Vascular complications in inflammatory bowel disease: An observational study

Complicações vasculares na doença inflamatória intestinal: Um estudo observacional

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RESUMO

Introdução: Doentes com doença inflamatória intestinal (DII) têm risco aumentado de tromboembolismo (TE). Estimar a magnitude desse risco é imperativa para melhor abordar os doentes com DII. O objetivo deste estudo consistiu em determinar os eventos tromboembólicos venosos (TEV), arteriais (TEA) e cardiovasculares (CV) e a mortalidade associada nos doentes internados com DII.

Metodologia: Estudo retrospetivo, incluindo todos os doentes com DII e internamento num hospital terciário entre 01-08-2006 e 31-05-2013 com TEV/TAE/CV. Caracterização da população pelas variáveis: DII, episódio tromboembólico, fatores de risco, profilaxia e prognóstico.

Resultados: Registámos 774 internamentos de doentes com DII, 28 (3,6%) com episódio tromboembólico – 57% sexo masculino; idade média 58±17 anos (13.8% <40 anos); duração média DII 13±13 anos; 57.1% colite ulcerosa (E1-21%; E2-43%; E3-36%) e 42.9% com doença Crohn (L1-70%; L2-10%; L3-20%; B1-25%; B2-42%; B3-33%). Medicação aquando da intercorrência: 5-ASA (57%), tiopurinas (23%), corticóides (15%), anti-TNF (12%). Dezassete apresentaram TEA/CV, 7 tiveram tromboembolismo pulmonar, 3 trombose venosa profunda, 1 trombose veia mesentérica superior. Pelo menos 39% destes doentes apresentava DII ativa. Seis TEV e 8 TEA/CV tinham outros fatores de risco concomitantes. Um caso recorreu. Mortalidade nula.

Discussão & Conclusão: Os TEV/TEA/CV não são raros na DII. Vários fatores podem contribuir para o seu desenvolvimento. A atividade da DII parece ter uma relação estreita com TEV, ao contrário dos TEA/CV, e outras características da DII parecem também influenciar o risco tromboembólico. Um esforço adicional deverá ser feito para aumentar a prescrição de profilaxia de TEV nos doentes com DII internados.

Palavras-chave: Doença Inflamatória Intestinal, Tromboembolismo venoso, Tromboembolismo arterial.

ABSTRACT

Background: *Increasing evidence has raised an alert about the potential risk of vascular complications in inflammatory bowel disease (IBD). Estimating its magnitude is imperative to better address IBD patients. The aim of this study was to determine the venous (VTE), arterial thromboembolic events rates (ATE) and cardiovascular events (CVE) and related mortality in IBD inpatients.*

Methods: *Retrospective study including all IBD inpatients from a tertiary hospital (1st/August/2006 to 31st/May/2013) with a VTE/ATE/CVE. Population characterization: IBD, vascular complication, risk factors, prophylaxis and outcome.*

Results: *We recorded 774 IBD admissions, 3.6% with thromboembolic episode: 57%-male; average age 58±17 years(13.8% <40years); average IBD duration 13±13years; 57.1% Ulcerative Colitis (E1-21%, E2-43%, E3-36%), 42.9%-Crohn's disease (L1-70%, L2-10%, L3-20%, B1-25%, B2-42%, B3-33%). Regarding therapeutics: 57% 5-ASA, 23% thiopurines, 15% corticosteroids, 12% anti-TNFα. Seventeen patients presented with ATE/CVE, 7-pulmonary thromboembolism, 3-deep vein thrombosis, 1-superior mesenteric vein thrombosis. At least 39% had active IBD. Six VTE + and 8 ATE/CVE had other possible concomitant risk factors. One recurrence. No deaths.*

Conclusion: *Both ATE/CVE/VTE are not uncommon in IBD inpatients and several factors appear to be relevant. IBD activity seems to have a close relationship with VTE, in contrast to ATE/CVE, and other IBD characteristics may also influence this risk. A higher effort should be evoked to increase the rate of venous thromboembolic prophylaxis in IBD inpatients.*

Keywords: *Inflammatory bowel diseases, Venous thromboembolism, Arterial thromboembolism*

BACKGROUND

Inflammatory bowel diseases (IBD), both Crohn's disease (CD) and ulcerative colitis (UC), are chronic gastrointestinal disorders with an unknown etiology. However, it is widely accepted that an uncontrolled inflammatory immune response in genetically predisposed individuals plays an important role in its pathogeny.[1] Systemic inflammation rises both risk of arterial (ATE) and venous thromboembolisms (VTE) and increasing evidence has raised an alert about the potential risk of vascular complications in IBD.[2]

With a prevalence between 1.2 and 6.7% in clinical studies,[2–5] VTE is a well-known and feared complication of IBD[2,6] associated to a non-negligible risk of recurrence[7] and morbimortality. However, despite several population-based studies,[8] the true magnitude of the risk still remains unclear, as a result of methodological differences and heterogeneity across studies. Additionally,

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the reason for this increased risk of VTE is not completely understood. Acquired risk factors appear to be relevant and many of the hemostatic alterations parallel inflammatory activity.[2] Deep venous thrombosis (DVT) and pulmonary embolism (PE), as well as unusual sites of VTE, such as cerebrovascular, portal and mesenteric veins, have been described.

Unlike VTE, the risk of ATE and cardiovascular events (CVE) in IBD is worse understood. Inflammation is involved throughout all stages of atherosclerosis pathogenesis, from plaque initiation to rupture and subsequent thrombosis.[9] C-reactive protein, often elevated during IBD flares, has also been associated with an increased risk of coronary artery disease independent of traditional cardiovascular risk factors.[10] Of note, other chronic inflammatory diseases, such as rheumatoid arthritis, are also associated with an increased of ATE and cardiovascular mortality.[11,12]

Estimating the magnitude of the risk of VTE and ATE/CVE is imperative to better address IBD patients, namely regarding thromboembolic prophylaxis in patients who are already naturally predisposed to bleeding events, a subject that is still under investigation.[13]

The aim of this study was to determine the VTE and ATE/CVE events and related mortality in inpatients with IBD.

METHODS

Study design

- Type of study: observational retrospective study.
- Setting and location: Gastroenterology department of Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal.
- Time frame: From 1st August 2006 to 31st May 2013.

Study population

- Inclusion criteria: all male and female patients, 18 years or older, with an established diagnosis of IBD and an admission between the time frame with an episode of VTE or ATE/CVE.
- Exclusion criteria: Patients with a VTE/ATE/CVE episode previous to the IBD diagnosis.

Definitions

- IBD diagnosis, both CD and UC, were based on clinical, endoscopic, histological and radiological criteria defined by European Crohn's and Colitis Organization;[14,15]
- The diagnosis of VTE followed international guidelines, based on appropriate imaging techniques.[16,17] DVT of the lower or upper limbs was established by Doppler ultrasound and PE was diagnosed performing a Helical Computer Tomography (CT) of the chest or, in the presence of a contraindication for it, a Pulmonary Scintigraphy. Where PE had occurred with concomitant DVT, the thromboembolic event was counted as PE only. Thrombosis of portal, superior mesenteric, splenic or cerebral veins were diagnosed by abdominal and brain Contrast Enhanced CT, respectively;

Myocardial Infarction (MI) was diagnosed using electrocardiogram and/or markers of MI,[18] while a Ischemic Stroke was diagnosed using Cranial CT scan or Magnetic Resonance Imaging (MRI)[19] and peripheral arterial ischemia using Doppler ultrasound and/or Angiography.

Variables collected

The study population was characterized using the following variables, all determined by review of hospital records and IBD database:

- IBD-related parameters – age at diagnosis; type (UC, CD); location, extension and behavior using Montreal classification;[20] activity at the time of the TE events described below; medication. As in other study,[21] we used corticosteroid prescription, admission due to IBD and initiation of anti-TNFα treatment as surrogate measures for an active disease. In this sense, we defined: an active disease, if there was a flare (i.e. a 120 days period from the first steroid or anti-TNFα day prescription and/or admission for IBD, following 120 days free of corticosteroid or admissions due to IBD) or a persistent activity (i.e. those periods succeeding flare periods if additional hospitalizations, anti-TNFα treatment or steroid prescriptions had taken place within the 120 days from flare start); an inactive disease as any period starting 120 days after last hospitalization, anti-TNFα or corticosteroid prescription and ended at the time of reinitiating of corticosteroid treatment or hospitalization.

TABLE 1
Descriptive analysis of IBD patients

Descriptive data of IBD patients (n=28)	
Characteristic	
Gender – n (%) Male Female	 16 (57.1%) 12 (42.9%)
Age (years) – mean ± SD < 40 years old – n (%) 40-60 years old – n (%) > 60 years old – n (%)	58 (17) 4 (13.8%) 8 (27.6%) 16 (58.6%)
Type of IBD – n (%) UC DC	 16 (57.1%) 12 (42.9%)
Disease duration (years) – median (IQR)	11.5 (0-52)
IBD Montreal Classification – n (%) Location and Extension Behavior	 E1 – 6 (21%), E2 – 12 (43%), E3 – 10 (36%) L1 – 20 (70%), L2 – 3 (10%), L3 – 5 (20%) B1 – 7 (25)%, B2 – 12 (42%) , B3 – 9 (33%)
Active IBD – n (%)	12 (42.9%)
IBD therapeutics at TE event – n (%) 5-ASA Thiopurines Infliximab Corticosteroids	 15 (57%) 6 (23%) 3 (12%) 4 (15%)

Abbreviations: n = number; SD = standard deviation; IQR = interquartile range; CD = Crohn's disease; UC = Ulcerative colitis; IBD = Inflammatory bowel disease; 5-ASA = 5-aminosalicylic acid.

- Vascular event-related – age of diagnosis, type (venous / arterial), location (venous – lower or upper limbs DVT, PE, portal, superior mesenteric, splenic or cerebral veins; arterial – MI, stroke, peripheral arterial ischemia).
- Other potential confounding variables for VTE[22] – recent trauma or surgery (up to 3 months),[23] pregnancy, oral contraceptive use at the time of VTE, active cancer, laboratory thrombophilia workup if available, smoking status (unknown, active smoker, non-smoker), pharmacologic VTE prophylaxis (enoxaparin 40mg subcutaneously per day);
- Other potential confounding variables for ATE/CVE[22] – smoking status, hypertension, diabetes mellitus, dyslipidemia;
- Complications-related – recurrence, 30-day mortality.

Statistical analysis

Categorical variables were presented as absolute (n) and relative (%) frequencies and continuous variables through descriptive statistics, namely means and standard deviations (SD), or medians and interquartile ranges for variables with skewed distributions. The analysis was performed with SPSS 20.0 software.

Ethical aspects

The proposed study protocol meets the ethical investigational principles originated from the Declaration of Helsinki. Exceptionally, given the public health interest of this retrospective study and the observational design of the protocol, a consent form was not sent to the patients, whilst safeguarding: data collection from the physician subject to professional confidentiality and ethical

code; the anonymity of the participants guaranteed by the assignment of an unique identification number that was only accessible to the investigators. All collected data was treated, published and presented in a grouped manner, in a way that participants' identification was not possible.

RESULTS

We recorded 774 admissions of patients with IBD, 28 (3.6%) with a TE episode.

Demographic and clinical data

The characteristics of IBD patients with a TE episode are described in Table 1: 57% male gender; average age 58 ± 17 years (13.8 % <40 years); average IBD duration 13 ± 13years; 57.1%-Ulcerative Colitis (E1-21%, E2-43%, E3-36%), 42.9%-Crohn's disease (L1-70%, L2-10%, L3-20 %, B1-25%, B2-42%, B3-33%). Regarding IBD medication: 5-ASA (57%), thiopurines (23%), corticosteroids (15%), anti-TNFα (12%). One patient was under combo therapy (azathioprine and anti-TNFα) and 3 patients were under 5-ASA and thiopurines.

Thromboembolic episode

The TE episodes are summarized in Figures 1 and 2. We registered 17 arterial (10 ischemic strokes, 6 MI, 1 peripheral arterial ischemia) and 11 venous (7 pulmonary thromboembolism - PTE, 3 deep vein thrombosis - DVT, 1 superior mesenteric vein thrombosis - SMVT) TE episodes. Six patients with VTE (54.5%) weren't under thromboembolic prophylaxis.

The characteristics of these two subgroups are detailed in Table 2.

Outcome

All patients with VTE[16,17] and ATE/CVE[24–26] were treated following international guidelines.

We registered one recurrence: 40-year female patient with ulcerative proctitis and peripheral venous insufficiency with an episode of PE with extensive commitment of pulmonary tree. Thrombolysis was attempted, but it was complicated by a hypovolemic shock due to hemoperitoneum. Considering the risk versus benefit for surgical embolectomy, she was referred to an inferior vena cava (IVC) filter. She was later discharged under oral anticoagulation. During follow-up period, a doppler ultrasound was requested due to the presence of varices in inferior limbs (internal safen vein territory) and large collateral circulation in the abdominal wall. A partial thrombosis in the IVC, probably in the area of the filter, plus a chronic thrombosis with partial recanalization of the left iliac vein axis and osteal and troncular left internal safen vein insufficiency were documented. As the varices were secondary, she didn't fulfill the indication for surgery, and as the patient was a definitive IVC filter carrier, maintenance of anticoagulation plus conservative measures were adopted.

No deaths were registered.

DISCUSSION

Our study showed that, in line with previous literature,[27] TE is not uncommon in IBD inpatients, accounting for 3.6% of diagnosis. ATE events (2.2%) were slightly more frequent than VTE (1.4%) in our series.

Regarding IBD characteristics and arterial TE, MI and strokes were more common in UC patients than in CD, as previously observed.[25, 26] As in general population, ATE events were more frequent in male gender and older ages, both well-known cardiovascular risk factors. Although Rungoe *et al* described higher cardiovascular risk in the first years after IBD diagnosis,[30] we weren't able to confirm it in our series, as the median IBD duration was 11.5 years. Nonetheless, this can be due to the fact that IBD diagnosis was made several years ago in a large percentage of cases and this was a retrospective study probably lacking some data, namely ATE events occurred at the onset of the disease. The fact that an active disease was not encountered in a major rate of cases (only in 17.6% of cases) could determine a minor role of the disease itself influencing the risk of ATE. IBD therapeutics may affect ATE risk.[30] An important percentage of patients were under steroids (20%), a drug known to increase the risk of TE.[30] It is also suggested[30] that 5-ASA and anti-TNFα diminish this risk. We encountered a considerable rate of patients under these medications, but the percentage of patients under these medications and without an ATE event may be higher.

TABLE 2
Descriptive analysis of IBD patients according to arterial/venous TE complication

Descriptive data of IBD patients		
Characteristic	**Arterial TE (n=17)**	**Venous TE (n=11)**
Gender – n (%) Male Female	 10 (58.9%) 7 (41.1)	 6 (54.5%) 5 (45.5%)
Age (years) – mean ± SD <40 years – n (%) 40-60 years – n (%) >60 years – n (%)	57 (17) 3 (17.6%) 4 (23.5%) 10 (58.8%)	59 (17) 2 (18.2%) 4 (36%) 5 (54.5%)
Type of IBD – n (%) UC DC	 12 (70.6%) 5 (29.4%)	 5 (54.5%) 6 (45.5%)
IBD duration (years) – median (IQR)	12.5 (0-52)	11 (0-36)
Montreal Classification – n (%) Location/Extension Behavior	 E1-5(30%), E2-9(50%), E3-3(20%) L1-10(60%), L2-3(15%), L3-4(25%) B1-2(13%), B2-9(52%), B3-6(35%)	 E1-1(10%), E2-2(20%), E3-8(70%) L1-6(54%), L2-3(23%), L3-3(23%) B1-4(37%), B2-4(37%), B3-3(26%)
Active disease – n (%) Active UC Active CD	4 (23.5%) 2 2	8 (81%) 3 5
Current IBD therapy – n (%) 5-ASA Thiopurines Infliximab Corticosteroids	 12 (73%) 10 (6%) 2 (13%) 3 (17.6%)	 4 (36%) 3 (27%) 1 (9%) 3 (27%)
Arterial Hypertension – n (%)	8 (47%)	0
Diabetes Mellitus – n (%)	3 (18%)	0
Dyslipidemia – n (%)	4 (23.5%)	0
Active smokers – n (%)	3 (17.6%)	2 (18.2%)
Surgery/Trauma – n (%)	0	5 (45.5%)
Pregnancy – n (%)	0	0
Active cancer – n (%)	0	0
Without VTE prophylaxis – n (%)	0	6 (54.5%)
Genetic hemostasis abnormalities Factor V Leiden – n (%) G20210A mutation – n (%) MTHFR C677T – n (%) Factor XIII val34leu – n (%) PAI-1 – n (%)	 0 0 1 heterozygote 0 1 homo- / 1 heterozygote	 0 0 0 1 homozygote 1 homo- / 2 heterozygotes

Abbreviations: n = number; SD = standard deviation; IQR = interquartile range; CD= Crohn's disease; UC= Ulcerative colitis; IBD= Inflammatory bowel disease; 5-ASA= 5-aminosalicylic acid.

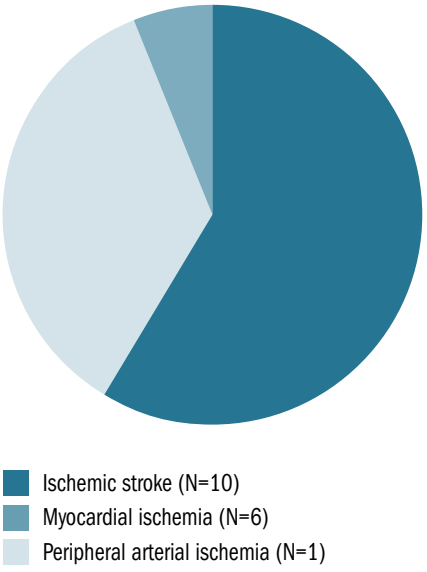

FIGURE 1. Type of arterial thromboembolic complications.

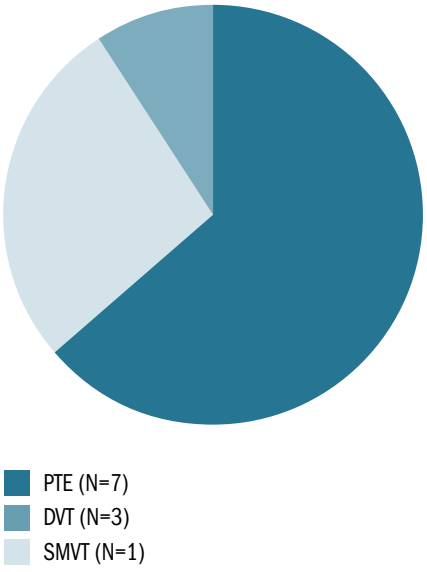

FIGURE 2. Type of venous thromboembolic complications.

Concerning IBD characteristics and VTE, the role of IBD type in the risk of this complication is still controversial.[27,31] It is well known that the absolute risk of VTE increases with age, and that explains the mean age of the event in our series (mean age of 59 years). Papay *et al* didn't find relevance in sex and disease duration,[32] as we did. Although IBD location and extension aren't consensual risk factors, some authors[33] defend that VTE is more frequent in more extensive disease, as we did. We found a high rate of ileal disease, but this is also the most frequent location of Crohn's disease. A comparison with IBD without VTE should be made in other to confirm the role of these disease parameters in VTE. We didn't find a predominant behavior of CD in VTE. Some studies[5] report a higher percentage of fistulising disease in VTE events, but, as mentioned before, we couldn't do a direct comparison to evaluate this parameter. Amongst IBD therapeutics, mesalazine has been reported not to influence platelet aggregation or fibrinolytic activity.[34] Steroids increase platelet function and induce states of hypercoagulability and hypofibrinolysis, explaining the high percentage of steroids in VTE.[35] Contrarily, there is increasing evidence that anti-TNFα reduces coagulation markers and activates fibrinolytic system,[31] probably explaining the low percentage of anti-TNFα users with VTE complication in our series.

Inflammation, probably through biological and biochemical effects exerted by the activation of the inflammatory pathways in the hemostatic system, takes an important role in ATE and VTE.[2] We found active IBD in 12 cases (42.9%; 4 ATE and 8 VTE).

Genetic abnormalities of hemostasis have been implicated in a low number of IBD patients with TE and are generally not found more often in IBD than in non-IBD conditions, suggesting that genetics may not explain a greater risk of VTE in IBD. In our sample, Factor V Leiden, the most prevalent thrombophilia reported in IBD,[31] wasn't encountered in any of our analyzed patients. Prothrombin G20210A mutation hasn't been definitively associated with thrombosis in IBD[31] and wasn't either found in any patient. Methylenetetrahydrofolate reductase (MTHFR) C677T mutation, increasing homocysteine plasma levels in homozygous carriers, hasn't been significantly associated to a higher thrombotic risk in IBD[31] and it was found in 3 heterozygotes. Factor XIII val34leu mutation, increasing FXIII activation rate and reducing the risk TE in 20 to 40% of cases,[31] has been encountered in similar prevalence in IBD patients and healthy controls and in thrombotic IBD patients and non-IBD thrombotic patients. We found a homozygote carrier of this mutation. PAI-1, a fibrinolysis inhibitor, homozygosity is associated with enhanced PAI-1 expression and contributes as an additional risk factor towards the development of VTE, but

it doesn't seem to differ between thrombotic IBD compared to non-IBD thrombotic patients.[31] We found 1 homozygote carrier.

Despite the publication of guidelines regarding TE prophylaxis in hospitalized IBD patients,[13] more than 50% of patients weren't under prophylaxis. Tinsley *et al* have previously also reported an elevated percentage of physicians not aware of any recommendations regarding this subject.[36]

It is estimated that the recurrence of VTE is 2.5 times superior to general population risk and of 33% at 5 years,[7] having active disease, male gender and age at the first VTE as risk factors. Unlike this data, we only reported 1 case of recurrent VTE, in a patient without active disease. It can be considered an iatrogenic complication of IVC filter. Complications of IVC filters are relatively common. One of the possible delayed complications is IVC thrombosis that can occur up to 22% of patients after 5 years and 33% after 9 years, independently of anticoagulation's use and duration.[37]

We didn't report any death. IBD has been associated with elevated standardized mortality ratios, with VTE being one of the top 4 death causes.[38] Cardiovascular events haven't been associated to higher mortality in IBD.[27]

To the best of the authors' knowledge, this study represents one of the largest case series of vascular complications in IBD inpatients, including venous and arterial events.

The retrospective design of the study, implying the lack of some records and shortage of data uniformisation, can be considered to be limitations of this study, as they didn't allow us to create a control group (for example: TE in inpatients without IBD and with general population) and explore risk factors for TE in IBD. Hospitalization is also a risk factor to TE itself,[39] and its role in TE etiology should be address independently. Other endpoints, as morbidity parameters, weren't included in this study due to the same reason mentioned before. Nonetheless, it may be interesting to analyze it in future studies. Additionally, the duration of illness was considered since de diagnosis and not since the onset of symptoms, as recommended, due to unavailable information the onset of symptoms.

CONCLUSION

This study reinforces that TE events are not uncommon in IBD inpatients and there are several factors that may predispose to their development.

IBD activity seems to have a close relationship with VTE, in contrast to ATE, and other IBD characteristics (as disease type, location/extension/behavior and therapeutics) may also influence that risk.

The concomitant presence of other risk factors demands (1) a better control of them in order to reduce the thromboembolic risk and (2) a development of other studies to determine the real role of IBD in TE's etiology.

Additionally, a higher effort should be evoked to increase the rate of venous thromboembolic prophylaxis in hospitalized patients with IBD, as recommended by international guidelines. ■

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