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Safety and Efficacy of Fondaparinux for Prophylaxis of Venous Thromboembolism after Colorectal Cancer Resection: A Propensity Score Matched Analysis

Yusuke Yamaoka[a] Masataka Ikeda[a] Masakazu Ikenaga[b]
Naotsugu Haraguchi[a] Masakazu Miyake[a] Mitsugu Sekimoto[a]

[a]Department of Surgery, National Hospital Organization, Osaka National Hospital, Chuo-ku, Osaka and
[b]Department of Surgery, Osaka Rosai Hospital, Kita-ku, Sakai, Osaka, Japan

Key Words
Colorectal cancer · Surgery · Fondaparinux · Venous thromboembolism · Bleeding · Postoperative complication

Abstract
Background/Aims: The aim of this study was to examine the safety and efficacy of fondaparinux (FPX) for venous thromboembolism (VTE) prophylaxis after colorectal cancer surgery. ***Methods:*** Records of 953 patients with colorectal cancer who underwent resection between 2006 and 2013 were reviewed. Patients were divided into two groups: the FPX group (n = 362), treated with subcutaneous FPX plus intermittent pneumatic compression (IPC) and the IPC group (n = 591), treated with IPC alone. The incidence of symptomatic VTE, major bleeding, minor bleeding, and other postoperative complications were compared using propensity score matching. ***Results:*** Symptomatic VTE occurred only in one patient (0.2%) in the IPC group. In the FPX group, the incidence of major and minor bleeding was 0.55% (2 of 362) and 9.4% (34 of 362), respectively. After propensity score matching, there were no differences between the two groups in the incidence of symptomatic VTE, major bleeding, and other common postoperative complications. Only the incidence of minor bleeding was significantly higher in the FPX group compared to the IPC group. ***Conclusion:*** FPX is potentially an effective form of VTE prophylaxis; it is safe in terms of both postoperative bleeding and other common complications after colorectal cancer surgery.

Introduction

It is well known that colorectal cancer (CRC) surgery is associated with increased risk of venous thromboembolism (VTE) [1]. Pharmacological VTE prophylaxis is considered to be the standard of care for patients with a low risk of bleeding, while mechanical prophylaxis is an alternative for patients at higher risk [2].

Fondaparinux (FPX) is a synthetic selective inhibitor of factor Xa. Several clinical trials have demonstrated not only its antithrombotic efficacy but also its favorable safety profile, including its prevention of VTE in patients undergoing major orthopedic surgery or high-risk abdominal surgery [3, 4]. In the randomized, double-blinded APOLLO study, the combination of intermittent pneumatic compression (IPC) and FPX reduced the incidence of VTE after abdominal surgery by 69.8% relative to IPC alone, with a low bleeding risk compared to placebo [5]. However, there are

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E-Mail karger@karger.com
www.karger.com/dsu

Masataka Ikeda
Department of Surgery
National Hospital Organization, Osaka National Hospital
2–1-14 Hoenzaka, Chuo-ku, Osaka 540–0006 (Japan)
E-Mail mikeda@onh.go.jp

few studies evaluating the safety and efficacy of FPX after CRC surgery. Therefore, little is known about the influence of FPX on the incidence of postoperative complications after CRC surgery, such as bleeding, anastomotic leakage, and intra-abdominal abscess. In this retrospective study we examined the safety and efficacy of FPX combined with IPC after CRC resection.

Materials and Methods

Study Population

We retrospectively reviewed the records of 1,127 Japanese patients who had undergone surgery for primary CRC between April 1, 2006 and March 31, 2013 at Osaka National Hospital. The exclusion criteria were as follows: concomitant treatment with another surgical procedure such as gastrectomy, esophagectomy, hepatectomy, splenectomy, or pancreatectomy (n = 43); bowel obstruction requiring preoperative surgical intervention or metallic stenting (n = 46); emergent surgery for perforation or bleeding (n = 12); a history of arteriosclerosis obliterans or VTE (n = 17); or postoperative administration of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) (n = 56). The remaining 953 patients served as our study cohort. All patients underwent elective resection of CRC under general anesthesia and received IPC from the beginning of anesthesia until full ambulation. Beginning in 2010, our institution adopted FPX for thromboprophylaxis after CRC surgery. The patients were divided into two groups. The FPX group was treated with IPC and subcutaneous FPX (2.5 or 1.5 mg) once daily for more than 4 days. The IPC group was treated with IPC alone as a control.

Safety and Efficacy Outcomes

The safety outcomes were the incidence of major bleeding, minor bleeding, and postoperative complications other than bleeding within 30 days after surgery, respectively. Major bleeding was defined by the presence of one or more of the following: fatal bleeding; bleeding that was retroperitoneal, intracranial, intraspinal, or involving any other critical organ; bleeding leading to reoperation or intervention; and a bleeding index of 2.0 or more. The bleeding index was derived by adding the number of units of packed red blood cells or whole blood transfused to the difference in the hemoglobin level (g/dl) before and after a bleeding event. Minor bleeding was defined as bleeding that did not meet any of the criteria for major bleeding. The incidence of anastomotic leakage, intra-abdominal abscess, bowel obstruction, wound complication, urinary tract infection, and complications of Grade IIIa or greater based on the Clavien-Dindo classification [6] were compared between the two groups. Mortality within 30 days of surgery was also assessed.

The efficacy outcome was the incidence of symptomatic VTE within 30 days of surgery. VTE was confirmed by computed tomography of the chest positive for pulmonary embolism (PE) or venous ultrasound imaging positive for deep vein thrombosis (DVT). All patients visited the outpatient clinic approximately 3 to 4 weeks after the day of hospital discharge, where symptoms of VTE, such as dyspnea, chest pain, and limb swelling or pain, were assessed.

Statistical Analysis

We performed propensity score matching to reduce the possibility of selection bias and to adjust for significant differences in baseline characteristics of patients in the FPX and IPC groups. To estimate the propensity score, logistic regression was performed with the following 20 variables: gender, age, preoperative body mass index, preoperative serum albumin, preoperative platelet count, preoperative chemotherapy or radiation therapy, hypertension, diabetes mellitus, cerebrovascular disease, ischemic heart disease, respiratory disease, chronic renal failure, American Society of Anesthesiologists (ASA) physical status classification, operative time, intraoperative blood loss, intraoperative blood transfusion, epidural catheter use, procedure type (laparoscopic surgery or open surgery), tumor location, and disease stage according to the TNM classification of the International Union Against Cancer (UICC), version 7.0. Each patient in the FPX group was matched to a patient in the IPC group on the basis of those variables. One-to-one pair matching was done without replacement, and propensity scores were matched with a caliper of 0.001. We compared clinical characteristics of the patients, the incidence of symptomatic VTE, major bleeding, minor bleeding, and postoperative complications between the two groups. Continuous variables were expressed as mean ± SD. In full cohort, categorical variables were compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using Student's t-test. In the propensity score-matched cohort, categorical variables were compared using McNemar test and continuous variables were compared using a paried t-test. All statistical analyses were performed using JMP software, version 11.0 (SAS Institute Inc., Cary, North Carolina, USA) and the statistical program R (http://.r-project.org/), with the advice of a trained statistician. A p value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

Baseline variables of patients in the FPX (n = 362) and IPC (n = 591) groups are listed in table 1. No statistical differences between the two groups were found in gender, age, preoperative therapy, preoperative comorbidities, operating time, intraoperative blood transfusion, use of epidural catheter, or tumor location. Preoperative body mass index (FPX: 23.0 ± 3.3 kg/m^2, IPC: 22.4 ± 3.5 kg/m^2), preoperative serum albumin (FPX: 4.09 ± 0.47 g/dl, IPC: 4.00 ± 0.57 g/dl) and the proportion of patients undergoing laparoscopic surgery (FPX: 59.4%, IPC: 34.7%) were higher in the FPX group. Preoperative platelet count (FPX: 26.2 ± 9.1/μl, IPC: 27.8 ± 9.3/μl) and the proportion of patients with stage IV disease (FPX: 6.9%, IPC: 12.4%) were lower in the FPX group. There was significantly less intraoperative blood loss in the FPX group (FPX: 67.4 ± 160.4 ml, IPC: 109.5 ± 262.7 ml). After propensity score matching, there were no significant differences in all the baseline variables between the FPX (n = 237) and the IPC (n = 237) groups. The median duration of FPX was 4 days

Table 1. Clinical characteristics of the study patients

Variable	Full cohort (n = 953)			Propensity score-matched cohort (n = 474)		
	FPX (n = 362)	IPC (n = 591)	p value*	FPX (n = 237)	IPC (n = 237)	p value**
Patient characteristics						
Gender (%)						
Male	214 (59.1)	350 (59.2)	0.974	139 (58.6)	141 (59.5)	0.847
Female	148 (40.9)	241 (40.8)		98 (41.4)	96 (40.5)	
Age, years	67.3±10.8	66.5±10.7	0.279	67.1±11.2	67.4±10.6	0.744
Preoperative body mass index, kg/mg^2	23.0±3.3	22.4±3.5	0.009	22.7±3.3	22.8±3.5	0.920
Preoperative serum albumin, g/dl	4.09±0.47	4.00±0.57	0.017	4.06±0.49	4.04±0.52	0.704
Preoperative platelet count, /μl	26.2±9.1	27.8±9.3	0.010	26.6±9.7	26.5±7.8	0.914
Preoperative chemotherapy or radiation therapy (%)	8 (2.2)	9 (1.5)	0.437	7 (3.0)	3 (1.3)	0.206
Preoperative comorbidities (%)						
Hypertension	141 (39.0)	235 (39.8)	0.803	87 (36.7)	99 (41.8)	0.248
Diabetes mellitus	68 (18.8)	85 (14.4)	0.072	37 (15.6)	42 (17.7)	0.535
Cerebrovascular disease	25 (6.9)	41 (6.9)	0.985	14 (5.9)	18 (7.6)	0.465
Ischemic heart disease	12 (3.3)	13 (2.2)	0.296	7 (3.0)	8 (3.4)	0.782
Respiratory disease	16 (4.4)	32 (5.4)	0.496	7 (3.0)	6 (2.5)	0.782
Chronic renal failure	9 (2.5)	21 (3.6)	0.360	12 (5.1)	12 (5.1)	1
ASA physical status classification class						
I	80 (22.1)	107 (18.1)	0.276	45 (19.0)	41 (17.3)	0.265
II	271 (74.9)	461 (78.0)		183 (77.2)	184 (77.6)	
III	11 (3.0)	23 (3.9)		9 (3.8)	12 (5.1)	
Surgical and treatment characteristics						
Operative time, min	200.3±91.7	190.1±95.2	0.106	193.2±93.4	202.8±99.7	0.264
Intraoperative blood loss, ml	67.4±160.4	109.5±262.7	0.006	72.2±146.0	83.4±146.8	0.396
Intraoperative blood transfusion (%)	11 (3.0)	28 (4.7)	0.199	9 (3.8)	8 (3.4)	0.808
Use of epidural catheter (%)	343 (94.8)	556 (94.1)	0.662	226 (95.4)	221 (93.2)	0.317
Procedure (%)						
Open surgery	158 (43.6)	395 (66.8)	<0.001	136 (57.4)	125 (52.7)	0.124
Laparoscopic surgery	204 (56.4)	196 (33.2)		101 (42.6)	112 (47.3)	
Tumor characteristics						
Tumor location (%)						
Right colon	95 (26.2)	182 (30.8)	0.218	67 (28.3)	78 (32.9)	0.653
Left colon	109 (30.1)	181 (30.6)		71 (30.0)	72 (30.4)	
Rectum	158 (43.6)	228 (38.6)		99 (41.8)	87 (36.7)	
UICC Stage						
0, I	105 (29.0)	182 (30.8)	0.021	79 (33.3)	75 (31.6)	0.164
II	110 (30.4)	163 (27.6)		68 (28.7)	70 (29.5)	
III	123 (34.0)	173 (29.3)		71 (30.0)	75 (31.6)	
IV	24 (6.6)	73 (12.4)		19 (8.0)	17 (7.2)	

Mean ± SD. [a] Respiratory disease includes chronic obstructive pulmonary disease and bronchial asthma. ASA = American Society of Anesthesiologists; UICC = International Union Against Cancer. FPX = the group receiving fondaparinux and intermittent pneumatic compression; IPC = the group receiving intermittent pneumatic compression. * Categorical variables were compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using Student's t-test. ** Categorical variables were compared using McNemar test and continuous variables were compared using a paired t-test.

(range 1–5 days). From a total of 953 patients, 946 were screened for symptoms of VTE at outpatient clinics. Four patients who died within 30 days of surgery and three patients who were transferred to another hospital could not be evaluated at outpatient clinics.

Safety and Efficacy Outcomes

Table 2 summarizes the safety and efficacy outcomes in each group. Only one patient developed symptomatic postoperative VTE in the IPC group. This patient died of PE 14 days after laparoscopic sigmoidectomy. There were

Table 2. Safety and efficacy outcomes

	Full cohort (n = 953)			Propensity score-matched cohort (n = 474)		
	FPX (n = 362)	IPC (n = 591)	p value*	FPX (n = 237)	IPC (n = 237)	p value**
Symptomatic VTE (%)	0 (0)	1 (0.2)	1	0 (0)	1 (0.4)	0.317
Major bleeding (%)	2 (0.6)	5 (0.8)	0.715	1 (0.4)	0 (0)	0.317
Fatal bleeding	0 (0)	0 (0)		0 (0)	0 (0)	
Bleeding in a critical organ	0 (0)	0 (0)		0 (0)	0 (0)	
Bleeding leading to reoperation or intervention	2 (0.6)	2 (0.3)		1 (0.4)	0 (0)	
Bleeding index >2.0	0 (0)	3 (0.5)		0 (0)	0 (0)	
Minor bleeding (%)	33 (9.1)	18 (3.0)	<0.001	24 (10.1)	10 (4.2)	0.013
Melena or anastomotic hemorrhage	13 (3.6)	11 (1.9)		10 (4.2)	5 (2.1)	
Bloody discharge or hemorrhage at the drain site	12 (3.3)	3 (0.5)		9 (3.8)	3 (1.3)	
Subcutaneous hemorrhage or hematoma	6 (1.7)	2 (0.3)		3 (1.3)	0 (0)	
Bleeding at epidural catheter insertion site	2 (0.6)	2 (0.3)		2 (0.8)	2 (0.8)	
Postoperative complications (%)						
Anastomotic leakage	24 (6.6)	27 (4.6)	0.170	17 (7.2)	11 (4.6)	0.239
Intra-abdominal abscess	9 (2.5)	17 (2.9)	0.720	6 (2.5)	6 (2.5)	1
Bowel obstruction	29 (8.0)	45 (7.6)	0.824	20 (8.4)	17 (7.2)	0.622
Wound complication	39 (10.8)	89 (15.1)	0.060	29 (12.2)	37 (15.6)	0.285
Urinary tract infection	15 (4.1)	16 (2.7)	0.225	10 (4.2)	7 (3.0)	0.467
Clavien-Dindo classification IIIa or greater	34 (9.4)	53 (9.0)	0.825	23 (9.7)	25 (10.5)	0.768
Death from any cause within 30 days of surgery (%)	0 (0)	4 (0.7)	0.304	0 (0)	2 (0.8)	0.157

[a] The bleeding index was calculated as follows: (number of units of packed red blood cells or whole blood transfused) + (([pre-bleeding] − [post-bleeding]) hemoglobin [g/dl]). VTE = Venous thromboembolism; FPX = the group receiving fondaparinux and intermittent pneumatic compression; IPC = the group receiving intermittent pneumatic compression. * Categorical variables were compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using Student's t-test. ** Categorical variables were compared using McNemar test and continuous variables were compared using a paired t-test.

no patients with symptomatic VTE in the FPX group. The incidence of major bleeding was 0.55% (2/362) in the FPX group and 0.85% (5/591) in the IPC group (p = 0.61). In the FPX group, one patient underwent endoscopic hemostasis for anastomotic bleeding after laparoscopic sigmoidectomy and one underwent reoperation for intra-abdominal hematoma after anterior resection. There were no instances of fatal bleeding or bleeding in a critical organ. The incidence of minor bleeding was 9.4% (34/362) in the FPX group and 2.9% (17/591) in the IPC group (p < 0.001). FPX was discontinued in 25 of 34 patients having minor bleeding. None of the patients with minor bleeding required treatment other than the discontinuation of FPX. Melena or anastomotic hemorrhage was the most frequent event, followed by bloody discharge or hemorrhage at the drain site.

After propensity score matching, there were no differences between the two groups in the incidence of symptomatic VTE, major bleeding, anastomotic leakage, intra-abdominal abscess, bowel obstruction, wound complication, urinary tract infection, postoperative complications of Clavien-Dindo classification IIIa or greater, and death within 30 days of surgery. Only the incidence of minor bleeding was significantly higher in the FPX group than in the IPC group (p = 0.013).

Discussion

Patients undergoing CRC surgery are at a higher risk of VTE than general surgery patients for multiple reasons, including the need for pelvic lymph node dissection, surgical positioning (lithotomy position), and the activation of the hemostatic system associated with cancer [7, 8]. Given that DVT develops in approximately 30% of CRC surgery patients who do not receive any thromboprophylaxis and fatal PE occurs in 1% [9], pharmacologic prophylaxis in addition to mechanical prophylaxis is

strongly recommended [2]. In this study, symptomatic VTE (PE) occurred in one patient (0.17%) in the IPC group (n = 591) but not in the FPX (n = 362) group, which received both IPC and FPX. Hata et al. reported no symptomatic VTEs within 7 days of surgery in 619 Japanese patients given FPX after CRC surgery [10]. Other studies have reported that the incidence of symptomatic VTE within 30 days of CRC surgery in patients receiving LMWH or UFH range from 0 to 1.8% [11–13]. FPX significantly reduces the incidence of VTE in patients undergoing major abdominal surgery with IPC [5], and it is as effective as perioperative LMWH in patients undergoing high-risk abdominal surgery [4]. The combination of IPC and FPX is potentially an effective form of thromboprophylaxis even in CRC surgery. The incidence of major bleeding and minor bleeding in the FPX group was 0.55 and 9.4%, respectively. These results are comparable to those of a prospective cohort study evaluating the safety of FPX for the prevention of VTE in Japanese patients undergoing CRC surgery, which reported incidences of 0.81 and 9.5%, respectively [10]. In several studies evaluating the safety of LMWH for the prevention of VTE after CRC surgery, the incidence of major bleeding and minor bleeding was reported to be 0.89–2.7% and 4.5–8.0%, respectively [13–15], similar to our results. These results suggest that FPX is comparable to LMWH in terms of prevention of symptomatic VTE and postoperative bleeding in patients undergoing CRC surgery.

In addition, our study compared the incidence of major bleeding, minor bleeding, and common postoperative complications after CRC surgery in patients receiving FPX versus those who did not by using propensity score matching. Propensity score matching is frequently used to reduce the bias caused by imbalanced covariates, which has been shown to result in similarly matched populations [16, 17]. Consequently, there were no significant differences in patient characteristics, preoperative comorbidities, type of surgery, and treatment or tumor characteristics between the two groups after matching. In the propensity score-matched cohort, there were no differences between the two groups in the incidence of major bleeding, anastomotic leakage, intra-abdominal abscess, bowel obstruction, wound complication, urinary tract infection, postoperative complications of Clavien-Dindo classification IIIa or greater, and death within 30 days of surgery. Only the incidence of minor bleeding was significant higher in the FPX group compared to the IPC group. FPX was discontinued in 25 of 34 patients having minor bleeding to make sure that the bleeding was stopped. Although bleeding was minor, treatment was nevertheless discontinued at a rate of 6.9% (25/362), whereas the rate of discontinuation of LMWH for VTE prophylaxis after bariatric surgery was reported to be 2.9% [18]. This was because FPX has a half-life of about 14–17 hours, which was longer than UFH or LMWH, and an antagonist of FPX in Japan is not available. Consequently, all minor bleeding in our study was not clinically significant. In hip and knee replacement surgery, the use of LMWH for the prevention of VTE has been considered a risk factor for surgical site infection because hematoma formation is significantly associated with the occurrence of surgical site infection [19–22]. There have been few studies evaluating the impact of anticoagulation on postoperative complications other than bleeding after colorectal surgery. A prospective cohort study reported that the use of UFH after colorectal surgery was significantly associated with surgical site infection [23]; however, this was not observed in our study. Thus, the use of FPX after CRC surgery was safe in terms of postoperative complications, including bleeding.

Before 2008, the Japanese government did not approve the use of FPX or LMWH as pharmacological VTE prophylaxis after abdominal surgery. This was because there had been no evidence on the superiority of pharmacological prophylaxis over mechanical prophylaxis in Japanese patients before that and the incidence of symptomatic VTE was lower in Japanese than in Western people, that was attributed to the ethnic difference [24]. Therefore, IPC was the most accepted VTE prophylaxis after abdominal surgery in many hospitals at that time [25]. In 2009, Sakon, et al. reported efficacy and safety of LMWH as pharmacological VTE prophylaxis in Japanese patients undergoing abdominal or pelvic cancer surgery in a randomized study [25]. Therefore, our institution adopted FPX for thromboprophylaxis after CRC surgery from 2010. However, in the latest Japanese guideline for prevention of VTE published by the Japanese society on thrombosis and hemostasis, only the use of IPC as VTE prophylaxis after abdominal cancer surgery is still allowed [26].

This study has several limitations. First, this is a retrospective study, so the primary endpoints (i.e., symptomatic VTE, bleeding, and other postoperative complications) could not be defined in advance. Second, the incidence of asymptomatic VTE was not evaluated because venography or ultrasonography was not routinely performed after surgery. Third, the duration of FPX administration was short. In a randomized study, 4 weeks of LMWH reduced the risk of VTE more than 1 week of LMWH after laparoscopic colorectal cancer surgery [13]. However, 4 to 8 days of FPX administration is the dura-

tion approved by the Japanese government [10]. Fourth, patients were compared over 2 time periods. Our institution adopted FPX from 2010. The number of patients receiving FPX was gradually increased and FPX was routinely used from 2011.

In conclusion, FPX is potentially an effective form of VTE prophylaxis. Although bleeding was minor, treatment was nevertheless discontinued at a rate of 6.9%. Consequently, all minor bleeding was not clinically significant. FPX is safe in terms of both postoperative bleeding and other common complications associated with CRC surgery.

Disclosure Statement

Drs. Y. Yamaoka, M. Ikenaga, N. Haraguchi, M. Miyake and M. Sekimoto have no conflicts of interest or financial ties to disclose.

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