A Randomized Study on 1-Week Versus 4-Week Prophylaxis for Venous Thromboembolism After Laparoscopic Surgery for Colorectal Cancer

Maria Cristina Vedovati, MD,* Cecilia Becattini, MD,* Fabio Rondelli, MD,† Michela Boncompagni, MD,‡ Giuseppe Camporese, MD,§ Ruben Balzarotti, MD,¶ Enrico Mariani, MD,|| Otello Flamini, MD,** Salvatore Pucciarelli, MD,†† Annibale Donini, MD,††† and Giancarlo Agnelli, MD*  

Objective: To compare the efficacy and safety of antithrombotic prophylaxis given for 1 week or 4 weeks in patients undergoing laparoscopic surgery for colorectal cancer.

Background: Extending antithrombotic prophylaxis beyond 1 week reduces the incidence of venous thromboembolism (VTE) after open abdominal surgery for cancer.

Methods: In consecutive patients who underwent laparoscopic surgery for colorectal cancer, complete compression ultrasonography of the lower limbs was performed after 8 ± 2 days of antithrombotic prophylaxis. Patients with no evidence of VTE were randomized to short (heparin withdrawal) or to extended (heparin continued for 3 additional weeks) prophylaxis. Complete compressive ultrasonography was repeated at day 28 ± 2 after surgery by investigators blinded to treatment allocation. The primary outcome of the study was the composite of symptomatic and ultrasonography-detected VTE at day 28 ± 2 after surgery.

Results: Overall, 301 patients were evaluated for inclusion in the study and 225 were randomized. VTE occurred in 11 of 113 patients randomized to short (9.7%) and in none of the 112 patients randomized to extended heparin prophylaxis, respectively (relative risk reduction: 91%, 95% confidence interval: 30%–99%; P = 0.005). The rate of bleeding was similar in the 2 treatment groups. Two patients died during the study period, 1 in each treatment group.

Conclusions: After laparoscopic surgery for colorectal cancer, extended antithrombotic prophylaxis is safe and reduces the risk for VTE as compared with 1-week prophylaxis (NCT01589146).

Keywords: antithrombotic prophylaxis, colorectal cancer, laparoscopic surgery, venous thromboembolism

Venous thromboembolism (VTE) is a potentially fatal but preventable complication after major surgery for cancer.1 Heparin prophylaxis reduces the incidence of venography-detected deep vein thrombosis (from 22% to 9%), pulmonary embolism (from 2% to 1.3%),2 fatal pulmonary embolism (from 0.8% to 0.3%), and of all-cause mortality (from 4.2% to 3.2%).3,4 Current guidelines recommend the use of in-hospital antithrombotic prophylaxis after open abdominal surgery for cancer.1 Antithrombotic prophylaxis extended to 4 weeks after surgery should be considered in patients at high risk for VTE and at low risk for bleeding complications.3 This recommendation is based on the consistent results of 2 randomized, double-blind studies.6,7

Since the 1990s, the laparoscopic approach has been increasingly used in abdominal surgery. The laparoscopic approach was an exclusion criterion in most clinical trials that showed a benefit of antithrombotic prophylaxis after major cancer surgery. The need for extended antithrombotic prophylaxis after laparoscopic surgery for cancer is unclear.8–12

We performed a randomized study to compare the efficacy and safety of antithrombotic prophylaxis given for 1 week or 4 weeks in patients undergoing laparoscopic surgery for colorectal cancer.

METHODS

Patients and Study Design

Consecutive patients who had undergone elective laparoscopic surgery for colorectal cancer in 5 hospitals (all in Italy) were considered for inclusion in the study. Patients were excluded in case of age less than 18 years, noncancer surgery, anticipated duration of surgery shorter than 45 minutes, conversion from laparoscopic to open surgery, other indication for anticoagulant treatment, major postsurgery complications leading to reoperation or bleeding before randomization, renal or hepatic failure (creatinine clearance <30 mL/min or a transaminase increase over 3 times upper limit normal), known cerebral metastases, bleeding disorders, intracranial hemorrhage or neurosurgery within the previous 6 months, known hypersensitivity to low-molecular-weight heparin (LMWH), previous heparin-induced thrombocytopenia, pregnancy or lactation, or refusal to participate.

Study Procedures

Study patients received antithrombotic prophylaxis for 8 ± 2 days starting on the evening before surgery. All LMWHs were allowed if given at doses approved for VTE prophylaxis in general surgery. A complete compression ultrasonography of the venous system of the lower limbs was performed at day 8 ± 2 after surgery.13 Patients with no evidence of VTE were randomized to short (heparin withdrawal) or to extended (heparin continued for 3 additional weeks) prophylaxis in an open fashion. A central randomization (1:1 short vs extended prophylaxis, in permuted blocks of 4, stratified according to study center) was used.

All randomized patients were reevaluated at day 28 ± 2 after surgery by complete compression ultrasonography of the lower limbs by an investigator blinded to treatment allocation. A clinical
follow-up visit was planned at 3 months after surgery. Patients were instructed to report to the study center immediately if they had symptoms suggestive of VTE or bleeding complications. Objective testing was required whenever VTE was suspected. In case of death, autopsy was encouraged.

**Study Outcomes**

The primary efficacy outcome was symptomatic VTE (deep vein thrombosis or pulmonary embolism) or deep vein thrombosis diagnosed at complete compression ultrasonography at day 28 ± 2 from surgery. Computed tomography or pulmonary angiography or ventilation/perfusion lung scanning was done to confirm the clinical suspicion of pulmonary embolism.

The primary safety outcome was major bleeding occurring in the 4 weeks after surgery. Major bleeding was defined according to International Society on Thrombosis and Haemostasis criteria 14: (1) fatal bleeding and/or (2) bleeding that is symptomatic and occurs in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a nonoperated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon) and/or (3) extrasurgical site bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of 2 or more units of whole blood or red cells, with temporal association within 24 to 48 hours to the bleeding and/or (4) surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a hemarthrosis delaying mobilization or wound healing, resulting in prolonged hospitalization or a deep wound infection and/or (5) surgical site bleeding that is unexpected and prolonged and/or sufficiently more to cause hemodynamic instability, as assessed by the surgeon.

Clinically relevant nonmajor bleeding was also reported and was defined as bleeding episodes not meeting criteria for major bleeding but associated with medical intervention. Study outcome events were locally adjudicated by a study investigator unaware of the patient’s treatment allocation.

**Data Collection**

For all patients, the following data were collected: demographic features, medical history, risk factors for VTE, surgery (type, duration, etc), type of anesthesia, length of immobilization, postoperative complications, cancer type and staging, and chemotherapy and radiotherapy. Preoperative immobilization was defined as bed rest for at least 3 days before surgery. Data on study outcome events included signs and/or symptoms of VTE and the cause of death.

**Statistical Analysis**

With an estimated rate of VTE of 12% in patients randomized to receive prophylaxis for 1 week, we assumed that 248 patients in each group would be necessary to show a 55% reduction by extended antithrombotic prophylaxis (2-sided α = 0.05, power 80%). To avoid exposure to a suboptimal prophylaxis, a prespecified interim analysis was planned after 200 patients had completed the 28-day study visit. The following stopping rules were defined a priori: an overall rate of VTE lower than 5% in patients randomized to short antithrombotic prophylaxis, an unequivocal reduction in the rate of VTE in the patients assigned to extended prophylaxis (P < 0.01), a risk for VTE in the extended prophylaxis group that was less than 20% lower than that in the group assigned to short prophylaxis or a rate of major bleeding higher than 5% in the extended group.

For the efficacy analysis, the intention-to-treat population was defined as all randomized patients who received at least 1 dose of the study medication and had 28 ± 2 days of follow-up. Safety analysis included all patients randomly assigned to study treatment who received at least 1 dose of the study medication.

Data were reported as frequencies or means ± SD according to variables. Continuous data were compared with the use of the t test. Categorical data were compared with use of either a χ² test or a Fisher exact test. The reported P values are based on 2-sided tests. To assess differences in the rates of VTE between the 2 treatment groups, the relative risk reduction and 95% confidence intervals (CIs) were calculated. Proportional hazards were calculated according to Cox regression statistics. The role of age more than 70 years, sex, stage of malignancy, and duration of surgery as predictor of VTE were evaluated at univariate analysis. Multivariable analysis was constructed from the set of significant (P < 0.05) univariable predictors. This was a no-profit study and the University of Perugia was the sponsor of the study.

The study was performed according to the provisions of the Declaration of Helsinki and good clinical practice. The trial was approved by local ethic committees. Written, informed consent was obtained from all patients or their legal guardians (NCT01589146). All the authors took part in the analysis and interpretation of data and approved the final version of the article.

**RESULTS**

From March 2010 to July 2012, 301 patients were evaluated and 225 patients were included in the study, 113 patients randomized to short and 112 to extended antithrombotic prophylaxis (Fig. 1). Causes for exclusion are listed in Figure 1. All patients received prophylaxis with LMWH from the evening before surgery up to randomization (Table 1). In this period, 84 patients (37%) received prophylaxis with enoxaparin at a dose of 4000 UI, 41 patients (18%) received dalteparin at the dose of 5000 UI, and 100 patients (45%) received nadroparin at the dose of 2850 UI. The mean duration of LMWH prophylaxis was 7 ± 2.1 days in patients randomized to short prophylaxis and 29 ± 2.2 days in patients randomized to extended prophylaxis. After randomization, 89 patients (79%) allocated to extended prophylaxis received enoxaparin at the dose of 4000 UI and 23 patients (21%) received dalteparin at the dose of 5000 UI. Demographic features, risk factors for VTE, type and stage of cancer, and duration of surgery were similar in the 2 study groups (Table 1). Bed rest was prolonged for 7 days postsurgery in 1 patient in the short prophylaxis group (due to sepsis) and in 2 patients in the extended prophylaxis group (1 patient due to leakage of the anastomosis and 1 patient due to sepsis).

One patient in each group underwent reintervention between randomization and day 28 ± 2 (1 for intussusception and 1 for pelvic abscess); 1 patient randomized to short prophylaxis underwent open surgery during the 3-month follow-up (for pelvic abscess).

**FIGURE 1.** Flowchart of the study. cCUS indicates complete compression ultrasonography; DVT, deep vein thrombosis; VKAs, vitamin K antagonists.
Venous Thromboembolism

VTE occurred in 11 of 225 patients (4.9%, 95% CI: 2.8%–8.5%) from randomization to day 28 ± 2. All these events occurred in patients randomized to short heparin prophylaxis (11 of 113; 9.7%, 95% CI: 5.5%–16.6%); no episode occurred in patients randomized to extended heparin prophylaxis (95% CI: 0%–3.3%) (P = 0.001). The study was interrupted after the results of the interim analysis were available and showed a reduction in the rate of VTE in patients assigned to extended heparin prophylaxis (P < 0.01).

VTE was proximal or symptomatic deep vein thrombosis in 2 patients, both presenting with signs and symptoms suggestive of VTE before the scheduled day 28 ± 2 examination (Table 2). The remaining 9 venous thromboembolic events were asymptomatic distal deep vein thrombosis. No episode of pulmonary embolism was observed.

During the 3-month follow-up period, VTE was suspected in 1 patient randomized to extended prophylaxis and in none of those randomized to short prophylaxis. Deep vein thrombosis was confirmed in this patient by complete compression ultrasonography. The overall 3-month incidence of VTE was 5.3% (12 events out of 225 patients; 95% CI: 3.1%–9.1%) and, in particular, 9.7% (11 events out of 113 patients; 95% CI: 5.5%–16.6%) in patients randomized to short heparin prophylaxis and 0.9% (1 out of 112; 95% CI: 0.2%–4.9%) in patients randomized to extended heparin prophylaxis (relative risk reduction: 91%, 95% CI: 30%–99%; P = 0.005). None of the patients complained for signs or symptoms suggestive of pulmonary embolism during the 3-month follow-up. The time course of VTE is shown in Figure 2.

At univariable analysis, age more than 70 years was a predictor of VTE (hazard ratio: 3.89, 95% CI: 1.17–12.93; P = 0.02), and advanced cancer (stage IV according to TNM Classification of Malignant Tumours [TNM]) was associated with a higher but not statistically significant risk of VTE (hazard ratio: 3.2, 95% CI: 0.42–24.90; P = 0.26). Age more than 70 years was confirmed to be an independent predictor of VTE at multivariable analysis (hazard ratio: 3.77, 95% CI: 1.13–12.55; P = 0.03).

Bleeding Complications

One patient randomized to short heparin prophylaxis experienced a major bleeding (intestinal bleeding with a blood loss of >20 g/L and requiring transfusions), and 1 patient randomized to extended prophylaxis experienced a clinically relevant nonmajor bleeding (rectal bleeding requiring heparin withdrawal) from randomization to day

| TABLE 2. Outcomes Distribution According to Randomization |
|----------------|-------------------------------|
|                | Short (113) | Extended (112) |
| Overall VTE at 4 wk | 11          | 0             |
| Symptomatic or proximal DVT | 2          | 0             |
| PE                | 0            | 0             |
| Overall VTE at 3 mo | 11          | 1             |
| Symptomatic or proximal DVT | 2          | 1             |
| PE                | 0            | 0             |
| Bleeding at 4 wk   | 1            | 1             |
| Major bleeding     | 1            | 0             |
| CRNM bleeding      | 0            | 1             |
| Bleeding at 3 mo   | 1            | 1             |
| Death at 4 wk      | 0            | 0             |
| Death at 3 mo      | 1            | 1             |

CRNM indicates clinically relevant nonmajor; DVT, deep vein thrombosis; PE, pulmonary embolism.
Four studies evaluated the incidence of postoperative VTE after laparoscopic surgery for colorectal cancer.\(^9\)\(^{12}\) Across these studies, the incidence of ultrasonography-detected deep vein thrombosis varied from 0% to 50%.\(^9\)\(^{10}\)\(^{12}\)

Recommendations for antithrombotic prophylaxis after laparoscopic surgery are different in the currently available international guidelines. The Society of American Gastrointestinal and Endoscopic Surgeons recommends the same regimens of antithrombotic prophylaxis for equivalent open or laparoscopic operations; the European Association for Endoscopic Surgery recommends intraoperative intermittent pneumatic compression of the lower extremities for all prolonged laparoscopic procedures.\(^8\)\(^{19}\) The Antithrombotic Conference of the American College of Chest Physicians recommends to tailor antithrombotic prophylaxis on the duration of surgery and additional risk factors for VTE rather than on the surgical approach (conventional vs laparoscopic).\(^1\)

In our study, the incidence of VTE, either symptomatic or ultrasonography-detected, was 5.3% at 3 months after surgery, which is higher than those previously described in administrative data sets. However, the selection of a high-risk population (cancer patients), the prospective design, and the use of systematic ultrasound screening could account for this increased incidence. The rates of VTE found in our study are consistent with those of previous studies after conventional surgery for cancer.\(^6\)

In our study, the incidence of bleeding events was low and similar in patients randomized to short and extended heparin prophylaxis. The incidence of death was low and similar in the 2 treatment groups. No death was deemed to be due to pulmonary embolism or bleeding.

Advanced age was an independent predictor of VTE. Cancer stage IV showed a trend in predicting VTE; the association was not significant probably due to limited number of patients. Advanced age and cancer stage may be important in identifying high-risk patients.

This study has several limitations. This was a study with an open design; however, randomization was central and the operator who performed ultrasonography was blinded to treatment assignment. The suboptimal sensitivity of ultrasonography as screening test for deep vein thrombosis could have underestimated the event rates. However, only 1 patient had a confirmed symptomatic venous thrombosis in the 3-month follow-up. An additional limitation of the study was that patients received different types of LMWH for prophylaxis of VTE. All types and doses of LMWH used in this study were validated in the extended prophylaxis of VTE after major orthopedic surgery.

CONCLUSIONS

Our study shows that after laparoscopic surgery for colorectal cancer, extended antithrombotic prophylaxis is safe and reduces the risk for VTE as compared with 1-week prophylaxis.

OTHER AUTHORS

Imier Angirman, MD, Department of Surgical, Oncological and Gastroenterological Sciences, Section of General Surgery, University Hospital of Padua, Italy; Carlo Castoro, MD, Veneto Oncologic Institute, Oncological Surgery, Padua, Italy; Stefano De Carli, MD, General Surgery, Niguarda Hospital, Milan, Italy; Michela Giustozzi, MD, Internal and Cardiovascular Medicine-Stroke Unit, University of Perugia, Perugia, Italy; Isacco Maretto, MD, Department of Surgical, Oncological and Gastroenterological Sciences, Section of Surgical Clinic I, University Hospital of Padua,
Italy; Lorenzo Mariani, MD, General Surgery, S. Giovanni Battista Hospital, Foligno, Italy; Giovanni Natalini, MD, General Surgery, S. Maria della Misericordia Hospital, Perugia, Italy; Teresa Paganelli, MD, General and Emergency Surgery, S. Maria della Misericordia Hospital, Perugia, Italy; Raffaele Pugliese, MD, General Surgery, Niguarda Hospital, Milan, Italy; Chiara Santorelli, MD, General and Emergency Surgery, University of Perugia, Perugia, Italy; Chiara Tonello, MD, Unit of Angiology, University Hospital of Padua, Padua, Italy; and Andrea Zanconato, MD, Department of Surgical, Oncological and Gastroenterological Sciences, Section of Surgical Clinic I, University Hospital of Padua, Italy.

ACKNOWLEDGMENTS

The authors are grateful to Lucina Peppoloni, MD, Pathology Institute, S. Giovanni Battista Hospital, Foligno, Italy. Maria Cristina Vedovati, MD, and Cecilia Bectattini, MD, provided a substantial contribution to the conception and design of the study, to the acquisition of data, to the analysis and interpretation of data, and to the draft of the article. Fabio Rondelli, MD, Michela Boncompagni, MD, Giuseppe Camporese, MD, Ruben Balzarotti, MD, Enrico Mariani, MD, Otello Flumini, MD, Salvatore Pucciarelli, MD, and Annibale Donini, MD, provided a substantial contribution to the acquisition and interpretation of data and to a critical revise of the manuscript for important intellectual content. Giancarlo Agnelli, MD, provided a substantial contribution to the conception and design of the study, to the analysis and interpretation of the data, and to a critical revise of the manuscript for important intellectual content.

REFERENCES


