such as VTE in the iliac veins and inferior vena cava [18]. Further, vast experience is required for technicians to diagnose DVT by DUS. Furthermore, diagnosis by DUS requires long periods of inspection time. Terao et al. reported that DUS is a highly sensitive and specific tool, especially for the examination of the lower extremities; they considered that DUS was nearly equivalent to venography [19]. Additionally, this technique is minimally invasive and convenient compared with multi-detector computed tomography from the viewpoint of radiation exposure and costs [18]. Therefore, if the occurrence of DVT after surgery is suspected, there is a limitation to detect DVT by DUS alone, but DUS of the lower extremities should be performed initially.

Based on the present study outcomes, we considered that although it is necessary to decide whether to administer VTE prophylaxis after LAC based on the patient status (e.g., high BMI score), VTE prophylaxis with FPNX will be not necessary for all LAC patients. If VTE prophylaxis with Xa inhibitor is necessary in the case of a high-risk group with VTE, enoxaparin should be used rather than FPNX. Sakon et al. reported that the use of enoxaparin (20 mg twice daily for 14 days beginning 24–36 h after surgery) in Japanese patients undergoing abdominal or pelvic cancer surgery yielded favorable efficacy outcomes (incidence of VTE of 1.2%) and safety (incidence of bleeding event of 9.2%) [20]. In comparison with enoxaparin, FPNX has a longer half-life and presently, there is no antidote [21]. If a bleeding event occurs in patients treated with enoxaparin, such bleeding tendency can be neutralizes with protamine. In the present study, the operative time >300 min was a

Table 5
Multivariate analysis of factors of bleeding events associate with withdraw FPNX.

Factor	Odd ratio	p value	95% confidence interval
Age ≥75 yeas old	5.626	0.09	−0.117–1.969
Male patients	2.219	0.512	−0.699–1.936
Operation time ≥300 min.	30.727	0.001	0.763–2.946
Operative blood loss volume ≥100 ml	1.318	0.779	−0.867–1.118
Pre operative D-dimer score <0.6	0.095	0.063	−2.781~−0.119

significant risk factor for bleeding events with FPNX treatment. Therefore, we consider that enoxaparin has safety advantage over FPNX in cases of prolonged LAC.

Recently, extended VTE prophylaxis have been performed after colorectal cancer surgery. Sammour et al. summarized five major clinical guidelines and five major published randomized controlled trials with specific focus on the efficacy and cost-effectiveness of extended VTE prophylaxis to prevent clinically relevant post-operative VTE after colorectal cancer surgery [22]. They reported that extended VTE prophylaxis reduces the incidence of asymptomatic screen detected DVT only, with no demonstrable reduction in symptomatic DVT, symptomatic PE, or VTE related death and evidence for cost-effectiveness is limited. From the above, we consider that extended VTE prophylaxis after LAC is not necessarily needed for all colorectal cancer patients. To validate the efficacy of extended VTE prophylaxis, the future study focused high risk group, such as those who are obese, have a past history of VTE and so on should be planned.

In conclusion, FPNX was found to be effective as VTE prophylaxis, but this treatment led to a considerable incidence of bleeding events. Our study included data of a single center, and thus, our study is limited in terms of arriving at definitive conclusions regarding the safety and efficacy of FPNX. In the future, a multicenter prospective randomized controlled study is necessary to validate the safety and efficacy of VTE prophylaxis with Xa inhibitor after LAC in Japanese patients with colorectal cancer.

Competing interests

The authors declare that they have no competing interests.

Ethical approval

We got Ethical Approval from Ethics Committee in Kansai Medical University Hospital.

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None.

Authors' contributions

KT made substantial contributions to the conception of the study, conducted a literature search, and drafted the manuscript. KT, YU, HM and KN contributed to the acquisition of the data. KT and MK reviewed the manuscript and gave the final approval for its publication. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflict of interests.

Trial registry number – ISRCTN

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Guarantor

The Guarantors of this manuscript are Katsuji Tokuhara and Prof. Masanori Kon.

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Disclosures

Katsuji Tokuhara, MD, PhD has no conflict of interest to declare.
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