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Review Article

Inflammatory Bowel Diseases and Thrombosis. An Update

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Abstract

Introduction: Inflammatory bowel diseases (IBD) are a group of affections characterized by a chronic inflammation of the mucosae of the digestive tract and primarily include Crohn's Disease (CD) and Ulcerative Colitis (UC). Although much has already been studied, aetiology and pathomechanisms are still unclear. IBD patients are at risk of many complications including the risk of thromboembolic events. Thrombotic complications in this kind of patients have already been recognised and demonstrated although further considerations have to be made regarding the incidence of such kind of events.

Aim and Methods: This article is intended to resume the state of the art on venous thromboembolic complications (VTE) which can affect these patients by heavily increasing morbidity and mortality rates. A literature search was conducted using Medline, Embase, Ovid Journals, and Science Direct. The keywords were "Inflammatory Bowell Disease", "Crohn's Disease", "Ulcerative Colitis", "Thrombosis" and "Inflammatory Bowel Diseases and Thrombosis".

Results: Very little is known in this respect and as extended RCTs (randomised controlled studies) have not yet been conducted it is not possible to clearly define what the clinical approach to prevention towards this complication must be. Recent studies evidence a strong correlation between IBD and VTE complications such as deep venous thrombosis (DVT) and pulmonary embolism (PE). Available prophylaxis and treatment options include pharmacological anticoagulant therapy (LMWH-Low Molecular Weight Heparin, Fondaparinux and UH-Unfractionated Heparin) and mechanical prophylaxis. Treatment options in case of acute VTE include anticoagulant therapy, fibrinolytic agents and in selected non-responsive cases vascular surgery.

Conclusions: As IBD patients have an increased risk of VTE complications, prophylaxis for VTE should be recommended in all patients who do not show contraindications to treatment.

Keywords: *Inflammatory Bowell Disease; Crohn's Disease; Ulcerative Colitis; Thrombosis; Venous Thromboembolic Complications; Deep Venous Thrombosis; Pulmonary Embolism; Prophylaxis*

Introduction

The increased risk of thromboembolic events in patients affected by inflammatory bowel diseases has already been recognised and demonstrated more than 80 years ago by Bargen and Barker at the Mayo Clinic in 1936 [1,2]. Since then, scientific literature has continued confirming such data, although further considerations have to be made regarding the incidence of such kind of events.

Aim and Methods

This article is an update on venous thromboembolic complications (VTE) which can affect the patients with Crohn's Disease and Ulcerative Colitis. A literature search was conducted using MedLine, PubMed and Science Direct. All published studies on "Inflammatory bowel disease and thrombosis" were identified using the following key words: "Inflammatory Bowell Disease", "Crohn's Disease and Thrombosis", "Ulcerative Colitis and Thrombosis", "Thrombosis and "Inflammatory Bowel Diseases and Thrombosis". Full articles and abstracts were included. Studies such as case reports, letters and commentaries were excluded from the analysis if appropriate data could not be extracted.

Discussion

Epidemiology: Thromboembolic complications such as Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) represent amongst IBD complications an important and underestimated factor to be borne in mind which can significantly influence patient's morbidity and mortality [3-5]. In fact, according to latest population-cohort studies, a 2 to 3 time fold increased risk of developing thromboembolic complications was reported for IBD patients compared to general population [5-15]. In particular as Grainge., et al. and Papa., et al. both demonstrate in their studies, the incidence of thromboembolic events varies depending on the activity phase of the disease, suggesting that there is a higher risk of thromboembolic complications especially during IBD flares, with similar relative risk values for both Crohn's Disease and Ulcerative Colitis [7,9,12-16]. Furthermore the highest risk of such complications is seen among patients younger than 40 years of age [6-8,14,17,18] and are more common in those patients who show increased inflammatory markers and where other complications such as strictures, abscesses or fistulising disease are present [6,19]. The incidence of these events also seems to be correlated to the extent of the disease itself as it is shown to be higher in patients with pancolitis in UC [18,20] and with colonic involvement in CD [19]. Even though, proctocolectomy is not proved to be protective in order to prevent recurrent thromboembolic events [20].

Risk factors: In accordance to the studies presented above, Miehsler., *et al*. have contributed to show why IBD has been established as a specific risk factor for thromboembolism itself [21]. Nonetheless pathomechanisms underlying this higher susceptibility of IBD patients to face thromboembolic complications are not yet clear [22]. Be it in general population, be it in IBD patients, it must not be forgotten that thromboembolism is a multifactorial event which can involve both hereditary and acquired factors which can combine and reasonably increase the prothrombotic risk for the patient [14,23,24]. The main risk factors for thromboembolism in IBD patients are reported in table 1 [4,9,10,13-15,18,22,25-32]. As previously mentioned there are some IBD-related risk factors which must be considered in addition to non-IBD-related risk factors.

IBD-related risk factors	Non-IBD-related risk factors	
	Genetic	**Acquired**
Active disease Fistulising disease Extent of the disease Localization of the disease Strictures Abscesses	Protein C deficiency Protein S deficiency Antithrombin deficiency Factor V Leiden gene mutation MTHFR mutation Plasminogen activator inhibitor type 1 gene mutation	Infections Inflammation Smoking Oral contraceptive use Pregnancy Fluid depletion Obesity Cancer Hyperhomocysteinemia Prolonged immobilization Previous thromboembolism Central venous catheters

Table 1: *Risk factors for thromboembolism in IBD patients.*

Physiopathological process underlying thrombosis: The physiopathology which underlies the tendency of IBD patients to be more prone to thrombosis has not yet been clarified [26]. The mainstay theory that explains the mechanisms of thrombosis is described by Virchow's triad [28,33,34]. As shown in figure 1, according to Virchow three are the key points that sustain any thrombotic process: hypercoagulability, stasis and endothelial dysfunction. Also thrombotic processes in course of IBD should therefore attain to a dysregulation of this balance. Two are the main pathomechanisms which have been identified to possibly trigger thrombosis in IBD. These are the alterations in the coagulation and fibrinolytic systems and platelet dysfunction [9,10,22,23,26,28,35].

Diagnosis: As outlined by the NICE guidelines for diagnosis of venous thromboembolism, if a patient shows signs or symptoms of VTE, taking the patients' medical history and performing a physical examination should be the first things to be done in order to exclude other possible causes [36]. If DVT is suspected with a likely DVT Wells Score of 2 (Criteria reported in Table 2) it should be considered to perform either a proximal leg venous ultrasound within 4 hours and if this is negative a D-dimer test, or directly a D-dimer test in addition to a 24 h dosage of a parenteral anticoagulant and a proximal leg venous ultrasound within 24 hours. Whenever D-dimer results positive but the proximal leg venous ultrasound results negative the US should be repeated 6 to 8 days later [36,37]. If PE is suspected with a likely PE Wells Score of 2 (Criteria reported in Table 3) an immediate computer tomography pulmonary angiogram (CTPA) must be performed. If this is not immediately possible, parenteral anticoagulant therapy should be started promptly and it should be followed by a CTPA as soon as possible [36,37].

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2
Clinical probability simplified score	**Points**
DVT likely	2 points or more
DVT unlikely	1 point or less

Table 2: *DVT Wells Score.*

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate >100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified score	**Points**
PE likely	More than 4 points
PE unlikely	4 points or less

Table 3: *PE Wells Score.*

The impact of prophylaxis on outcome: As seen above, thromboembolism is a multifactorial process which represents an important feature to be considered in IBD patients [3]. Even though up to today no randomised controlled studies (RCTs) were set up to evaluate and assess the efficacy of thromboprophylaxis specifically in IBD patients [8,21]; seen the incidence of VTE and PE characterizing such disease and the recommendations by several guidelines for conditions associated with a higher risk of VTE and PE, adoption of thromboprophylactic measures is highly recommended in IBD patients. It has to be said that due to the lack of consciousness of the importance of thrombotic risk in these kind of patients and to the lack of clear data on the use of oral anticoagulants in course of IBD, these measures are often not complied [4,9,28,38,39].

Two are the main kind of prophylactic measures that should be considered: pharmacological prophylaxis and non-pharmacological prophylaxis. Both these measures act on at least one of the key points of Virchow's Triad [28,33,34].

Non-pharmacological prophylaxis: Non-pharmacological prophylaxis consists of hydration, vitamin supplementation to correct deficiencies that can determine hyperhomocysteinemia (typically B6, B12 and Folates), early mobilization after surgery and mechanical prophylaxis. This can consist of either intermittent pneumatic compression devices (IPC) [15] or graduated compression stockings (GCS). While intermittent pneumatic compression devices reduce stasis by augmenting the pulsatile venous flow and determine secretion of tissue plasminogen activator (tPA) from the endothelial cells increasing fibrinolytic activity, graduated compression stockings (GCS) act by reducing venous stasis and inhibiting Xa coagulation pathway. GCS's drawbacks are represented by the possible onset of skin ulcers. In addition to this GCS's preventive role against post-thrombotic syndrome following DVT is yet uncertain [36]. Mechanical prophylaxis represents also an important measure that can be adopted in those patients who cannot receive pharmacological prophylaxis because of an active bleeding or of a high bleeding risk [15]. Such patients should be switched to pharmacological prophylaxis once the risk is eliminated [8,23,39]. In addition, according to the pathomechanisms underlying IBD, it can be supposed that a control of the disease activity should determine benefits in terms of reduction of the thromboembolic risk [8,40].

Pharmacological prophylaxis: As also recommended by the latest American College of Chest Physicians Evidence-Based Clinical Practice, the British Society of Gastroenterology and the European Crohn's and Colitis Organisation guidelines, Low Molecular Weight Heparin (LMWH) and Unfractionated Heparin (UH) represent the standard of care treatment for thromboprophylaxis in patients affected by IBD [5,8,13,15,23,25,41-45]. Thromboprophylaxis in IBD patients is recommended for hospitalized patients with active flares of disease in the absence of active bleeding and is suggested for those patients who do not show signs of severe bleeding [15]. In addition evidence confirms that presence of bleeding at the admission of hospitalization is not to be considered as a reason to avoid administration of thromboprophylaxis [8,15,38]. Thromboprophylaxis is also suggested in IBD outpatients with moderate to severe flares of disease who have VTE background history [15,38]. According to Kohoutova., *et al*. studies, thromboprophylaxis should be also suggested for all patients with active CD and for UC patients with endoscopically confirmed findings of extensive disease [38]. Said this, the latest Consensus Statements of the Canadian Association of Gastroenterology, being based on a cost-effect for every quality-adjusted life year (QUALY) analysis, strongly discourages anticoagulant thromboprophylaxis in outpatients with active disease if there is not a history of previous VTE [15]. Unfractionated Heparin (UH) and Low Molecular Weight Heparin (LWMH) can be administered both intravenously and subcutaneously but unfortunately oral administration is not possible because of poor absorption. 5000 units of UH are usually administered subcutaneously 2 hours to then be repeated every 8 to 12 hours [39,46]. In both kinds of treatments monitoring is not needed at prophylactic doses but if necessary measurements of activated partial thromboplastin time can be made in order to prevent overdosing UH and a dosage of anti-FXa levels can be performed in order to adjust dosage of LWMH [39]. The use of oral prophylaxis with vitamin K antagonists (VKA) for VTE has not gained much success because contrarily to UH and LWMH which are easy to use and do not need monitoring, oral anticoagulants such as Warfarin are easier to administer but need monitoring and to balance a correct dosing of the drug [47]. Nevertheless, although not practical, it might be used in this indication as it is an effective drug in the prophylaxis of VTE [28,36,39,47]. As regards Aspirin (ASA) prophylaxis, the ASPIRE trial shows no significant decrease in events of VTE compared to placebo, thus not recommending ASA as a prophylactic treatment to prevent VTE [39,46,48,49].

Treatment

Anticoagulant therapy: Therapeutic gearing for the treatment of venous thromboembolism in IBD patients is the same as patients without IBD and it consists of different kinds of possible treatments [23,39]. Above all stands pharmacological treatment. In a first instance it is recommended to administer the same drugs used in thromboprophylaxis with a difference in dosages, meaning UH and LWMH. In fact according to latest NICE guidelines for venous thromboembolic diseases, if not otherwise contraindicated either low molecular weight heparin (LMWH) or Fondaparinux should be offered to patients with confirmed venous thromboembolism. UH should be considered in those patients with severe renal impairment (eGFR < 30 ml/min/1.73m2), with increased risk of bleeding and in patients with PE and haemodynamic instability. In this last case, if thrombotic obstruction is massive and represents a life-threating condition, the use of fibrinolytic agents is also recommended [36]. Treatment should be started as soon as possible and prolonged for at least 5 days or until INR maintains beyond 2 for at least 24 hours.

Fibrinolytic agents: In those cases where anticoagulant therapy alone is not feasible there is the possibility to use fibrinolytic agents. As mentioned before their use is especially recommended in case of massive PE with haemodynamic instability. Even though it is not usually required in ileofemoral DVT, in selected cases which present good functional status, a low bleeding risk and have had symptoms for no longer than 14 days, the use of fibrinolytic agents can be considered as a possible therapeutic option [36,39]. As further treatment options to be considered only for selected patients there is also a more invasive non-pharmacological approach which can consist either of the application of inferior vena cava filters (IVC) or of endarterectomy [39,50].

Inferior Vena Cava Filter: When previous treatments are not attainable because of a high risk of bleeding in patients with PE or DVT burdened by the presence of floating thrombi despite the establishment of an appropriate anticoagulant therapy, the positioning of an inferior vena cava filter should be considered as an option [8,36,39].

Thromboendarterectomy: When treatment with fibrinolytic agents fails or is contraindicated, selected patients can undergo thromboendarterectomy. It is however to be considered as the last therapeutic resource because of its complication rates and because it is an invasive procedure which has to be performed by experienced vascular surgeons [39].

Conclusions

Patients affected by IBD are at risk for VTE as they have a 2 to 3 time fold increased risk of developing thromboembolic complications compared to general population. The highest risk of such complications is seen among younger patients and if other disease-related complications such as strictures, abscesses or fistulising disease are present. Thromboembolism is a multifactorial process which represents an important feature to be considered in IBD patients as it can significantly influence patient's morbidity and mortality [4,28,51-57]. As extended RCTs aimed to study prophylactic regimes for IBD patients have not yet been conducted, it is not possible to clearly define what the clinical approach to prevention towards this complication must be. Nevertheless, as the increased risk of VTE complications has been demonstrated, clinicians should attain to general guidelines for the prevention of VTE. As pharmacological oral prophylaxis with VKA needs monitoring and is therefore unpractical, current prophylactic options focus on anticoagulant therapy with LMWH and UH associated to mechanical prophylaxis. Treatment options in case of acute VTE include anticoagulant therapy, fibrinolytic agents and in selected non-responsive cases vascular surgery. As IBD patients have a demonstrated 2 to 3 fold increased risk of VTE complications, prophylaxis for VTE should be recommended in all patients who do not show contraindications to treatment.

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