

Prevalence of asymptomatic deep vein thrombosis in patients with inflammatory bowel diseases in the ambulatory surgery setting

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Abstract

Introduction: Patients suffering from inflammatory bowel disease (IBD) are reported at higher risk of venous thromboembolism (VTE). This is relevant in IBD patients scheduled for surgery. We aimed to seek for differences in the prevalence of asymptomatic lower extremity deep venous thrombosis (DVT) in IBD patients observed in outpatient surgery setting compared with controls.

Methods: All consecutive patients diagnosed with IBD observed in outpatient setting between December 2013 and June 2014 were prospectively included. A sex, age, and gender matched cohort of non-IBD patients served as control group. All patients underwent clinical examination and ultrasound (US) assessment of their lower extremity venous vascular system performed by a clinician blind to patient diagnosis.

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Results: A total of 40 IBD patients and 40 controls agreed to participate. One IBD patient and one control were found with non-occlusive chronic DVT. No differences were observed in valvular incompetence between the two groups. Neither acute DVT nor severe venous incompetence were observed. Surgery was only performed in one control.

Conclusion: Our data show that patients with IBD in remission are not at higher risk of either asymptomatic DVT or venous insufficiency compared with general population, suggesting that the higher risk of VTE events may rely on complex inflammatory mechanisms related with immune response. Screening asymptomatic IBD patients for DVT showed no advantages, suggesting that routine control in ambulatory surgery units is not warranted.

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are considered a risk factor for venous thromboembolism (VTE). Despite a retrospective analysis of IBD patients from an US Centre with extensive expertise in the field showed low prevalence of VTE [1], more recent population-based studies recently found that IBD patients have a 3-fold increased risk of VTE compared with general population [2,3]. However, the mechanisms responsible for this pro-thrombotic status in IBD patients is still poorly understood [4].

Venous valvular dysfunctions are a risk factor for VTE, and are observed in up to 83% of patients following deep vein thrombosis (DVT) despite anticoagulant therapy [5,6]. Our aims were 1) to seek for potential differences in the incidence of venous valvular dysfunctions and asymptomatic DVT in IBD patients compared with control patients admitted at our ambulatory surgery unit, and 2) to investigate whether screening asymptomatic IBD patients for DVT in outpatient surgery setting could be advantageous in reducing admission time.

Methods

We prospectively enrolled willing IBD patients consecutively observed in outpatient setting at the Ambulatory Surgery Unit of our Department between December 2013 and June 2014. All patients had received IBD diagnosis following the accepted criteria [7,8]. Patients were considered for inclusion aged between 16 and 65 years, without active disease requiring modification of medical therapy or surgical

treatment.

A cohort of age-, sex-, and gender-matched non-IBD controls was established. All patients were screened for prior medical history of VTE, varicose veins and/or lower limb oedema, and underwent a complete physical examination with careful assessment of lower limbs.

Patients received Doppler ultrasound evaluation (US), performed by an ultrasonographer with extensive experience, who was blind to the patient diagnosis. With the patient in supine position, the common, deep, and superficial femoral and popliteal venous segments were evaluated for venous thrombosis with a standard probe. Compressibility/collapse of each venous segment was assessed, and valvular competence was measured. Valve incompetence was graded as normal, mild or severe based on the peak Doppler velocity of the reflux signal.

For the secondary aim, we sought whether US evaluation changed the management of IBD patients compared with controls. Patients accessing the Ambulatory Surgery Unit for control had a Medical Chart opened at the time of US examination, meaning that, should asymptomatic vein disorders be found, a treatment could be proposed and undertaken in shorter times, by avoiding the usual waiting list for outpatient surgical procedures. The number of IBD patients taking advantage from this policy was compared with controls to assess the effectiveness of such prophylactic pathway in reducing waiting time for surgery, and expedite the work of the Unit.

Results

Forty IBD patients fit in the criteria and agreed to study participation. Sixteen had CD, and 24 UC. Median age was 42 (range 17-62) years, with 29 females. Forty matched controls were included, observed for other-than-IBD benign diseases.

Varicose veins were observed in 7 IBD patients (17.5%) and in 12 controls (30%), $p=0.29$. No signs of post-thrombotic syndrome were observed in any patient.

One patient in each group (2.5%) was found with chronic DVT, while mild valvular incompetence was found in 12 (30%) and 11 (27.5%) IBD and controls, respectively ($p>0.99$). No patients with severe venous incompetence were observed. Patients were prescribed compressive stockings, and surgery was offered when indicated. Only one patient from controls received surgical treatment, whereas IBD patients declined or did not need surgical procedures ($p>0.99$).

Discussion

In our study, we did not find an increased rate of valvular dysfunction or asymptomatic DVT in IBD patients compared with patients without IBD, although IBD are an independent predictor of VTE. Neither clinical nor Doppler US-detected differences were observed between the two groups. Routine examination did not modify the management of IBD patients in terms of ambulatory surgery procedures.

The reported incidence of VTE in IBD greatly varies among studies, but most population-based big studies agree that these are an independent risk factor of VTE, increasing a three times as high risk compared with general population [2, 3].

However, our findings were not completely unattended. The risk of VTE in IBD patients is increased in those with moderately to severely active disease and in-hospital setting [9]. Patients with remitting IBD may not be at higher risk of VTE when compared with those with active flares [10] and needing surgery for refractoriness to therapy.

IBD are complex diseases, involving complex aetiopathogenesis. The mechanisms underlying the development of such diseases include the immune system, a genetic predisposition, and exogenous factors [11–19]. This justifies the frequent association of IBD with the so-called extra-intestinal manifestation (EIMs), IBD-associated disorders occurring in other organs, as well as with malignancies of intestinal [20, 21] and extra-intestinal origin [22]. Haematological disorders resulting in a pro-thrombotic status could be regarded as an EIM [4].

IBD patients may have disease onset at any age [23–27], but may require invasive surgery [28–31] irrespective of age, as this is not regarded as a limit for advanced surgical procedures itself [32–46]. Another facet to evaluate is the potential need for combined treatment (medical and surgical) [47–54], or the need of repeated procedures for complications [43, 55–62], which may further increase the risk of VTE. This is consistent with complex autoimmune mechanisms playing a role in thrombogenesis in IBD, which may escape the common known pathways.

With these observations in mind, we tried to assess the impact of this preventive pathway in reducing waiting lists for ambulatory procedures in these patients, by recording them with a Medical Chart at the Ambulatory Surgery Unit, where visits and US were performed. A report including 315 and 363 patients operated on in 2011 and 2012, respectively, at a Day Surgery Unit from UK [63] showed that waiting for being operated on and booking mistakes left room for improvement. Ambulatory and Day Surgery waiting lists in some Countries are long, i.e. in Italy, and it can take months before

being called for the procedure. This is a relevant point, as Ambulatory Surgery Units were developed specifically to resolve the issue of the long waiting list, simplifying the scheduled work of Surgical Units [64]. Besides problems in communications between caregivers and patients [65], other factors have been investigated, which could account for excessive waiting and surgical lists overrun [66, 67].

Faiz et al. [66] showed that overruns of the surgical list are responsible of poor staff morale, and can be reduced by lowering the number of scheduled procedures. However, this does not come without a cost, because of the potential reduced productivity due to inadequately balanced list sizes.

Studies from the same UK based group have shown that statistically designed tools can ease planning the activity of the Ambulatory Units, and increase the performance rates and patient satisfaction [67, 68]. The latter observation is much more relevant in IBD patients, who often have psychological repercussions due to their diseases themselves [27]. The proposed approaches [66–68] are useful, but rarely applied in everyday practice of Ambulatory Surgery Units. By admitting patients at the outpatient surgical procedure Unit at the time of prophylactic examination, with no additional waiting list, we were not able to find this approach effective, irrespective of baseline disease. On the contrary, most accesses were avoidable, and only delayed the scheduled activity of the Unit, suggesting that such approach in IBD patients is useless for patients, and detrimental and time consuming for the Hospital.

Notwithstanding, although routinely screening asymptomatic IBD patients for alterations of lower extremities venous valvular system may be inappropriate [10], our paper advocates the need for further researches to identify the factors responsible for higher risk of VTE in IBD patients, allowing prevention of these events especially in those with active disease or candidate to surgery.

References

- Talbot RW, Heppell J, Dozois RR, et al. Vascular complications of inflammatory bowel disease. *Mayo Clin Proc* 1986;**61**:140–5.
- Miehler W, Reinisch W, Valic E, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 2004;**53**:542–8.
- Bernstein CN, Blanchard JF, Houston DS, et al. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb Haemost* 2001;**185**:430–4.
- Canero A, Parmeggiani D, Avenia N, et al. Thromboembolic tendency (TE) in IBD (Inflammatory bowel disease) patients. *Ann Ital Chir* 2012;**83**:313–7.
- O'Shaughnessy AM, Fitzgerald DE. The patterns and distribution of residual abnormalities between the individual proximal venous segments after an acute deep vein thrombosis. *J Vasc Surg* 2001;**33**:379–84.
- Gosk-Bierska I, McBane RD, Waszczuk E, et al. Prevalence of lower extremity venous disease in inflammatory bowel disease. *Int Angiol* 2007;**26**:67–71.
- Van Assche G, Dignass A, Panes J, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 2010;**4**:7–27.
- Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis* 2012;**6**:965–90.
- Nguyen GC, Bernstein CN, Bitton A, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology* 2014;**146**:835–48.
- Nguyen GC, Wu H, Gulamhusein A, et al. The utility of screening for asymptomatic lower extremity deep venous thrombosis during inflammatory bowel disease flares: a pilot study. *Inflamm Bowel Dis* 2013;**19**:1053–8.
- Latella G, Rogler G, Bamias G, et al. Results of the 4th scientific workshop of the ECCO (I): Pathophysiology of intestinal fibrosis in IBD. *J Crohns Colitis* 2014;**8**:147–65.
- Lawrance IC, Rogler G, Bamias G, et al. Cellular and molecular mediators of intestinal fibrosis. *J Crohns Colitis* 2014 Oct 8. pii: S1873–9946(14)00289-X. doi: 10.1016/j.crohns.2014.09.008. [Epub ahead of print]
- Pellino G, Sciaudone G, Selvaggi F, et al. Delayed diagnosis is influenced by the clinical pattern of Crohn's disease and affects treatment outcomes and quality of life in the long term: a cross-sectional study of 361 patients in Southern Italy. *Eur J Gastroenterol Hepatol* 2015;**27**:175–81. doi: 10.1097/MEG.0000000000000244.
- Romano M, Cuomo A, Tuccillo C, et al. Vascular endothelial growth factor and cyclooxygenase-2 are overexpressed in ileal pouch-anal anastomosis. *Dis Colon Rectum* 2007;**50**:650–9.
- Pellino G, Sciaudone G, Candilio G, et al. Rectosigmoid stump washout as an alternative to permanent mucous fistula in patients undergoing subtotal colectomy for ulcerative colitis in emergency settings. *BMC Surg* 2012;**12** Suppl 1:S31. doi: 10.1186/1471-2482-12-S1-S31
- Canani RB, Cirillo P, Mallardo G, et al. Effects of HIV-1 Tat protein on ion secretion and on cell proliferation in human intestinal epithelial cells. *Gastroenterology* 2003;**124**:368–76
- Sciaudone G, Pellino G, Selvaggi F. Diagnostic pitfalls: cancerization in IBD versus mantle cell lymphoma presenting with multiple lymphomatous polyposis. *Inflamm Bowel Dis* 2011;**17**:E28–30. doi: 10.1002/ibd.21642.
- Sciaudone G, Pellino G, Guadagni I, et al. Disseminated *Cryptococcus neoformans* infection and Crohn's disease in an immunocompetent patient. *J Crohns Colitis* 2011;**5**:60–3. doi: 10.1016/j.crohns.2010.08.003.
- Pellino G, Sciaudone G, Canonico S, et al. Nerve sheath in longstanding fibrostenosing Crohn's disease: is there a connection? *Inflamm Bowel Dis* 2013;**19**:E16–9. doi: 10.1002/ibd.22847.
- Egan L, D'Inca R, Jess T, et al. Non-colorectal intestinal tract carcinomas in inflammatory bowel disease: results of the 3rd ECCO Pathogenesis Scientific Workshop (II). *J Crohns Colitis* 2014;**8**:19–30. doi: 10.1016/j.crohns.2013.04.009.
- Selvaggi F, Pellino G, Canonico S, et al. Systematic Review of Cuff and Pouch Cancer in Patients with Ileal Pelvic Pouch for Ulcerative Colitis. *Inflamm Bowel Dis* 2014;**20**:1296–308. doi: 10.1097/MIB.0000000000000026
- Pellino G, Sciaudone G, Paturelli M, et al. Relatives of Crohn's disease patients and breast cancer: An overlooked condition. *Int J Surg* 2014;**12** Suppl 1:S156–8. doi: 10.1016/j.ijsu.2014.05.022.
- Pellino G, Sciaudone G, Miele E, et al. Functional outcomes and quality of life after restorative proctocolectomy in paediatric patients: a case-control study. *Gastroenterol Res Pract* 2014;**2014**:340341. doi: 10.1155/2014/340341.
- Pellino G, Sciaudone G, Candilio G, et al. Complications and functional outcomes of restorative proctocolectomy for ulcerative colitis in the elderly. *BMC Surg* 2013;**13** Suppl 2:S9. doi: 10.1186/1471-2482-13-S2-S9
- Pellino G, Sciaudone G, Candilio G, et al. Restorative proctocolectomy with ileal pouch-anal anastomosis is safe and effective in selected very elderly patients suffering from ulcerative colitis. *Int J Surg* 2014;**12** Suppl 2:S56–9.
- Pellino G, Sciaudone G, Candilio G, et al. Preventive NPWT over closed incisions in general surgery: does age matter? *Int J Surg* 2014;**12** Suppl 2:S64–8. doi: 10.1016/j.ijsu.2014.08.378.
- Pellino G, Sciaudone G, Caserta V, et al. Fatigue in inflammatory bowel diseases: relationship with age and disease activity. *Int J Surg* 2014;**12** Suppl 2:S60–3. doi: 10.1016/j.ijsu.2014.08.379.
- Pellino G, Sciaudone G, Candilio G, et al. Effects of a new pocket device for negative pressure wound therapy on surgical wounds of patients affected with Crohn's disease: a pilot trial. *Surg Innov* 2014;**21**:204–12. doi: 10.1177/1553350613496906.
- Selvaggi F, Pellino G, Canonico S, et al. Is omitting pouchography before ileostomy takedown safe after negative clinical examination in asymptomatic patients with pelvic ileal pouch? An observational study. *Tech Coloproctol* 2012;**16**:415–20. doi: 10.1007/s10151-012-0838-1
- Pellino G, Sciaudone G, Canonico S, et al. Role of ileostomy in restorative proctocolectomy. *World J Gastroenterol* 2012;**18**:1703–7. doi: 10.3748/wjg.v18.i15.1703
- Selvaggi F, Giuliani A, Gallo C, et al. Randomized, controlled trial to compare the J-pouch and W-pouch configurations for ulcerative colitis in the maturation period. *Dis Colon Rectum* 2000;**43**:615–20.
- Canonico S, Benevento R, Perna G, et al. Sutureless fixation with fibrin glue of lightweight mesh in open inguinal hernia repair: effect on postoperative pain: a double-blind, randomized trial versus standard heavyweight mesh. *Surgery* 2013;**153**:126–30. doi: 10.1016/j.surg.2012.06.024.
- Pellino G, Sciaudone G, Candilio G, et al. Early postoperative administration of probiotics versus placebo in elderly patients undergoing elective colorectal surgery: a double-blind randomized controlled trial. *BMC Surg* 2013;**13** Suppl 2:S57. doi: 10.1186/1471-2482-13-S2-S57.
- Selvaggi F, Sciaudone G, Guadagni I, et al. Ileal pouch-anal anastomosis after stapled haemorrhoidectomy for unrecognized ulcerative colitis. *Colorectal Dis* 2010;**12**:e172
- Pellino G, Sciaudone G, Candilio G, et al. Stepwise approach and surgery for gallbladder adenomyomatosis: a mini-review. *Hepatobiliary Pancreat Dis Int* 2013;**12**:136–42.
- Selvaggi F, Cuocolo A, Sciaudone G, et al. FGD-PET in the follow-up of recurrent colorectal cancer. *Colorectal Dis* 2003;**5**:496–500.
- Gagliardi G, Pucciarelli S, Asteria CR, et al. A nationwide audit of the use of radiotherapy for rectal cancer in Italy. *Tech Coloproctol* 2010;**14**:229–35
- Accardo G, Esposito D, Barbato F, et al. Pheochromocytoma: from the bench to the surgery. *Minerva Chir* 2014;**69**(2 Suppl 1):97–103
- Selvaggi F, Pellino G, Pellegrino T, et al. Role of scintigraphy in differential diagnosis of adrenal lesions. *Minerva Chir* 2014;**69**(2 Suppl 1):105–9
- Selvaggi F, Sciaudone G, Giuliani A. New ambulatory treatment with radiofrequency for internal symptomatic hemorrhoids: morbidity evaluation. *Gastroenterol Clin Biol* 2005;**29**:939–40.
- Selvaggi F, Sciaudone G, Giuliani A, et al. A new type of stricturoplasty for the treatment of multiple long stenosis in Crohn's disease. *Inflamm Bowel Dis* 2007;**13**:641–2
- Selvaggi F, Guadagni I, Pellino G, et al. Perianal Paget's disease happening with mucinous adenocarcinoma of the anal canal: managing rarities. *J Cutan Pathol* 2010;**37**:1182–3.
- Selvaggi F, Fucini C, Pellino G, et al. Outcome and prognostic factors of local recurrent rectal cancer: a pooled analysis of 150 patients. *Tech Coloproctol* 2014 Nov 11. doi: 10.1007/s10151-014-1241-x [Epub ahead of print]
- Selvaggi F, Pellino G, Sciaudone G, et al. Development and validation of a practical score to predict pain after excisional hemorrhoidectomy. *Int J Colorectal Dis* 2014;**29**:1401–10. doi: 10.1007/s00384-014-1999-3
- Benevento R, Santoriello A, Pellino G, et al. The effects of low-thrombin fibrin sealant on wound serous drainage, seroma formation and length of postoperative stay in patients undergoing axillary node dissection for breast cancer. A randomized controlled trial. *Int J Surg* 2014;**12**:1210–5.
- Müller-Lissner SA, Bartolo DC, Christiansen J, et al. Interobserver agreement in defecography—an international study. *Z Gastroenterol* 1998;**36**:273–9.
- Sciaudone G, Pellino G, Guadagni I, et al. Infliximab avoiding colectomy and maintaining remission in pediatric immunosuppressive-naïve ulcerative colitis achieving remarkable mucosal healing. *Panminerva Med* 2010;**52**:91–2.
- Sciaudone G, Pellino G, Guadagni I, et al. Education and imaging: gastrointestinal herpes simplex virus-associated erythema multiforme (HAEM) during infliximab treatment for ulcerative colitis. *J*

Gastroenterol Hepatol 2011;**26**:610.

49. Sciaudone G, Pellino G, Riegler G, et al. Infliximab in drug-naïve patients with failed ileorectal anastomosis for Crohn's disease: a new chance for sparing the rectum? **Eur Surg Res** 2011;**46**:163–8. doi: 10.1159/000324398.
50. Sciaudone G, Di Stazio C, Limongelli P, et al. Treatment of complex perianal fistulas in Crohn disease: infliximab, surgery or combined approach. **Can J Surg** 2010;**53**:299–304.
51. Secondulfo M, Riegler G, De Magistris L, et al. Intestinal permeability assessment before and after ileal pouch-anal anastomosis. **Minerva Gastroenterol Dietol** 2004;**50**:155–63
52. Pellino G, Selvaggi F. Surgical treatment of perianal fistulizing Crohn's disease: from lay-open to cell-based therapy - an overview. **ScientificWorld Journal** 2014;**2014**:146281. doi: 10.1155/2014/146281
53. Selvaggi F, Pellino G, Canonico S, et al. Effect of Preoperative Biologic Drugs on Complications and Function After Restorative Proctocolectomy with Primary Ileal Pouch Formation: Systematic Review and Meta-analysis. **Inflamm Bowel Dis** 2015;**21**:79–92. doi: 10.1097/MIB.0000000000000232.
54. Musto D, Martorelli L, Cirillo A, et al. Distal esophageal involvement in Crohn disease: short treatment with adalimumab. **Endoscopy** 2010;**42 Suppl 2**:E299.
55. Selvaggi F, Pellino G. Pouch-related fistula and intraoperative tricks to prevent it. **Tech Coloproctol**. 2015 Jan 4. doi 10.1007/s10151-014-1257-2 [Epub ahead of print]
56. Selvaggi F, Sciaudone G, Limongelli P, et al. The effect of pelvic septic complications on function and quality of life after ileal pouch-anal anastomosis: a single center experience. **Am Surg** 2010;**76**:428–35.
57. Sciaudone G, Pellino G, Guadagni I, et al. Wireless capsule endoscopy years after Michelassi stricturoplasty for Crohn's disease. **Acta Chir Belg** 2010;**110**:213–5.
58. Sciaudone G, Di Stazio C, Guadagni I, et al. Rectal diverticulum: a new complication of STARR procedure for obstructed defecation. **Tech Coloproctol** 2008;**12**:61–3
59. Selvaggi F, Pellino G, Sciaudone G. Surgical treatment of recurrent prolapse after stapled haemorrhoidopexy. **Tech Coloproctol**. 2014 Sep;**18(9)**:847-50. doi: 10.1007/s10151-014-1180-6.
60. Sciaudone G, Pellino G, Fiorelli A, et al. Transtube exploration with flexible bronchoscope to extract trapped abdominal drains. **Surg Laparosc Endosc Percutan Tech** 2013;**23**:362–4.
61. Selvaggi F, Giuliani A, Sciaudone G, et al. Quality of life in patients with ileal pouch for ulcerative colitis. **Chir Ital** 2004;**56**:239–46.
62. Selvaggi F, Cuocolo A, Giuliani A, et al. The role of scintigraphic defecography in the assessment of bowel function after restorative proctocolectomy for ulcerative colitis. **Int J Colorectal Dis** 2006;**21**:448–52.
63. Thurairatnam RR, Mathew GS, Montgomery J, et al. The role of patient satisfaction surveys to improve patient care in day surgery. **Ambul Surg** 2014;**20**:16–8
64. Sierra E, Pi F, Domingo J, et al. Ambulatory surgery to cope with long patient waiting lists **Ambul Surg** 1995;**3**:19–22
65. Anatol T, Hariharan S. Paediatric ambulatory surgery cancellations in a caribbean developing country. **Ambul Surg** 2007;**13**:1–18
66. Faiz O, Mcguire AJ, Tekkis P, et al. Is it possible to predict list overruns in a NHS day surgery unit? **Ambul Surg** 2007;**13**:67–71
67. Faiz O, Mcguire AJ, Tekkis P, et al. Measuring general surgical workload in the day surgery unit. **Ambul Surg** 2007;**13**:86–90
68. Faiz O, Tekkis P, Mcguire AJ, et al. Optimising operating list scheduling in the day surgery department: can statistical modelling help? **Ambul Surg** 2007;**13**:114–9