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ORIGINAL SCIENTIFIC REPORT

Incidence of Venous Thromboembolism Following Laparoscopic Surgery for Gastrointestinal Cancer: A Single-Center, Prospective Cohort Study

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Abstract

Background The occurrence of venous thromboembolism (VTE), manifesting as deep vein thrombosis or pulmonary embolism, after gastric and colorectal cancer surgery remains poorly characterized. The purpose of this study was to investigate the incidence of VTE following laparoscopic surgery in Japanese patients with gastric and colorectal cancer and identify the associated risk factors.

Methods We prospectively analyzed VTE events after laparoscopic surgery for gastric and colorectal cancer from April 2012 to March 2013 in our institute. Deep vein thrombosis was diagnosed with Doppler ultrasound sonography of the lower limb. Thromboprophylaxis, graduated compression stockings, and intermittent pneumatic compression were used in all patients. Fondaparinux sodium was used in several patients. We examined all patients' plasma D-dimer levels throughout the perioperative period.

Results In total, 101 patients were enrolled in this study; 71 who underwent laparoscopic surgery for gastrointestinal cancer were finally analyzed. Thirteen patients (18.3 %) developed asymptomatic VTE. There were no relationships between the development of VTE and perioperative factors such as cardiovascular disease, operation time, blood loss, postoperative complications, and fondaparinux administration. Neoadjuvant treatment (chemotherapy or chemoradiotherapy) was significantly associated with VTE ($p < 0.05$). Plasma D-dimer levels were higher 7 days after surgery in patients with than without VTE, although the levels remained high after surgery in all patients.

Conclusions The incidence of VTE among Japanese patients who underwent laparoscopic surgery for gastrointestinal cancer was not low. In particular, clinicians should consider the higher risk of VTE in patients undergoing neoadjuvant therapy.

Introduction

Venous thromboembolism (VTE), manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a common complication of cancer and abdominal surgery. VTE is clinically silent unless actively searched for and seldom causes serious conditions; however, once discovered, VTE requires many medical resources for treatment. Therefore, the establishment of safe VTE prophylaxis is important. Although the incidence of VTE has long been believed to be lower in Japan and other Asian countries

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than in Western countries, a recent study in Japan reported that VTE occurred in 24.3 % of patients undergoing abdominal surgery, including one patient with symptomatic PE [1]. In particular, patients undergoing surgical treatment of cancer have a twofold higher risk of postoperative DVT and a more than threefold higher risk of fatal PE than do patients undergoing similar operations for conditions other than cancer [2, 3].

Despite the establishment of several guidelines [3, 4], many surgeons in Asian countries do not use pharmacological prophylaxis because in patients undergoing laparoscopic surgery, the incidence of VTE is believed to be low while the incidence of postoperative bleeding is believed to be high. Buchberg et al. [5] reported that laparoscopic surgery was associated with a lower risk of DVT than was open surgery for patients with colorectal cancer. Therefore, we need to know the incidence of VTE in patients undergoing laparoscopic surgery for gastrointestinal cancer in Japan. In the present study, we prospectively examined the incidence of VTE in Japanese patients undergoing laparoscopic surgery for gastric and colorectal cancer. We also identified the risk factors for VTE in these patients.

Materials and methods

Patients

We prospectively analyzed VTE events that occurred after laparoscopic surgery for gastric and colorectal cancer from April 2012 to March 2013 in our institute. DVT was diagnosed with Doppler ultrasound sonography. Thromboprophylaxis, graduated compression stockings, and intermittent pneumatic compression were used in all patients. Although fondaparinux sodium (FPX) was scheduled to be administered to all patients, only about half of the patients received FPX because of concern regarding bleeding.

Study protocol and patient recruitment

The inclusion criteria for this study were planned elective laparoscopic surgery for gastric and colorectal malignancy and having provided written informed consent. The exclusion criteria were as follows: treatment with anticoagulants, dextran, thrombolytics, or antiplatelet agents within the past week; active bleeding; thrombocytopenia, defined as a platelet count of $<10 \times 10^4/\mu L$; disorders associated with an increased risk of bleeding, such as gastrointestinal tract ulcers, diverticulitis, colitis, acute bacterial endocarditis, severe uncontrolled hypertension, or severe uncontrolled diabetes mellitus; severe hepatic dysfunction (Child class C); a known history of hypersensitivity to unfractionated heparins, low-molecular-weight heparins, or heparinoids; a history of intracranial bleeding; a history of surgical intervention of the central nervous system or ocular surgery within the past 3 months; severe renal dysfunction, defined as a creatinine clearance of <20 ml/min; a history of major orthopedic, abdominal, or cardiovascular surgery within the past 3 months; clinical signs of VTE; a history of arterial thromboembolism; drug abuse or alcohol dependence; another elective surgical intervention during the study period; pregnancy or lactation; and deemed by the attending physician as unfit for the study.

VTE prophylaxis and evaluation

Thromboprophylaxis, graduated compression stockings, and intermittent pneumatic compression were used in all patients. Administration of FPX (Arixtra; GlaxoSmithKline, Harlow, UK) began 24 h after surgery, once hemostasis was established, following the Japanese regimen for VTE prevention. FPX (2.5 mg) was given once daily for 2–8 days. The day of surgery was defined as day 1.

The study protocol included approved use of epidural anesthesia when necessary. The catheter had to be removed on day 1, and FPX was required to be administered for 12 h after catheter withdrawal. In the event of VTE, bleeding, or any other clinical events, administration of the study drugs was discontinued and treatment was left to the investigator's discretion.

We examined the patients' D-dimer levels preoperatively and on postoperative days (PODs) 1, 3, and 7. All patients were examined for DVT by Doppler ultrasound of the lower limbs preoperatively and POD 7.

Medication

The use of aspirin, nonsteroidal anti-inflammatory drugs, unfractionated heparins, low-molecular-weight heparins other than the study drugs, heparinoids, or vitamin K antagonists was prohibited. All other types of treatment, including chemotherapy and radiotherapy, were permitted. The use of compression stockings was encouraged.

Data analysis

Data collected included patient age, sex, body mass index, concomitant disease, and history of VTE. Perioperative factors such as thromboprophylaxis, operative time, operation site, transfusions, chemotherapy, and radiotherapy were also recorded.

Exact confidence intervals were calculated for the incidence of DVT and PE. Risk factors for DVT and PE were

evaluated by logistic regression for continuous predictors, and Fisher's exact test was used to determine categorical significance. A p value of <0.05 was considered to indicate statistical significance. Statistical analyses were carried out with SPSS software (Version 13.0; SPSS Inc., Chicago, IL).

This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by an independent ethics committee, and written informed consent was obtained from all patients before the operations.

Results

In total, 101 patients were enrolled in this study from April 2012 to March 2013. A flow chart of the patient enrollment is shown in Fig. 1. Twenty-five patients were excluded before surgery: 5 were taking anticoagulants, 12 did not undergo preoperative ultrasonography of the lower extremity, and 8 did not undergo measurement of D-dimer levels. Five patients were excluded postoperatively because R0 resection was not done. Of the 71 remaining patients, 36 (50.7 %) and 35 (49.3 %) underwent laparoscopic gastrectomy and colectomy, respectively. Preoperative ultrasonography did not reveal DVT in the lower limbs of any patients. Thirteen patients (18.3 %) developed postoperative asymptomatic VTE. All VTE occurred in the form of DVT; no patients developed PE. The diagnosis of DVT was based on Doppler ultrasound on POD 7. The patients' clinical features are summarized in Table 1. There were no associations between VTE and age, operation method, operation time, blood loss, postoperative complications, or body mass index.

Thirty patients received FPX, and seven of these patients developed VTE. There was no significant difference in the incidence of VTE between patients who did and did not receive thromboprophylaxis. Only preoperative chemotherapy was significantly associated with DVT ($p = 0.018$).

The median preoperative D-dimer level was 1.4 (0.5–7.5) μg/ml. Figure 2 shows the postoperative D-dimer

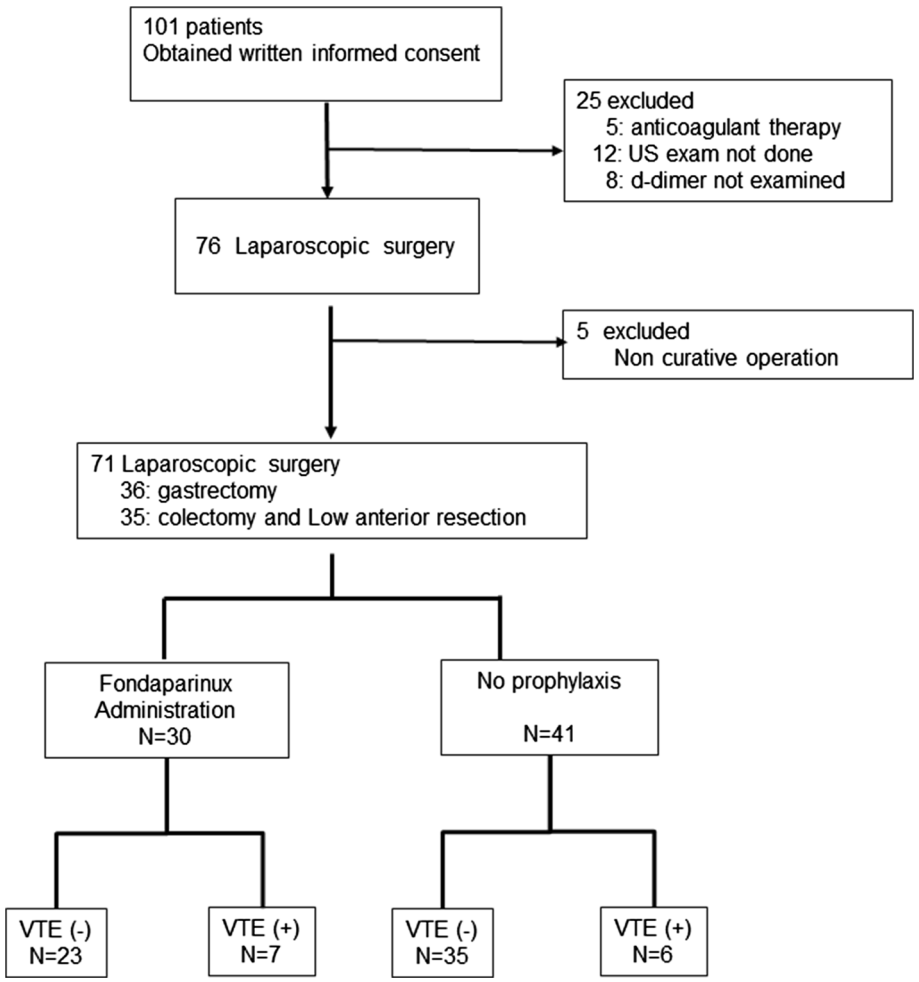

Fig. 1 Flow chart of patient enrollment is shown. In total, 101 patients were enrolled in this study from April 2012 to March 2013. Twenty-five patients were excluded before surgery, and five patients were excluded postoperatively because R0 resection was not done. Finally, 71 patients were examined

Table 1 Clinical and treatment-related factors in patients with and without venous thromboembolism

Factors	VTE (−) ($n = 58$)	VTE (+) ($n = 13$)	
Age	64.36 ± 11.7	64.11 ± 5.5	NS
Gender M/F	29/29	10/3	NS
Operation			
Gastrectomy	29 (50)	7 (54)	
Colectomy/LAR	29 (50)	6 (46)	NS
Fondaparinux			
Administration	23 (40)	7 (54)	
None	35 (60)	6 (46)	NS
BMI	22.2 ± 13.4	20.9 ± 7.1	NS
Blood loss(g)	132	65	NS
Operation times(min)	301 (145-804)	332 (226-817)	NS
Preoperative therapy			
None	53 (91)	8 (62)	
Chemo(radio)therapy	5 (9)	5 (38)	$p = 0.018$
Complications			
None	55 (85)	11 (95)	
Leakage	1 (5)	1 (2.5)	
Colitis	0	1 (2.5)	
SSI	1 (5)	0	
Ascites	1 (5)	0	NS

Data are presented as *n* (%), mean ± standard deviation, or mean (range)

VTE venous thromboembolism, *M* male, *F* female, *LAR* low anterior resection, *BMI* body mass index, *SSI* surgical site infection, *NS* not statistically significant

levels. The D-dimer levels were not significantly different between patients with and without VTE. However, the variation in the D-dimer levels was interesting: in patients with VTE, the levels on POD 7 were higher than those on POD 3, while in patients without VTE, the levels on POD 7 were lower than those on POD 3.

Discussion

Thromboembolic events are a major cause of morbidity and mortality in patients undergoing abdominal surgery. VTE has historically been perceived as a rare complication. Studies of Western populations have shown that the incidence of DVT ranges from 15 to 30 % among patients with cancer not receiving thromboembolic prophylaxis [3], and a meta-analysis by Colditz et al. [6] estimated that the incidence of fatal PE ranges from 0.1 to 0.8 %. Patients with cancer requiring curative abdominal surgery are considered to be at a particularly high risk for VTE, and thromboprophylaxis is strongly recommended [3]. Although the incidence of VTE has long been believed to be lower in Japanese patients than in Western patients, a recent study in Japan found that VTE occurred in 24.3 % of patients undergoing abdominal surgery, including one patient with symptomatic PE [1]. According to the guidelines of the Society of American Gastrointestinal and Endoscopic Surgeons and the European Association for Endoscopic Surgery, routine thromboprophylaxis is also strongly recommended for patients undergoing laparoscopic surgery [4]. Colorectal surgery is associated with a particularly high risk of postoperative thromboembolic complications relative to other general surgeries [7]. The incidences of DVT and PE in patients undergoing surgery for colorectal cancer who do not receive thromboembolic prophylaxis are approximately 40 and 5 %, respectively. On the other hand, some studies have found an association between VTE and laparoscopic gastric bypass surgery [8], but not between VTE and gastric cancer. Larsen et al. [9] reported a 5.2 % incidence of VTE of the upper gastrointestinal tract. In the present study, the incidence of VTE in patients with gastric cancer was equivalent to that in patients with colon cancer, and the 18.3 % incidence of VTE in patients undergoing laparoscopic surgery is not low. VTE is usually considered to occur more frequently in the pelvic organs. However, VTE also occurs in patients with gastric cancer, and thromboprophylaxis is recommended for patients undergoing laparoscopic surgery for treatment of cancer.

Many surgeons believe that the use of pharmacological prophylaxis increases the risk of postoperative bleeding [10, 11]. Importantly, surgical treatment of cancer is also associated with an increased risk of bleeding. Notably, the APOLLO trial compared FPX + intermittent pneumatic compression with intermittent pneumatic compression alone and found that the incidences of major and minor bleeding were 1.6 % (10/635) and 0.8 % (5/635), respectively [12]. The incidence of bleeding was not difference using FPX or not. On the other hand, VTE occurred 18.3 %, and it is necessary to consider whether the bleeding of VTE is risky for the patients.

In the present study, neoadjuvant therapy for cancer was a risk factor for VTE. Patients who undergo preoperative chemotherapy or radiotherapy might be at high risk for VTE. Blom et al. [13] reported that chemotherapy, but not radiation therapy, was associated with an increased risk of VTE among 66,329 registered patients with cancer. Preoperative chemoradiotherapy is also a risk factor for DVT [14, 15]. In another study, Byrne et al. [15] revealed an 11 % incidence of VTE in 36 patients who underwent neoadjuvant chemoradiation treatment with curative intent for esophageal cancer. All patients underwent neoadjuvant chemotherapy and esophagectomy with standard perioperative thromboprophylaxis including enoxaparin sodium (Clexane; Sanofi, Paris, France) [15]. Haddad and Greeno [16] described the mechanism of thrombosis induced by

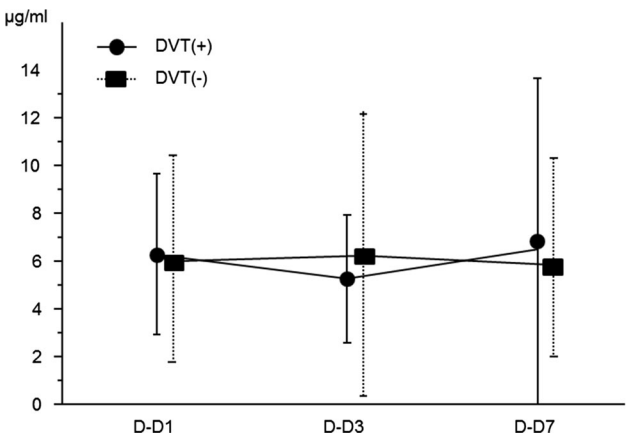

Fig. 2 Postoperative D-dimer levels. The D-dimer levels were not significantly different between patients with and without VTE. The levels on POD 7 were higher than those on POD 3, while in patients without VTE, the levels on POD 7 were lower than those on POD 3

chemotherapy. In the present study, 50 % of patients who received preoperative chemoradiotherapy developed VTE. Therefore, VTE more frequently occurs in patients who have undergone preoperative therapy than in patients who have not.

D-dimer levels are used for the diagnosis of DVT and PE [17, 18]. Wells et al. [19] showed that a diagnosis of DVT can be excluded without ultrasound in patients with normal D-dimer levels. We measured D-dimer levels preoperatively and on PODs 1, 3, and 7 and performed ultrasound examination of the lower limbs preoperatively and on POD 7. Figure 2 shows that the D-dimer levels were not significantly different between the patients with and without VTE. According to recent reports, a high D-dimer level does not indicate the occurrence of DVT. The present study indicates that DVT should be suspected when a patient has a higher D-dimer level on POD 7 than on POD 3.

In conclusion, we found that the incidence of asymptomatic VTE is not lower in Japanese than in Western patients undergoing surgery for gastric and colorectal cancer. This study also revealed that the incidence of VTE is not lower in association with laparoscopic surgery than open surgery for gastric and colorectal cancer. Finally, our results suggest that the use of pharmacological thromboprophylaxis might not completely prevent VTE in patients undergoing laparoscopic surgery, especially those who have received preoperative therapy (chemotherapy or radiation), and that D-dimer levels can be used as an index of thrombosis. Thromboprophylaxis should be strongly considered in patients who have undergone preoperative chemotherapy. Large prospective randomized controlled trials should be conducted to further evaluate the risk of VTE in Asian patients and to establish guidelines for optimal prophylaxis.

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