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Deep Venous Thrombosis After Surgery for Inflammatory Bowel Disease: Is Standard Dose Low Molecular Weight Heparin Prophylaxis Enough?

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Abstract
Background Inflammatory bowel disease (IBD) and colorectal surgery are risk factors for deep venous thrombosis (DVT). The aim of this prospective study was to evaluate the effectiveness of standardized prophylactic low molecular weight heparin (LMWH) therapy in patients who underwent surgery for ulcerative colitis (UC) and Crohn's disease (CD).

Patients and methods Since 1999 all patients operated on for colorectal diseases in our institute have received 4,000 IU/day LMWH from the day of operation to discharge. The complete series of patients who had major colorectal surgery from 1999 until 2006 were reviewed for overt DVT episodes. Furthermore, 60 consecutive patients who were admitted for surgery for IBD were prospectively enrolled in the 2004–2006 period. Each patient underwent venous color Doppler ultrasound scan at admission and at discharge. Demographic data, disease activity, and clotting parameters were collected. Data were analyzed with Spearman's correlation test, multiple regression, and receiver operating characteristics (ROC) curves analysis.

Results The rate of DVT in UC patients was significantly higher than in colorectal cancer patients ($p = 0.009$), and the odds ratio (OR) for postoperative DVT in UC patients was 7.4 (95% CI 1.4–44.4; $p = 0.017$). Female gender, UC diagnosis, active rectal bleeding, aPTT value, aCL IgM, aβ2 IgM, and pANCA levels significantly correlated with postoperative DVT. At multivariate analysis only aCL IgM levels were found to be independently associated with postoperative DVT ($p = 0.05$).

Conclusions In conclusion, our study showed that prophylactic therapy with 4,000 IU/day LMWH was not completely effective for the prevention of postoperative DVT in patients with CD, and even less so in those with UC. In these patients, a more tailored prophylactic therapy should be considered, and further randomized controlled trials testing the effectiveness of different prophylactic protocols would be advisable. Furthermore, aCL IgM serum levels might be helpful in identifying IBD patients who are at higher risk of postoperative DVT.

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Introduction

Deep venous thrombosis (DVT) has been recognized as an extradigestive tract complication of Crohn's disease (CD) and ulcerative colitis (UC) since 1936 [1]. A very recent study by Nguyen and Sam has demonstrated that DVT is increasingly prevalent among hospitalized IBD patients and has substantial mortality and economic impact [2]. In fact, an elegant study from the University of Vienna had already established that CD and UC are independent disease-specific risk factors for thromboembolism [3]. The incidence of such complications varies according to the different methodological approaches from 1.2 to 6.7% in clinical studies, reaching 39% in post-mortem studies [3, 4]. Inflammatory bowel disease activity positively correlates with venous thromboembolic risk, and coagulation activity is higher during exacerbations, probably because of a secondary effect of tissue damage and destruction [5, 6].

Several other factors have been investigated for their supposed influence in this phenomenon. In particular, the hypercoagulability state was well assessed by the demonstration that the coagulation and the fibrinolytic cascade were activated in UC with a neat imbalance in favor of coagulation [7]. On the one hand, a possible cause of this imbalance might be the increase in plasma levels of thrombin-activatable fibrinolysis inhibitor reported in IBD patients [8]. Moreover, activated protein C resistance is not associated with IBD, but its presence increases the risk of thromboembolism [8]. Furthermore, low vitamin B6 plasma levels, an independent risk factor for thrombosis, are frequent in patients with IBD, especially those with active disease [9]. Similarly, hyperhomocysteinemia, linked to both arterial and venous thrombosis, is significantly more common in patients affected by IBD than in healthy controls [10]. In this context no specific risk factor seems to have a prominent role: as in the general population, DVT seems to be a multifactorial age-related event. In a determinate time a combination of genetic and environmental factors increases the risk to levels that exceed the thrombosis threshold [11].

Abdominal surgery, in general, and colorectal surgery, in particular, can be fully included in these risk factors group for venous thromboembolism [12]. In the absence of an adequate DVT prophylaxis, the asymptomatic calf vein thrombosis incidence after colorectal surgery may reach 41% of patients [13]. Patients operated for malignancy seemed to have a lower incidence of DVT than patients with IBD submitted to equivalent surgery [14]. Nevertheless, even if inflammatory or neoplastic causes of the operation play an important role, the length of the intervention, the extent of the surgical trauma, the compression of or damage to the pelvic veins, and the length of postoperative immobilization are further factors that may facilitate the onset of deep venous thrombosis [15].

Nowadays the prophylactic therapy for venous thromboembolism after colorectal surgery is based on low doses of calcium heparin, low molecular weight heparin (LMWH), or graduated compression stocking [12, 14]. The most effective prophylaxis may be obtained with the combination of heparin and graduated compression stocking [12, 16]. Although low doses of unfractioned heparin and low molecular weight heparin were demonstrated to be equally effective in preventing DVT after colorectal surgery, low-dose heparin is currently more economically attractive [17].

The primary aim of this study was to evaluate the efficiency of the standard prophylactic low molecular weight heparin (LMWH) therapy in preventing the postoperative DVT in patients who underwent surgery for UC and CD in comparison with patients who underwent colorectal procedures for diagnoses other than IBD. The secondary endpoint was to identify possible predictors of DVT in IBD patients submitted to surgery.

Patients and methods

Study design and patient characteristics

The study was performed according to the Helsinki declaration principles. All patients admitted for colorectal surgery in the institute of Clinica Chirurgica I of the University of Padova since 1999 have received postoperative LMWH at the daily prophylactic dose of 4,000 IU for the duration of their postoperative hospital stay, as well as graduated compression stockings, which were used for the duration of the surgical procedure. In the first part of the study all the records of patients who had a surgical procedure for colorectal diseases from 1999 (start of the routine use of postoperative LMWH in our department) until 2006 were reviewed, and the DVT rate of the different groups were compared. Data about diagnosis, surgical procedures, hospital stay duration, and complications were retrieved from the prospectively collected databases of colorectal cancer, UC, CD, and diverticular disease.

Furthermore, all the consecutive CD and UC patients admitted to our department for colorectal surgery between December 2004 and April 2006 were asked to participate in a prospective assessment of the predictors of DVT. Patients who presented hereditary hypercoagulation disorders or other bowel diseases associated with IBD, such as colon cancer, were excluded form this cohort. Adequate informed consent was obtained from all persons involved and, finally, 35 CD patients and 25 UC patients consented to be enrolled in this part of study. Seventeen of them underwent

proctocolectomy, 22 had ileo-colic resection, 10 had ileostomy closure, and 11 underwent perianal procedures. In this part of the study, on the day of admission adequate blood samples were collected and a complete medical history was taken, with particular interest on coagulation disorders and familial predisposition. The patients' medical records were reviewed and data were abstracted, included the following: duration, extension, and activity of the IBD; drugs (5-ASA, steroids or immunosuppressors), including doses and number of cycles since disease onset; dates and findings of all colonoscopies, colonic biopsies; surgery with its indications, findings, and histology; date of the last follow-up and vital status; presence and date of DVT and pulmonary embolism episodes.

The clinical disease activity was quantified with a modified version of the Harvey-Bradshaw Activity Index (HBAI) [18, 19] that included the number of soft stools produced per day, abdominal pain, general well-being, extraintestinal complications, and the presence of an abdominal mass. Inflammatory bowel disease was considered active when the HBAI score was above 5.

The characteristics of patients who underwent colorectal surgery form 1999 until 2006 are shown in Table 1, and those of the cohort of IBD patients operated on during the 2004–2006 period are shown in Table 2.

Lower limb doppler ultrasound scan (US)

In the cohort of IBD patients operated on during the 2004–2006 period, the rate of DVT was assessed with a preoperative Doppler US of the lower limbs performed on the day of admission and a postoperative one performed on the day of discharge by the same operator (F.P.) with the same US instrument (Esaote, Italy, vascular probe 7.5 MHz). Detection of DVT was based on venous compressibility at Doppler US (CUS), independent of the symptoms. At Doppler US, CUS was considered positive in the usual site of detection (femoral and popliteal veins) but also in the distal veins. The presence of DVT, its localization, and its extension were then recorded.

Blood tests

In the cohort of IBD patients operated on during the 2004–2006 period, blood samples were taken from the fasting patients on the day before surgery to assess the possible predictors of DVT. Venous blood for coagulation test was collected in siliconized glass tubes containing one-tenth

Table 2 Characteristics of patients who had surgery for IBD in the institute of Clinica Chirurgica I (University of Padova) in the period 2004–2006 and had pre- and postoperative lower limb Doppler US

	UC patients Median (range)	CD patients Median (range)
Patients, *n*	25	35
Male	18	21
Age, years	49 (44–54)	49 (43–56)
Disease duration, months	134 (99–169)	123 (83–164)
Hospital stay, days	8 (2–12)	7 (2–14)
Past history of DVT	1	0
Weight, kg	71 (65–77)	64 (58–71)
Operation type, *n*	15 restorative proctocolectomy	3 partial colectomy
	8 ileostomy closure	19 ileocolonic resection
	2 perianal surgery	13 perianal surgery
Complication	2 anastomotic leak	1 anastomotic leak
	2 obstruction	1 obstruction
		1 duodenal perforation
		2 rectal bleeding
Reoperation	0	1

UC ulcerative colitis, *CD* Crohn's disease

Table 1 Characteristics of patients who had colorectal surgery in the institute of Clinica Chirurgica I (University of Padova) in the period 1999–2006

	Colorectal cancer	Diverticular disease	CD	UC
Procedures	377	55	169	154
Gender: male/female	218	21	103	98
Age at operation, years	66 (20–94)	65 (35–93)	36 (14–75)	47 (19–78)
Procedures				
Small bowel resection	0	0	144	1
Stoma surgery	5	4	3	51
Segmental colectomy	302	47	8	1
Total colectomy	14	0	11	76
Rectal surgery	56	0	5	70
Perineal surgery	6	1	1	4

volume of 3.8% trisodium citrate. Plasma was obtained by centrifugation at 2,000×*g* at room temperature. A standard coagulation panel that included activated partial thromboplastin time (aPTT), prothrombin time (PT), INR ratio, and platelet count was obtained for patients affected by CD and UC, as well as for controls. In patients with CD and UC anticardiolipin antibodies (aCL Abs) enzyme-linked immunosorbent assay (ELISA), aβ2-GPI antibodies ELISA [20], kaolin clotting time (KCT), and dilute Russell viper venom time (dRVVT) for the detection of lupus anticoagulant activity were performed on plasma as described by Pengo et al. [21].

Systemic inflammatory activity was assessed on the basis of erythrocyte sedimentation rate (ESR), white blood cell count (WBC), polymorphonuclear cell count (PMN), and C-reactive protein (CRP) values. The ESR was measured by the Westergren method, and CRP was detected by immunonephelometry (normal: <6 mg/l; pathological >6 mg/l). Total protein and albumin were assessed by the biuret method. The WBC, PMN, and hemoglobinemia (Hb) values were obtained with standard full blood cell count. Fibrinogen, fibrinogen degradation peptides (FDP), triglyceridemia, colesterolemia, albuminemia, homocysteinemia, and creatinine values were also obtained.

Detection of cytoplasmic (cANCA) and perinuclear (pANCA) staining of neutrophils was performed by an indirect immunofluorescence technique on ethanol fixed buffy coat leukocytes. An FITC conjugated rabbit antihuman IgG antibody (Rabbit/Kaninchen/Lapin/Anti-human/Humain-Dako, Copenhagen, Denmark) was used for the detection of bound IgG antibodies, followed by an initial 1:20 and progressively higher dilutions in phosphate buffered saline [22]. Expressions of pANCA and cANCA were scored absent (0), low (1 = between 1:20 and 1:80 dilutions), moderate (2 = between 1:160 and 1:320 dilutions), and high (3 = above 1:640 dilutions).

Statistical analysis

Data were presented as median (range) or number of patients and (%) where appropriate. Data elaboration was performed with Statsoft Statistica 7.1 and MedCalc 9.3 software. The nonparametric Mann-Whitney U two-tailed test was used to compare continuous variables, and the Yates corrected χ^2 Fisher's exact test was used for dichotomic ones. Linear associations were quantified with Spearman's rank correlation test. All the continuous variables that were found to be significant at the univariate analysis were included in a multiple linear regression model in order to identify the independent predictor of DVT, and the dichotomic variables were analyzed with logistic regression. Receiving operator characteristics (ROC) for possible predictors (sensitivity and specificity) of DVT were assessed by curve analysis as described by Henderson [23]. Statistical significance was set at $p < 0.05$.

Results

Postoperative DVT rates in patients who had colorectal surgery

Among the 755 colorectal surgical procedures performed in the institute of Clinica Chirurgica I of the University of Padova from 1999 until 2006, 6 clinically overt postoperative DVT episodes were recorded. All of them occurred in patients affected by inflammatory bowel disease (IBD; $p = 0.014$). Two occurred in two patients operated on for terminal ileum CD (clinical DVT rate in CD: 1.2%); the other four cases occurred in patients affected by UC after two proctectomy and J pouch constructions (the second stage of a three-stage restorative proctocolectomy), a proctocolectomy (the first stage of a two-stage restorative proctocolectomy), and an ileostomy closure (clinical DVT rate in UC: 2.6%). One of them had also a pulmonary embolism treated with the positioning of a filter in the inferior vena cava. No symptomatic DVT were recorded among patients operated on for colorectal cancer or diverticular disease.

As shown in Fig. 1, DVT rate in UC patients was significantly higher than in colorectal cancer patients ($p = 0.009$) and the odds ratio (OR) for postoperative DVT in UC patients was 7.4 (95% CI 1.4–44.4), $p = 0.017$. By univariate analysis, the only other clinical predictor of DVT was "surgical procedures that implied the rectum

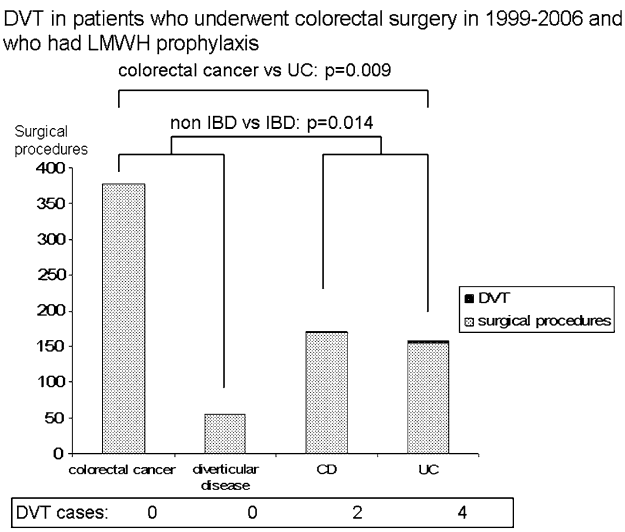

Fig. 1 Deep vein thrombosis in patients who underwent colorectal surgery in 1999–2006 and who had low molecular weight heparin (LMWH) prophylaxis

resection" (OR 4.8 [95% CI 0.9–24.3], $p = 0.055$). Unexpectedly, neither duration of the operation nor disease activity seemed associated with DVT. However, at multiple logistic regression analysis, only UC showed a trend to be an independent predictor of DVT after colorectal surgery and prophylaxis with LMWH (OR 5.9 [95% CI 0.9–39.7], $p = 0.065$).

Predictors of postoperative DVT in patients operated on for IBD

In the cohort of IBD patients operated on during the 2004–2006 period, disease activity in UC and CD patients was moderate, and no significant difference was observed in terms of Harvey-Bradshaw activity index, rectal bleeding prevalence, hemoglobin and CRP concentration, and ESR. Only daily bowel movements were significantly more frequent in UC patients than in CD ones. Disease activity parameters are shown in Table 3. As shown in Table 4, clotting parameters were similar in UC and CD. Only fibrinogen concentration was significantly higher in CD patients.

During the postoperative follow-up, no patients showed any clinical sign or symptoms of pulmonary embolism or DVT. Nevertheless, at the postoperative Doppler US, a DVT was observed in the right popliteal vein of a UC patient after ileostomy closure and in the subpopliteal venous supply of two other UC patients (subclinical DVT rate in UC: 12%). This patient is included in the overall count of DVT in IBD. Although, none of the patients with CD showed any signs of DVT at the postoperative lower limb Doppler US study, no significant difference was observed between UC and CD patient in terms of DVT rate. Two intestinal bleeds required transfusion in the IBD group, but neither patient needed surgical intervention. No other heparin-related side effect occurred.

Clotting parameters that could play a role in postoperative DVT were analyzed with ROC curves. An aPTT value of 29 s or lower showed a sensitivity of 100% and a specificity of 53.8% with a positive likelihood ratio of 2.17 ($p = 0.002$). aCL IgM levels above 6 kU/l showed a sensitivity of 100% and a specificity of 75% with a positive likelihood ratio of 4 ($p = 0.001$). Aβ2 IgM levels above 6 kU/l showed a sensitivity of 100% and a specificity of 60% with a positive likelihood ratio of 2.5 ($p = 0.019$). A low expression, or higher, of pANCA showed a sensitivity of 100% and a specificity of 92% with a positive likelihood ratio of 12.5 ($p < 0.001$).

The analysis of the possible predictors of postoperative DVT also included demographic and clinical parameters. Different type of surgery, type of anesthesia, length of the operative intervention, extent of the surgical trauma, and length of the postoperative immobilization did not show any relation with the rate of postoperative DVT. In contrast, female gender, UC diagnosis, active rectal bleeding, aPTT value, aCL IgM, aβ2 IgM, and pANCA levels significantly correlated with postoperative DVT. All these variables were then included in a multiple regression analysis model that showed that only aCL IgM levels are independently associated with postoperative DVT ($p = 0.05$). Univariate and multivariate analyses are shown in Table 5.

Table 4 Clotting parameters in UC and CD groups at admission

	UC patients Median (range)	CD patients Median (range)	*p* value
Fibrinogen	3.8 (1.9–6.1)	5.4 (3.2–9.6)	0.04
FDP	121 (25–1476)	125 (21–676)	0.81
PLTs $\times$ 10^9 l	329 (159–647)	320 (112–1189)	0.51
PT (%)	81 (51–126)	89.5 (46–103)	0.37
INR	1.15 (0.89–1.59)	1.12 (0.97–1.69)	0.58
aPTT, s	29 (24–36)	30 (27–37)	0.18
dRVVT	29 (23.0–51.0)	30 (23.0–60.0)	0.72
KCT	0.9 (0.6–1.6)	0.9 (0.6–1.5)	0.98
aCL IgG, kU/l	7.0 (2.0–24.0)	13.0 (3.0–40.0)	0.12
aCL IgM, kU/l	4.0 (2.0–34.0)	4.0 (2.0–28.0)	0.58
aβ2 IgG, kU/l	7.5 (2.0–81.0)	10.0 (2.0–47.0)	0.39
aβ2 IgM, kU/l	3.0 (2.0–23.0)	5.0 (2.0–15.0)	0.20

FDP fibrinogen degradation product, *PLTs* platelets, *PT* prothrombin time, INR international normalized ratio, aPTT activated partial thromboplastin time, *dRVVT* dilute Russell's viper venom test, KCT kaolin clotting time, aCl IgM immunoglobulin antibodies to cardiolipin

Table 3 Disease activity in UC and CD patients at admission

	UC patients Median (range)	CD patients Median (range)	*p* value
Harvey-Bradshaw activity index	7 (3–25)	7 (5–17)	0.31
Daily bowel movement, *n*	3 (1–20)	1.5 (0–12)	0.03
Rectal bleeding, *n*	6 (25%)	3 (8.5%)	0.14
Hb (g/l)	12.3 (10.9–13.6)	12.8 (11.7–13.8)	0.38
CRP (mg/l)	10.3 (3.1–17.5)	14.9 (7.9–21.8)	0.30
ESR (mm/h)	27.9 (19.7–36.0)	34.7 (27.3–42.1)	0.30

Hb hemoglobin, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

Table 5 Univariate and multivariate analysis of possible predictors for postoperative DVT in UC and CD

	Spearman univariate rank correlation		Multiple regression analysis	
	ρ	p value	β	p value
Gender (Male = 0; Female = 1)	0.30	0.02	0.18	0.30
Diagnosis (UC = 0; CD = 1)	–0.27	0.03	–0.05	0.82
Rectal bleeding (no = 0; yes = 1)	0.32	0.03	0.21	0.24
aCL IgM >6	0.36	0.02	0.49	0.05
aβ2 IgM >4	0.31	0.04	–0.26	0.21
aPTT ≤29	–0.28	0.00	–0.06	0.69
pANCA >1	0.33	0.03	0.20	0.42

$R^2 = 0.59$; $p < 0.005$

Discussion

Colorectal surgery is a well assessed independent risk factor for venous thromboembolism [12, 13] and nowadays the prophylactic therapy based on low molecular weight heparin and/or graduated compression stockings is mandatory after such procedures [12, 14]. Similarly, CD and UC are independent and disease-specific risk factors for thromboembolism, with an incidence that varies from 1.2 to 39% [1–4]. In these patients, DVT rate is increasing, and this preventable complication is a cause of mortality and economic burden [2]. All the efforts toward universal implementation of prevention, early detection, and prompt therapy are essential elements in improving health outcomes for IBD inpatients [2]. Therefore, the primary endpoint of the present study was to assess the validity of the standard prophylactic therapy in case of the combination of these two independent risk factors.

In our series, patients operated on for IBD, and particularly for UC, had a significantly higher incidence of postoperative DVT than patients with colorectal cancer submitted to comparable surgery. These data are consistent with those reported by Catheline et al. [14]. Furthermore, in the second phase of the present study, when preoperative and postoperative Doppler US studies were performed, two further asymptomatic DVT were observed, in spite of the standardized prophylaxis. This finding suggested that postoperative subclinical DVT in UC patients could be rather more common than previously suspected from the clinically evident DVT rate. Therefore, in spite of prophylactic therapy with 4,000 IU/day LMWH, UC was still found to be a significant risk factor for DVT. Although prophylactic therapy with 4,000 IU/day LMWH seemed to be completely effective for the prevention of postoperative DVT in patients with colorectal cancer and, probably, in those with diverticular disease (the sample size of this group was rather small), it clearly was not in patients with CD and even less so in those with UC. In these patients, a more tailored prophylactic therapy should be considered and a randomized controlled trial testing the effectiveness of a daily dose of LMWH based on patient weight versus the current standard 4,000 IU dose would be advisable.

Identifying IBD patients at higher risk of DVT could become useful to plan a more adequate prophylactic therapy. The univariate analysis of predictors of postoperative DVT showed that female gender, UC diagnosis, active rectal bleeding, aPTT value, aCL IgM, aβ2 IgM, and pANCA levels seemed significantly correlated with postoperative DVT. All these variables were then included in a multiple regression analysis model that showed that only aCL IgM levels were independently associated with postoperative DVT.

Anticardiolipin antibodies are a heterogeneous family of autoantibodies directed against protein–phospholipid complexes, and the presence of these antibodies is one of two laboratory diagnostic criteria for antiphospholipid syndromes characterized by venous and arterial thrombosis, recurrent abortion, and thrombocytopenia [24]. In patients with cardiovascular disease a significant association between endothelial dysfunction and elevated levels of aCL was observed [25]. A recent study showed that the aCL IgG and IgM isotypes seem to define different clinical subsets of patients with thromboembolic events, with aCL IgG being most prevalent in the group having DVT and aCL IgM being found primarily among patients with cerebrovascular infarction [26].

Nevertheless, in our study group aCL IgM, and not aCL IgG, was significantly and independently associated with postoperative DVT. Inflammatory bowel disease activity positively correlates with venous thromboembolic risk, and coagulation activity is higher during exacerbations, probably because of a secondary effect of tissue damage and destruction [5, 6]. In fact, in patients with active IBD, soluble trombomodulin, a marker of endothelial damage, is significantly increased [27]. Therefore, peaks of aCL IgM, instead of stable aCL IgG levels, might be related to a flare of IBD and therefore, even if not necessarily causative, they might be associated with DVT. In fact, other known causes of thrombosis have been associated with IBD activity: low vitamin B6 plasma levels, an independent risk

factor for thrombosis, are especially frequent in patients with active IBD [9].

Moreover, the aCL IgM levels are clearly pathological when above 15 kU/l, and the threshold in diagnosis of antiphospholipid syndrome is 40 kU/l [24]. Thus a practical limit of our findings is the low threshold value that indicated an increased risk of postoperative DVT in IBD patients. In fact, in the general population an aCL IgM level just above 6 kU/l is within the normal range [24], and it would not indicate any increased risk of DVT or raise any suspicion.

For ethical reasons, the study design did not include a control IBD population not treated for DVT prevention, and this could be considered a limit of the study. Moreover, the relatively small sample size of the prospective cohort suggests caution when interpreting the results of this multivariate analysis. Finally, the last limit of this study was the unexpected absence of DVT among the colorectal cancer patients. The true incidence of DVT in this group of colorectal cancer patients was probably underestimated based on the method of detection (revision of a surgical database). However, the same method was used to retrieve DVT data in IBD patients, so the possible bias should not have influenced the comparison between the two groups.

In conclusion, our study showed that prophylactic therapy with 4,000 IU/day LMWH was not completely effective for the prevention of postoperative DVT in patients with CD, and even less so in those with UC. In treating these patients, a more tailored prophylactic therapy should be considered, and further randomized controlled trials testing the effectiveness of different prophylactic protocols would be advisable. Furthermore, aCL IgM serum levels might be helpful to identify IBD patients who are at higher risk of postoperative DVT.

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