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Association of Venous Thromboembolism and Inflammatory Bowel Disease

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ABSTRACT

Introduction: Studies have shown that patients with inflammatory bowel disease (IBD) have an increased risk for venous thromboembolism (VTE). VTEs causes significant morbidity and mortality.

Methods: We carried out a comprehensive search through different online databases including PubMed, Google Scholar, Scopus, and Medline. We focused on some of patients-related factors that may affect the risk of VTE incidence among IBD patients and also reviewed current guidelines on the prophylactic regimen of the IBD patients.

Results: Based on the previous studies, the hypercoagulable nature of the disease results from a complex interaction between the systems participating in the coagulation cascade, including endothelial cells, platelets, and coagulation factors. There are a number of clinical factors that increase the probability of VTE development which include disease activity, age, pregnancy, surgery, and medical treatment.

Conclusion: Taken together, these data suggest to initiate prophylactic regimen in IBD patients and to adjust it regarding to the patient's condition and the presence of other predisposing factors.

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Introduction

Inflammatory bowel diseases (IBDs) include two main diseases: 1) Crohn's disease and 2) Ulcerative colitis which cause inflammation in the gastrointestinal tract (1). The prevalence of IBDs has increased dramatically over the past decade, and it has been one of the major concerns of the world (2). The number of IBD patients exceeds 13 million in the Europe while this number ranges from 2 to 4 million in the North America (3).

There are several studies demonstrating that IBD patients have 2 to 3 times greater

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risk for venous thromboembolism (VTE) development. Interestingly, the higher risk specifically occurs in IBD patients, however patients with other chronic inflammatory diseases such as rheumatoid arthritis or celiac disease did not experienced the increased risk (4). Although the higher risk for VTE development in IBD patients is obvious, the underlying mechanism is still unclear.

In the present review, we focused on the VTE epidemiology among IBD patients and the patient-related factors that may affect VTE risk. We also, provided an overview of the mechanism which leads to hypercoagulation in these patients. According to the burden of VTE in patients with IBD, we reviewed the latest guideline recommendations on VTE prevention.

Material and Methods

In order to perform this study, we carried out a comprehensive search through different online databases including PubMed, Google Scholar, Scopus, and Medline between the years 2000 to 2022. We utilized the following keywords: “Inflammatory bowel disease”, “Venous Thromboembolism”, “Inflammation”, and “Prevention”. The inclusion criteria were that the abstract of the article be related to the main research topic with the focus on the prevalence, pathophysiology, treatment and prevention of VTEs among IBDs patients. The exclusion criteria were studies focusing on the VTE incidence in non-IBD patients. We reviewed the higher incidence of VTEs and examined the possible pathophysiologic pathways involved in its development. We also categorized the final results to make them further easier to access.

Results

1. Epidemiology of VTEs in IBD patients

Deep vein thrombosis (DVT) and pulmonary embolism (PE) occur with a higher incidence in patients with IBD (5-8). The frequency of DVT was found to be 30.7% per 10,000 persons in a cohort study on IBD patients. Moreover, overall relative risk of VTE was 3.47 (7). The findings of this study aligned with a recent Denmark'Suge study which showed that in patients with UC and CD, 24.4% and 23.3 % of cases of VTE are caused by IBD, respectively. The epidemiology of VTE in IBD patients was 32.1 per 10000 person-year while the rate of IBD among normal persons with similar age and gender was 13.4 cases per 10000 person-years (9). Despite a rise in VTE incidence with advancing age, most studies found that patients aged between 35 to 50, were at the greatest risk for VTE than patients with 40 years or younger. However, no significant differences between the gender or UC and CD were found (6, 7, 10, 11). VTE occurs more frequently in IBD patients with pancolitis, as it was reported that the rate of VTE increases while the disease is flared (5, 9). An epidemiological study conducted by Grainge and collegues (12) evaluated the VTE risk during multiple phases of IBD activity. They reported that during the flare phase of IBD, VTE events are more likely to occur. Furthermore, patients during their remission period had 2.1 higher risk for development of VTE. According to these results, IBD patients have a procoagulant tendency (13). Researchers found that neither rheumatoid arthritis nor celiac disease led to a greater risk of VTE than controls (4). In line with this, it is shown that pregnant women affected by UC and CD were 8.44 and 6.12 times more prone to experience VTE, respectively, compared to the pregnant women without IBD (14). Data show that VTE- related hospitalizations result in a 2.5-fold increased mortality rate in IBD patients with VTE (8). The Mayo Clinic reviewed 98 IBD patients with VTE over a decade and reported that the rate of mortality was 22% (6), as similar as the 18% mortality rate, previously reported by a cohort study on IBD patients with VTE (15). DVT most commonly occurs in the veins of lower extremities and lungs, and with less frequency in the brain, retina, and mesenteric veins (16-19). A study was recently carried out to find out where and what characteristics of VTEs occur among patients with IBD (20). From 157 IBD patients with at least one VTE, 142 (90.4%) experienced DVT and/or PE, and 15 (9.6%) had cerebral, portal, mesenteric, splenic, or internal jugular vein thrombosis. Table 1 shows a summary of studies that investigated differences between VTE among IBD and non-IBD patients.

Table 1. A summary of studies investigated differences between VTE among IBD and non-IBD patients

Study	Number of patients IBD	Non-IBD	Patients and Setting	Outcome	Risk measure
Bernstein et al. (7)	5529	55000	Hospitalized patients	Hospitalization for VTE	IRR 3.47 (2.94, 4.09)
Grainge et al. (12)	13756	71672	Ambulatory and hospitalized patients	All VTEs	HR 3.4 (2.7, 4.3)
Huerta et al. (65)	-	-	Ambulatory and hospitalized patients	All VTEs	OR 1.84 (1.29, 2.63)
Nguyen et al. (8)	116842	522703	Hospitalized patients	All VTEs	OR 1.85 (UC) (1.70, 2.01) OR 1.48 (CD) (1.35, 1.62)
Miehsler et al. (4)	618	618	Ambulatory and hospitalized patients	All VTEs	OR 3.6 (1.7, 7.8)
Novacek et al. (61)	86	1255	Ambulatory and hospitalized patients	Recurrent VTEs	HR 2.5 (1.4, 4.2)
Kappelman et al. (9)	49799	477504	Ambulatory patients	All VTEs	HR 2 (1.8, 2.1)
Nguyen et al. (14)	-	-	Pregnant women	All VTEs	OR 6.12 (2.91, 12.9)

2. Factors related to VTE risk

Age

It is shown that VTE occurs in IBD patients since their childhood. In comparison to non-IBD patients, VTE risk was six times more probable. Besides, they realized that younger IBD patients had more risk to suffer from VTE events than those over 60 years old (9). In consistent with this, in a research in the USA, similar findings was reported in a retrospective cohort study on children and adolescents with IBD (21).

According to such studies, despite the higher probability of VTE incidence among younger IBD patients, such events occur infrequently. Therefore, the guidelines from Canadian Association of Gastroenterology do not suggest prophylactic regimen for IBD patients under the age 18 who have never had a VTE (22). In a retrospective study in Japan, it was found that older age is a risk factor for developing VTEs (23). In addition, it is shown that older age is correlated with higher risk of VTE development after hospital discharge (24, 25). As the prevalence of IBD increases and patients over 60 constitute a higher proportion of the population, the role of age in VTE may become of greater importance (26).

IBD activity

The literature has shown that VTE has a strong association with the active phase of IBD. Researchers found that IBD flares are associated with higher VTE risks than patients in remission. An analogous result was seen among pregnant IBD patients who were experiencing flare-ups and were more prone to develop VTEs (27). In addition, a retrospective study of IBD patients who suffered a VTE event, found 71% to have had active disease when the incident happened (28). The extensity of IBD is also associated with VTE risk. Som et al. found 76% of UC patients with VTE had pan-colonic involvement. A comprehensive study in east Asia also found 71% of UC patients with a history of VTE had pancolitis. They also found that 79% of patients with CD had extensive surfaces involved (56% with ileocolitis, 23% with colonic, and 21% with ileitis). A VTE affected every CD patient with ileocolonic involvement (29). Moreover, hospitalization is correlated with a higher rate of VTE in IBD patients, based on disease activity and location. According to Grainge et al. (12), IBD patients were hospitalized due to IBD, regardless of whether they were actively ill, or had a higher chance for VTE. In a study by Nguyen et al., VTE occurrence was compared between hospitalized IBD and non-IBD patients. They reported higher numbers of

VTE and VTE-related mortality among IBD patients (8). Furthermore, a Korean study found that in patients admitted for a non-disease flare of IBD, VTE incidence was 2 times higher than in controls (30). Considering the higher incidence of VTE among IBD patients, Canadian Association of Gastroenterology recommend initiating thrombo-prophylactic regimen for IBD patients hospitalized for non-IBD-related indications and those patients experiencing flares (22).

Pregnancy

Different hemodynamic changes during pregnancy contribute to increasing the chance of venous thromboembolism, including changes in blood flow, particularly in veins, mechanical obstructions caused by the uterus, and endothelial injury (31). Women with IBD have higher risk of VTE development through their pregnancy and postpartum period. An extensive Danish cohort study involving almost 2 million delivered pregnancies in 33 years since 1980, indicates that women with IBD have two times greater risk to experience VTE during the pregnancy period. The relative risk of VTE development for IBD patients and those without IBD was 2.1 (27). Recent national meta-analyses, similarly, found a greater two-fold risk of VTE during pregnancy in women with IBD, which persisted during pregnancy (32). In line with this, a recent meta-analysis on cohort studies from different countries presented similar results. The authors demonstrated that IBD women had almost 2-fold higher for VTE development during their pregnancy and post-partum period. Further analysis revealed that VTE risk was greater in UC patients. Accordingly, future studies should be focused on identification of pregnant and postpartum IBD women who have the most probability for VTE. Furthermore, the cost-efficiency of VTE prevention in this group of patients should be assessed. It is worth mentioning that despite of well-established role of pregnancy in VTE development in IBD patients, it is still unclear if there is a synergistic relationship with IBD that result in a dramatic increase in VTE risk.

Medical treatment

A limited amount of data is available regarding the risk of VTE when amino-salicylates are used concomitantly (33). There has also been a link between immune modulators such as azathioprine and 6-mercaptopurine reducing platelet aggregation in mild UC cases (34). VTE tends to be decreased by these medications. IBD patients, however, need more detailed studies regarding the association.

Although corticosteroids are beneficial in acute phase of IBD, they are linked with higher risk of VTE. Sarlos et al. (35), found that taking corticosteroid increases VTE incidence 2.2 times in IBD patients. The enhanced VTE risk may result from disease activity rather than corticosteroid usage (36), but studies investigating VTE risk among general populations have represented similar risks. Cortisol excess is speculated to be the mechanism. Cushing's syndrome patients are more probable to develop VTE because they produce excessive pro-coagulation factors and have impaired fibrinolytic capacity (37, 38). Immunomodulator medications, such as anti-TNF drugs, may reduce the risk of VTEs. According to Yoshida et al. (39) hypercoagulability was directly related to TNF in colitis-induced-mouse models. Therefore, TNF suppression may have a protective effect on VTEs in IBD patients. A review study showed that using TNF medications led to lower risk of VTE development. On the other hand, using corticosteroid resulted in a four-fold increase in VTE risk (40). Higgins et al. (41) used a nationwide United States insurance database to determine that biologics recipients were five times less probable to have VTE events than those who received corticosteroids. Ananthakrishnan et al. found similar results while evaluating the rate of VTE events following discharge. They reported that anti-TNF therapy decreases the risk of VTE (38). The armamentarium of IBD therapies has recently ended to include new medications called small molecule inhibitors. Recently, Tofacitinib, a JAK inhibitor, has been approved to treat moderate to severe UC cases. The FDA has recently published safety data suggesting that its daily usage with the total dose of 20 mg could elevate the risk of

VTE. A study in 2019 revealed that out of 1157 UC patients treated with tofacitinib and placebo 5 and 2 patients developed a VTE, respectively (42). According to incidence rates, a DVT occurs as frequent as 0.04 patients-per-100- patients-years, while a PE occurs in 0.16 patients-per-100-patient-years. The safety data on tofacitinib is limited at present and further investigations and large scale clinical trials are needed.

Surgery

VTE is also a well-known complication occurring with a high frequency following surgeries (43), particularly those undergoing colorectal surgeries (44). Based on a trial in Canada, over 9% of patients who underwent colorectal surgeries experienced VTE while they were receiving adequate anti-coagulant therapy (45). IBD patients enduring colorectal operations have a higher risk for VTE development. In a national cohort study, IBD patients who underwent any type of surgery had an increased VTE risk. Interestingly, patients required IBD-related surgery were at the highest VTE risk. Alhassan et al. studied surgical admissions in the United States within 2012 and 2106. They confirmed that IBD patients undergoing a surgery related to their disease had higher risk for VTEs during their hospitalization and after their discharge (46). These findings were confirmed in a meta- analysis, which revealed that IBD patients with a history of colorectal surgery have a greater risk for postoperative VTE compared with non-IBD patients (54). UC patients may have greater risk for VTE occurrence than CD patients. Through investigating the Swiss IBD patient population, Alatri and colleagues (47) found that IBD-related surgery was an independent predictor factor for VTE in the UC patient population but not in CD patients. Several other studies represented the similar results. In consistence with this, a recent meta-analysis concluded that UC patients are at higher postoperative VTE risk than CD patients (48). Even though RCTs have proved the advantages of long term chemoprophylaxis in high-risk patients, there is not enough research regarding IBD surgery (49, 50). Different guidelines recommend extended prophylactic anti-coagulant duration in high-risk patients, defined as a 6% risk of overall VTE (44, 51). Decision making regarding post-discharge prophylaxis should be performed based on the patient's risk stratification.

3. Prophylactic and therapeutic approaches for VTE in IBD

Although, in IBD, VTE seems to depend on a several factors, the acquired risk factors may have more important roles. In hospitalized IBD patients, hydration, vitamin correction (especially B6 and B12) and early mobilization following surgery should all be considered to downregulate homocysteine levels (52). Using compression stockings, pneumatic devices, as well as early mobilization following surgery are the routine strategies for VTE prevention which should be considered in IBD patients too. Moreover, we are inclined to assume that disease activity control could lead to a decrease in VTE, as it reduces coagulation promoting factors which are strongly correlated with active inflammation. Several number of IBD medications have demonstrated anti-inflammatory and anticoagulant properties. For instance, Mesalamine reduces platelet activation (40). Beside this, in vitro studies have shown that azathioprine and 6-mercaptopurine suppress platelet aggregation (41). Furthermore, Infliximab stabilizes haemostatic factors and downregulates circulating microparticles in CD patients. Several clinical guidelines have suggested utilizing prophylactic anticoagulation in IBD patients during conditions with greater risk of VTE development, especially hospitalized patients with active inflammation (53-56). Low-molecular-weight heparin (LMWH) and unfractionated heparin (UH) are used for VTE prevention in IBD patients. Several RCTs presented that using pharmacological prophylaxis has an association with the incidence of VTE in severely ill patients (57, 58). Scarpa et al. (59) examined 755 colorectal surgeries, 383 of them were related to IBD. Each patient received 4000 IU/d of LMWH after surgery until they were discharged. A total of six patients suffered thromboembolic events out of 755. All of these patients had IBD. Two of six and four of six CD UC patients, respectively, were diagnosed. Irish researchers observed similar

results in their study of 180 intra-abdominal surgeries performed on 79 patients with UC, which evaluated the rates of postoperative VTE in the 180 cases. Despite receiving the same anti-VTE prophylaxis perioperatively, three out of 83 (17%) UC patients developed VTE after their surgeries (60). Study authors Nguyen et al. Studied 73197 patients who were discharged from CD hospitals, and 43645 patients who were discharged from UC hospitals. In their study, VTE rates for UC patients were 21 cases per 1000 hospitalized patients, and for CD patients, 13.9 ca per 1000 hospitalized patients. The authors of the study pointed out that only 18% of CD and 11% of UC patients underwent IBD-related surgery during their hospitalizations, and bowel surgery is crucial to the development of VTE (60). Nguyen et al. did a retrospective study on 73197 discharged CD patients, and 43645 discharged UC patients. For patients with UC and CD, the VTE rates were 21 and 13.9 per 1000 hospitalized patients, respectively. On the other hand, in another study (8), only 18% of CD patients and 11% of UC patients had a surgery, and bowel surgery plays a crucial role in developing VTE.

Patients with IBD who have VTE are treated similarly to their counterparts without IBD (54). In patients with no evidence of bleeding or any indication for initiating thrombolysis, LMWH is an ideal option, and it will be switched to oral vitamin K antagonists like warfarin. As soon as initiating anticoagulant therapy, the chance of recurrence of VTE and anticoagulant-related bleeding risk should be evaluated and monitored closely. The duration of anticoagulant therapy is not well known. According to some studies, in one-third of IBD patients with an unprovoked episode of VTE for the first time, a second episode occurs within five years. Furthermore, in comparison to normal population with an unprovoked VTE episode, the chance of VTE recurrence is 2.5 times higher in IBD patients (61). Nguyen et al. (62) examined the duration of anticoagulation among IBD patients. Researchers found that long-term anti-coagulation therapy (more than six months) can decreases recurrent VTE in IBD patients who have had unprovoked VTE. Patients with VTE who develop the condition without active disease or any underlying risk factors (62), may be more appropriate for extended anticoagulation. Massive and life-threatening VTEs in IBD patients have been treated successfully with catheter-directed thrombolysis in severe cases (63). A vena cava filter may also be placed in patients with recurrent PE or DVT and patients with bleeding risk (64).

It is recommended that regarding to the absence of a guideline for the prophylaxis or treatment of VTEs among IBD patients, a reasonable solution is following anticoagulation recommendations for normal population and to adjust duration of therapy for IBD patients regarding to their disease activity and the possible presence of other VTE risk factors. Anti-coagulation therapy period can be extended in IBD patients with unprovoked VTE episodes, because the risk of recurrence may be higher than the normal population.

Discussion and Conclusion

While individuals with inflammatory bowel disease (IBD) do not have a genetic predisposition for developing VTE, this condition remains a significant cause of mortality and morbidity in IBD patients. The persistent inflammation associated with IBD can induce complex changes in the interaction among endothelial cells, platelets, and the coagulation pathways. Several factors have been identified that contribute to an increased likelihood of VTE development in individuals with IBD, including inflammation, advanced age, surgical procedures, certain medications, and pregnancy.

Despite variations in guidelines for non-IBD patients, a consensus guideline recommends VTE prophylaxis for individuals with IBD, particularly those experiencing a disease flare-up. The risk of DVT may differ depending on the location of inflammation within the gastrointestinal tract. For example, individuals with Crohn's disease affecting the colon (known as colonic Crohn's disease) or pancolitis (involving the entire colon) in ulcerative colitis are associated with a higher risk of DVT compared to other disease locations. Moreover, older age is also linked to a higher frequency of VTE among individuals

with IBD.

Certain medications used in IBD treatment, such as corticosteroids and immunomodulators, have been associated with an increased risk of DVT. However, further research is still required to determine the overall contribution of medications to the association between DVT and IBD.

To enhance the identification of prognostic factors in VTE and develop guidelines for prophylaxis and treatment specifically tailored to individuals with IBD, future large-scale prospective studies are recommended.IBD patients.

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