Risk factors for bleeding in patients receiving fondaparinux after colorectal cancer surgery

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Abstract:
Objective: The aim of this study was to identify risk factors for bleeding complications in patients who receive Venous thromboembolism (VTE) prophylaxis with fondaparinux (FPX) after colorectal cancer surgery. Methods: Records of 546 patients who underwent VTE prophylaxis with intermittent pneumatic compression and FPX after colorectal cancer surgery between January 2009 and May 2014 were reviewed. Patient characteristics, surgical procedures, and patient laboratory data were examined to identify risk factors for bleeding complications using univariate and multivariate logistic regression. Results: We reviewed the records of 324 males and 222 females. Median age and BMI were 68.5 years and 22.7 kg/m², respectively. The number of laparoscopic surgeries was 366. Median operative time and blood loss were 188.5 min and 20 ml, respectively. The incidence (%) of bleeding events was 5.3%. In univariate analysis, age >80 years, BMI >25.0 kg/m², hypertension, and antithrombotic therapy were associated with a significantly higher incidence of bleeding events. Multivariate analysis identified age >80 years (odds ratio 5.814; 95% confidence interval 2.502-13.278) as an independent risk factor. Conclusion: Age >80 is a risk factor for bleeding in patients who receive FPX for VTE prophylaxis after colorectal cancer surgery.
Keywords:
colorectal cancer, laparoscopic surgery, venous thromboembolism, fondaparinux, bleeding

Introduction
Venous thromboembolism (VTE) is a major complication after surgery. It occurs more frequently after colorectal surgery than after any other type of surgery. The mortality rate is high (4.3-56.7%) and perioperative prophylaxis is essential.

Japanese guidelines for VTE prophylaxis after general surgery recommend mechanical and/or pharmacological VTE prophylaxis. Pharmacological VTE prophylaxis reduces the rate of VTE but leads to bleeding events. However, few studies have identified bleeding risk during pharmacological prophylaxis.

The aim of this study was to identify risk factors for bleeding in patients receiving fondaparinux (FPX) after colorectal cancer surgery.

Methods
A total of 571 consecutive patients, including patients with varicose veins, received FPX with intermittent pneumatic compression (IPC) during and after colorectal cancer surgery at Osaka National Hospital between January 1, 2009 and May 31, 2014. Patients with multiple synchronous malignancies, unfractionated heparin therapy, or urgent surgery were excluded. We retrospectively analyzed clinical factors and identified risk factors for bleeding in patients receiving FPX with IPC after colorectal cancer surgery. Adverse events were observed until hospital discharge.

Our VTE prophylaxis protocol after colorectal cancer surgery is shown in Figure 1. Patients wore elastic stockings before surgery and underwent IPC immediately after induction of anesthesia until they began to walk again. FPX (2.5 mg once daily) was injected subcutaneously from the eve-
Figure 1. Our protocol of VTE prophylaxis for colorectal cancer surgery.

Figure 2. Our protocol of VTE prophylaxis for colorectal cancer surgery in the patients who received epidural anesthesia.

ning of postoperative day (POD) 1 to the evening of POD 4. Figure 2 shows the VTE prophylaxis protocol for patients who received epidural anesthesia. FPX was not injected on the evening of POD 2 because the epidural catheter was removed in the morning of POD 3. Patients with age ≥80 years, estimated glomerular filtration rate (eGFR) <50 ml/min, or body weight <40 kg received either a reduced dose of FPX (1.5 mg once daily) with IPC or IPC alone.

Bleeding was classified as major if the event was at least one of the following: fatal, retroperitoneal, or intracranial; involved a critical organ (intraocular, adrenal, endocardial, or spinal bleeding); occurred at a surgical site that required surgical intervention; clinically overt with a decrease in hemoglobin of at least 2 g/dl; or needed transfusion of ≥800 ml red blood cells or whole blood. Minor bleeding was defined as bleeding that did not meet any of the major bleeding criteria.

All continuous data are expressed as medians (range). Frequency distributions for categorical data were compared using the \( \chi^2 \) test. The association between bleeding event and bleeding risk factors was assessed using multivariate logistic regression. Results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical analyses were performed with JMP 11.0 SAS software (SAS Institute Inc.).

The study was done in accordance with the Declaration of Helsinki (1975, as revised in 2008). The study protocol was approved by the ethics committee of the National Hospital
Table 1. Background Clinical Characteristics of the Patients (n=546).

| Sex       | Male        | Female     |
|-----------|-------------|------------|
|           | 324 (59.3%) | 222 (40.7%)|
| Age (years), median [range] | 68.5 [27-92] |
| Weight (kg), median [range]   | 58.0 [31.5-111.4] |
| BMI (kg/m²), median [range]   | 22.7 [14.3-39.5] |
| Tumor location, n (%)         | Right side colon 155 (28.4%) |
|                             | Left side colon 221 (40.8%) |
|                             | Rectum 170 (31.1%) |

Table 2. Surgical Characteristics (n=546).

| Approach n (%)          | Laparotomy 180 (33.0%) |
|                        | Laparoscopy 366 (67.0%) |
| Operation time in minutes, median [range] | 188.5 [74-1047] |
| Blood loss in ml, median [range] | 20 [0-2340] |

Table 3. Incidence of Bleeding Events (n=546).

| Major bleeding, n (%) | 1 (0.2%) |
| Minor bleeding, n (%)  | 28 (5.1%) |
| Subcutaneous hemorrhage/hematoma | 3 (0.5%) |
| Bloody drain discharge hemorrhage at drain site | 1 (0.2%) |
| Melena                  | 17 (3.1%) |
| Bleeding of epidural catheter insertion site | 0 (0%) |
| Hematuria               | 6 (1.1%) |
| Vaginal hemorrhage      | 1 (0.2%) |
| Symptomatic VTE, n (%)  | 0 (0%) |

Risk factors for bleeding events

To assess risk factors for bleeding, univariate analysis was performed for major and minor bleeding events with patient-related factors (age, sex, BMI, and comorbidities), patient laboratory data (preoperative liver function results and platelet count), and surgery-related factors (approach, operative time, operative blood loss, and lateral lymph node dissection). Table 4 shows that age ≥80 years, BMI ≥25 kg/m², hypertension, and antithrombotic therapy were associated with a significantly higher incidence of bleeding events. We then performed multivariate analysis using factors with p values of <0.05. This revealed that age ≥80 years (OR 5.188, 95% CI 2.226-11.814) was an independent risk factor for bleeding.

Discussion

This study investigated risk factors for bleeding in patients receiving FPX after colorectal cancer surgery. Age ≥80 years was associated with an increased bleeding risk. Although not significant, hypertension, BMI ≥25 kg/m², and antithrombotic therapy tended to be associated with more bleeding events.

Previous studies have rarely analyzed bleeding risk in patients receiving pharmacological VTE prophylaxis after surgery, partly because of the heterogeneity in patients’ backgrounds, such as disease and surgical procedures. As only patients with colorectal cancer were enrolled in this study, we could analyze the association between bleeding events and patient and surgical characteristics.

ACCP guidelines mention some risk factors for bleeding after abdominal surgery, such as male sex, preoperative hemoglobin level <13 g/dl, and complex surgery. However, there was no correlation between these factors and bleeding events in this study. The patient with major bleeding in this study did not have any of the bleeding risk factors discussed in the ACCP guidelines. This may be plausible because the guidelines are based on studies conducted in western countries and did not focus on colorectal cancer surgery. Another Japanese study identified a preoperative platelet count of <15 × 10⁹/μl, male sex, and intraoperative blood loss <50 ml as risk factors for bleeding after colorectal cancer surgery. In this study, the bleeding rate of patients with a preopera-
Table 4. Univariate/multivariate Analysis of Factors in Patient and Surgical Characteristics Associated with Bleeding Events.

| Variable                              | n   | Incidence of bleeding | p value | Odds ratio | p   | 95%CI    |
|---------------------------------------|-----|-----------------------|---------|------------|-----|----------|
| Age                                   |     |                       |         |            |     |          |
| <80                                   | 478 | 3.6%                  | <0.001  | Reference  |     |          |
| ≥80                                   | 68  | 17.6%                 |         | 5.188      | 0.002| 2.226-11.814 |
| Sex (Male/Female)                     |     |                       |         |            |     |          |
| Male                                  | 324 | 4.6%                  | 0.391   |            |     |          |
| Female                                | 222 | 6.3%                  |         |            |     |          |
| BMI (kg/m²)                           |     |                       |         |            |     |          |
| <25.0                                 | 413 | 4.1%                  | 0.038   | Reference  |     |          |
| ≥25.0                                 | 133 | 9.0%                  |         | 2.134      | 0.076| 0.922-4.821 |
| Hypertension                          |     |                       |         |            |     |          |
| yes                                   | 207 | 8.2%                  | 0.020   | 1.551      | 0.306| 0.667-3.633 |
| no                                    | 339 | 3.5%                  |         |            |     |          |
| Diabetes mellitus                     |     |                       |         |            |     |          |
| yes                                   | 100 | 9.0%                  | 0.089   |            |     |          |
| no                                    | 446 | 4.5%                  |         |            |     |          |
| Antithrombotic therapy                |     |                       |         |            |     |          |
| yes                                   | 62  | 11.3%                 | 0.046   | 1.434      | 0.481| 0.503-3.683 |
| no                                    | 484 | 4.5%                  |         |            |     |          |
| Approach                              |     |                       |         |            |     |          |
| Laparotomy                            | 180 | 4.4%                  | 0.520   |            |     |          |
| Laparoscopy                           | 366 | 5.7%                  |         |            |     |          |
| Operation time (min)                  |     |                       |         |            |     |          |
| <60                                   | 248 | 4.4%                  | 0.250   |            |     |          |
| ≥60                                   | 298 | 6.0%                  |         |            |     |          |
| Blood loss (ml)                       |     |                       |         |            |     |          |
| <50                                   | 390 | 5.1%                  | 0.765   |            |     |          |
| ≥50                                   | 156 | 5.8%                  |         |            |     |          |
| Pre-op AST level (IU/L)               |     |                       |         |            |     |          |
| <20                                   | 252 | 6.0%                  | 0.536   |            |     |          |
| ≥20                                   | 294 | 4.8%                  |         |            |     |          |
| Pre-op ALT level (IU/L)               |     |                       |         |            |     |          |
| <15                                   | 246 | 5.7%                  | 0.720   |            |     |          |
| ≥15                                   | 300 | 5.0%                  |         |            |     |          |
| Pre-op Hemoglobin level (g/dL)        |     |                       |         |            |     |          |
| <13.0                                 | 305 | 5.6%                  | 0.758   |            |     |          |
| ≥13.0                                 | 241 | 5.0%                  |         |            |     |          |
| Pre-op Platelet count (×10⁹/µl)       |     |                       |         |            |     |          |
| <15                                   | 26  | 11.5%                 | 0.184   |            |     |          |
| ≥15                                   | 520 | 5.0%                  |         |            |     |          |

The retrospective platelet count <15 × 10⁹/µl was relatively high. However, there were 26 such patients and we did not identify an association between preoperative platelet count and bleeding.

We found that age ≥80 years was an independent risk factor for bleeding in patients receiving FPX after colorectal cancer surgery. This may be biologically plausible because pharmacokinetic and pharmacodynamic changes occur with advanced age, which tend to increase sensitivity to drugs. Reduced functional reserve with aging might also lead to increased sensitivity by impairing homeostatic compensatory mechanisms.

There are some limitations to this study. First, due to its retrospective nature, there might be subconscious selection bias. Second, there was no control group. Lastly, the number of bleeding events was relatively small, which might affect the precision of the results.

In conclusion, we found that age ≥80 years was an independent risk factor for bleeding in patients receiving FPX after colorectal cancer surgery. Further studies with a larger population are needed to more fully investigate the risk of bleeding.

Conflicts of Interest
There are no conflicts of interest.
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