Incidence and risk factors for venous thromboembolism after laparoscopic surgery for colorectal cancer

The incidence of venous thromboembolism (VTE) after abdominal cancer surgery is estimated to be approximately 2- to 3-fold that observed after non-cancer surgery.[1] Antithrombotic prophylaxis reduces the incidence of VTE by approximately 70% in this setting.[2] Thus current guidelines recommend the use of heparin prophylaxis after cancer surgery.[1] In a randomized study on cancer surgery, the incidence of venography-detected deep vein thrombosis or confirmed pulmonary embolism was 18.2% with unfractionated heparin and 14.7% with low molecular weight heparin.[3] A 2.1% incidence of symptomatic VTE at 30 days after major cancer surgery has been reported, despite the use of antithrombotic prophylaxis.[4]

The laparoscopic approach for major cancer surgery has become increasingly common. Patients operated by the laparoscopic approach were excluded from most of the studies on prophylaxis of VTE after cancer surgery.[5] Conflicting data regarding the incidence of VTE after laparoscopic surgery for colon-rectal cancer have been reported.[6-8]

We performed a prospective study to evaluate the incidence of and the risk factors for VTE in patients who had elective laparoscopic surgery for colorectal cancer.

Consecutive patients who had elective, laparoscopic surgery for colorectal cancer were considered for inclusion in the study. Exclusion criteria were: refusal of consent, age under 18 years, surgery for non-cancer disease, duration of surgery less than 45 min, conversion to open surgery, an indication for anticoagulant therapy, contraindication for or known hypersensitivity to heparin, renal or hepatic diseases, known cerebral metastases, generalized bleeding disorders, cerebral hemorrhage or neurosurgery within the previous six months, pregnancy or lactation.

Patients were included in the study on the day of surgery. A complete compression ultrasonography (cCUS) of the lower limbs was obtained at day 8±2 after surgery.[9] On suspicion of deep vein thrombosis or pulmonary embolism during the study period, confirmation by objective testing was required. Antithrombotic prophylaxis with low molecular weight heparin was given to all patients from the day of surgery until cCUS, according to local practice.

Study outcomes assessed were symptomatic, objectively confirmed VTE (deep vein thrombosis or pulmonary embolism) and asymptomatic deep vein thrombosis by cCUS at day 8±2 from surgery. Major VTE, defined as symptomatic VTE and/or proximal deep vein thrombosis, was also assessed. Deaths occurring from the day of sur-

Table 1. Demographic characteristics of the study patients.

	Patients (n=305)	Post-operative VTE YES (N=54)	Post-operative VTE NO (N=251)	*P*
Age (years) median±SD	66.5±11.2	73±10	65±11	<0.001
Range	(28-89)			
Sex (male) n. (%)	164 (53.8)	26 (48)	138 (55)	Ns
95% CI	(48-59)			
Obesity (BMI ≥ 30) n. (%)	21 (6.9)	7 (13)	14 (6)	0.05
95% CI	(4-9)			
Previous VTE, n. (%)	5 (1.6)	–	5 (2)	Ns
95% CI	(0.2-3)			
Pre-operative immobilization, n. (%)	3 (1)	–	3 (1)	Ns
95% CI	(0-2)			
Hypertension, n. (%)	71 (23.3)	11 (20)	60 (24)	Ns
95% CI	(19-28)			
Diabetes, n. (%)	15 (4.9)	4 (7)	11 (4)	Ns
95% CI	(2-7)			
Ischemic heart disease, n. (%)	23 (7.5)	6 (11)	17 (7)	Ns
95% CI	(4-10)			
COPD, n. (%)	9 (3.0)	1 (2)	8 (3)	Ns
95% CI	(1-5)			
Heparin prophylaxis				
Enoxaparin 4000 UL o.d., n. (%)	93 (30.5)	8 (15)	85 (34)	Ns
	(25-36)			
Dalteparin 5000 UL o.d., n. (%)	45 (14.8)	3 (6)	42 (17)	Ns
	(11-19)			
Fraxiparin 0.3 mL o.d., n. (%)	167 (54.8)	43 (80)	124 (49)	Ns
	(49-60)			
IPC, n. (%)	2 (0.7)	–	2 (1)	Ns
	(0.2-1)			

VTE: venous thromboembolism; BMI: body mass index; COPD: chronic obstructive pulmonary disease; IPC: intermittent pneumatic compression; NS: not significant.

Table 2. Surgical features of study patients.

	Patients (n= 305)	Post-operative VTE YES (n=54)	Post-operative VTE NO (n=251)	P
Cancer				
Stage 0-1, n. (%)	157 (51.5)	24 (44)	133 (53)	ns
95% CI	(46-57)			
Stage 2, n. (%)	76 (24.9)	19 (35)	57 (23)	0.06
95% CI	(20-30)			
Stage 3, n. (%)	64 (21.0)	9 (17)	55 (22)	ns
95% CI	(16-26)			
Stage 4, n. (%)	8 (2.6)	2 (4)	6 (2)	ns
95% CI	(0.8-4)			
Neo-adjuvant CHT, n. (%)	17 (5.5)	2 (4)	15 (6)	ns
95% CI	(3-8)			
Neo-adjuvant RT, n. (%)	16 (5.2)	4 (7)	12 (5)	ns
95% CI	(3-8)			
Surgery				
Duration of surgery (minutes) – median ± SD	170 ± 73	154 ± 61	172 ± 77	ns
Range	(60-540)			
Right hemicolectomy, n. (%)	107 (35.1)	25 (46)	82 (33)	ns
95% CI	(30-40)			
Left hemicolectomy, n. (%)	53 (17.4)	7 (13)	46 (18)	ns
95% CI	(13-22)			
AAR/Miles/sigmoid resection, n. (%)	136 (44.6)	21 (39)	115	ns
95% CI	(39-50)			
Subtotal colectomy, n. (%)	9 (3.0)	1 (2)	8 (3)	ns
95% CI	(1-5)			
Post-operative bed rest (h), median±SD	32 ± 20	28 ± 13	33 ± 22	ns
Range	(24-168)			

95% CI: 95% confidence interval; VTE: venous thromboembolism; ARR: anterior rectal resection; NS: not significant.

gery up to day 8±2 were reported. The presumed cause of death was reported, although autopsy was not mandatory.

Safety was assessed as major or clinically relevant non-major bleeding from the day of surgery up to day 8±2 from surgery. Major bleeding was defined according to the International Society of Thrombosis and Haemostasis criteria for surgical patients.[10] Bleedings not meeting criteria for major bleeding and that required any medical intervention were defined as clinically relevant non-major bleeding. Study outcome events were locally evaluated and centrally adjudicated.

With an assumed 18%-15% incidence of VTE after laparoscopic surgery for cancer, similar to that observed after conventional open surgery for cancer,[3] we would have 45-50 outcome events in a sample of 300 patients. With this number of outcome events we would have 90% power to evaluate risk factors for VTE by logistic regression analysis with an alpha of 0.05.

Multivariable analyses were performed by logistic regression statistics and constructed from the set of significant ($P \leq 0.05$) univariate predictors of VTE. Pre-defined predictors of VTE were: age, gender, obesity (Body Mass Index ≥30), comorbidities (systemic arterial hypertension, ischemic heart disease, diabetes, chronic obstructive pulmonary disease), stage of malignancy, neo-adjuvant chemotherapy, neo-adjuvant radiotherapy, type of surgery, duration of surgery, duration of immobilization, etc.

Table 3. Study outcomes.

Study outcomes events	Patients (n=54)
Venous thromboembolism at day 8 ± 2, n. (%)	54 (17.7)
Symptomatic, n. (%)	2 (0.7)
Proximal DVT, n. (%)	3 (1)
PE , n. (%)	–
Asymptomatic or distal DVT, n. (%)	49 (16)
Major or CRNM bleeding at day 8 ± 2 , n. (%)	6 (2)
Major bleeding, n. (%)	4 (1.3)
CRNM bleeding , n. (%)	2 (0.7)
Death at day 8 ± 2, n. (%)	–

DVT: deep vein thrombosis; PE: pulmonary embolism; CRNM: clinically relevant non-major.

All analyses were performed using SPSS 20 software.

Overall, 331 patients were evaluated for inclusion in the study; 26 patients were excluded and 305 were included (Figure 1). The main features of included patients are reported in Table 1. A total of 157 patients had cancer stage 0 or 1 (51%); the remaining had cancer stage 2 or higher (Table 2). Cancer was metastatic in 8 patients. Mean dura-

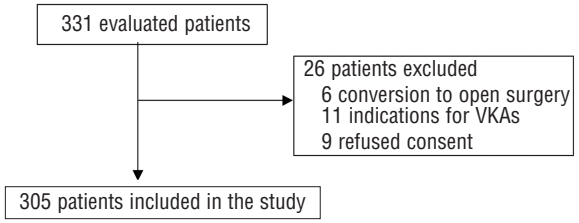

Figure 1. Flow chart of the study.

tion of surgery was 170±73 min and mean duration of post-surgical immobilization 32±20 h. All patients received prophylaxis with low molecular weight heparin from 12 h after surgery to ultrasound assessment.

Overall, VTE was diagnosed in 54 patients (17.7%; 95%CI: 13.4%-22.0%); all the events were deep vein thrombosis of the lower limbs (Table 3). Deep vein thrombosis was symptomatic in 2 patients (0.7%) and proximal in 3 patients (1.0%), for an overall incidence of major VTE of 1.6% (95%CI: 0.2%-3.0%). Distal vein thrombosis was found in the peroneal (12 patients, 3.9%), tibial (7 patients, 2.3%) and muscular (33 patients, 10.8%) veins. Bilateral deep vein thrombosis was observed in 19 patients (6.2%).

Univariate analysis showed an association between VTE and obesity (Odds Ratio [OR] 2.9; 95%CI: 1.32-6.55; P=0.008), advanced age (≥70 years) (OR 4.37; 95%CI: 2.37-8.06; P<0.001), and cancer stage 2 (OR 2.10; 95%CI: 1.19-3.70; P=0.011). No association was found between VTE and sex, comorbidities, duration of surgery, neo-adjuvant chemo- or radiotherapy, type of surgery (left or right hemicolectomy, rectal anterior resection, Miles or subtotal colectomy) and cancer stage lower or higher than 2.

At multivariable analysis, obesity (OR 2.91; 95%CI: 1.02-8.30) and advanced age (≥70 years) (OR 4.75; 95%CI: 2.42-9.29) were independent predictors for VTE. No correlation was observed between VTE and sex, comorbidities, surgical site, surgical time or stage of malignancy.

After surgery, 6 patients experienced a bleeding complication that was major in 4 (1.3%; 95%CI: 0-2.6%) but fatal in none. Major bleeding was one case of intraperitoneal bleeding requiring further surgery in a 75-year old female, bleeding in the surgical site requiring transfusion of more than 2 packed units in 2 patients (an 81-year old female and a 62-year old male), and a drop in hemoglobin level of 5 g/dL requiring transfusion with no evidence of bleeding in the surgical site in an 81-year old female.

Clinically relevant non-major bleedings were rectal bleeding and a drop in hemoglobin level of 2 g/dL not requiring transfusion in one patient each.

None of the patients died within the study period.

This study shows that there is a substantial incidence of VTE after laparoscopic surgery for colon-rectal cancer despite antithrombotic prophylaxis. In our study, the majority of events were asymptomatic distal vein thrombosis of the lower limbs.

Only limited evidence of the incidence of VTE and on the clinical benefit of antithrombotic prophylaxis after laparoscopic surgery for colorectal cancer is currently available.[5,11,12]

Similar rates of symptomatic VTE have been reported after open or laparoscopic surgery for colorectal cancer in retrospective studies.[5,13] In our study, the incidence of post-operative VTE was 17% despite the use of heparin prophylaxis. This rate seems to support the concept that the risk of post-operative VTE is not related to the surgical technique (open *vs.* laparoscopic) but to major risk factors such as duration of surgery, presence of cancer and age.

Major surgery is one of the main risk factors for VTE and international guidelines recommend antithrombotic prophylaxis in the peri-operative period. Recent guidelines suggest the use of a risk stratification model to identify those patients at sufficiently high risk for post-operative VTE to require pharmacological prophylaxis.[1] In this model, either duration of surgery over 45 min or the presence of cancer gives patients a moderate risk for post-operative VTE which is considered sufficient to require antithrombotic prophylaxis with unfractionated or low molecular weight heparin. The risk stratification model assigns a similar risk for VTE to major open or laparoscopic surgery, the only influencing factor being duration of surgery over 45 min. In our study, advanced age and obesity were independent predictors of post-operative VTE, while some plausible risk factors (surgical time, cancer stage, etc.) were not found to be associated with study outcome.

None of the patients in our study had pulmonary embolism after surgery. The large majority of post-operative VTE were deep vein thrombosis of the leg. This finding is consistent with the results of previous trials in cancer surgery based on venography or ultrasonography screening.[2,3]

In our study, deep vein thrombosis was screened by ultrasonography. Venography has for decades been considered the gold standard for the diagnosis of asymptomatic deep vein thrombosis. However, venography is invasive and requires the use of contrast media. In more recent times, ultrasonography has been increasingly used to assess deep vein thrombosis in studies on prevention of venous thromboembolism.[14,15] Indeed, advantages related to non-invasiveness are considered to overwhelm the potential for false positive results in the distal veins associated with compression ultrasonography.

The non-randomized nature of our study does not allow any conclusions to be drawn about the individual efficacy and safety profile of different low-molecular weight heparins. This should be assessed in further studies.

In conclusion, approximately 15% of patients have post-operative VTE after laparoscopic surgery for colorectal cancer. Approximately 2% of these events are symptomatic or located in the proximal veins. Obesity and advanced age are risk factors for venous thromboembolic complications. Further studies with a larger sample size are awaited to confirm our results.

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