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Venous thromboembolism with inflammatory bowel disease

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Abstract

Venous thrombosis and thromboembolism appear to be increased in patients with inflammatory bowel disease. Although several acquired and genetic risk factors are known, about half that develop a thromboembolic event have no identifiable risk factor. Control of the inflammatory process is thought to be the key factor in risk reduction for thrombotic events. Prophylactic use of anticoagulants is not universally recommended, but possible use should be reviewed in an individual patient after evaluation of the risks, such as hemorrhage, compared to potential benefits. Particular consideration should be given if there has been a prior thrombotic event, if hospitalization will require surgery, or if an underlying coagulation disorder is present.

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INTRODUCTION

Some studies^[1-5], but not all^[6], have suggested that there is a higher incidence of venous thrombosis and thromboembolism in the clinical course of inflammatory bowel disease, especially in hospitalized patients^[5]. In a population-

based study^[3], the risk was estimated to be about three-fold. Moreover, thromboembolism appears to develop with inflammatory bowel disease at a younger age^[7]. Finally, thrombosis has also been reported in children with inflammatory bowel disease^[8].

ACQUIRED RISK FACTORS

Several risk factors have been hypothesized to contribute to development of thrombosis with inflammatory bowel disease. Some include the inflammatory process per se (with associated reactive thrombocytosis)^[9], prolonged immobilization, surgical treatment, fluid depletion, central venous catheters (often for nutritional support), hyperhomocysteinemia, vitamin deficiencies, smoking and use of oral contraceptives^[10]. Although hemostatic changes are frequent in inflammatory bowel disease patients, the precise reasons for thromboembolism during the course of inflammatory bowel disease are not known. Importantly, approximately half of the patients with inflammatory bowel disease that develop a thromboembolic event have no identifiable risk factor^[11].

A number of specific coagulation abnormalities have been recorded in patients with inflammatory bowel disease that may lead to a thromboembolic event. Increased levels of factors V, VII and VIII, lipoprotein(a) and fibrinogen, all risk factors for thrombosis, may occur. In addition, a reduction in natural anticoagulant factors including antithrombin III, protein C and protein S may develop^[10]. Homocysteinemia, another prothrombotic risk factor, may result from reduced folate, vitamin B6 or vitamin B12 levels. All of these vitamins may become deficient in patients with inflammatory bowel disease because of drug interference, impaired intake or malabsorption. To date, however, no consistent relationship with homocysteinemia and development of thromboembolism has been defined in patients with inflammatory bowel disease^[12,13]. Finally, changes associated with subclinical activation of the coagulation cascade^[14-16] along with diminished factor X III have been reported^[16,17].

GENETIC RISK FACTORS

Genetic factors may also play a role in patients with inflammatory bowel disease and have been reviewed elsewhere^[18]. Some may be more significant during remission or less active phases of inflammation^[19]. Factor V Leiden causes the activated form of factor V to be relatively resistant to degradation by activated protein C with

increased generation of thrombin. Factor V Leiden is often detected with venous thrombosis, but, to date, no difference between patients with inflammatory bowel disease and those without inflammatory bowel disease has been defined^[18]. In addition, a genetic variation of the prothrombin gene, *G20210A*, may be associated with deep venous thrombosis, but no definite association between this gene mutation and inflammatory bowel disease has been detected^[18]. Also, a mutation in the methylenetetrahydrofolate reductase gene, *C677T*, may cause hyperhomocysteinemia but no differences have been detected between inflammatory bowel disease patients with thrombosis compared to controls with thrombosis^[18]. Finally, an inherited Val34Leu factor XIII polymorphism has been found to be similar in inflammatory bowel disease compared to the general population^[20,21].

MANAGEMENT OF THROMBOTIC RISK AND THROMBOSIS

The key to reduction of risk for thrombotic events in inflammatory bowel disease patients appears to be the control of the inflammatory process *per se*. Also, some of the medications used to treat ulcerative colitis and Crohn's disease may directly inhibit platelet activation. These include 5-aminosalicylic acid (5-ASA)-containing medications (eg, mesalazine, olsalazine)^[22], azathioprine and its metabolite, 6-mercaptopurine (6MP)^[23] and infliximab^[24]. Correction of altered nutrition and vitamin deficiencies is also important, especially if surgery and prolonged periods of immobilization are expected. Smoking should be discouraged and ongoing use of medications associated with increased thrombosis risk should be reviewed, specifically, oral contraceptives.

Use of prophylactic anticoagulation (eg, subcutaneous heparin) is not universally recommended, but should be considered on an individual patient basis after evaluation of the potential risks compared to the potential benefits of prophylaxis. In a New York series, the risk of death due to pulmonary embolism was recorded in a single patient after surgical treatment from among 1000 patients with Crohn's disease (0.1%)^[25]. Such information must be balanced by the potential risk of heparin treatment in inflammatory bowel disease, including the risk of hemorrhage^[26]. Certainly, a case can be made for prophylaxis if there has been a prior thrombotic or thromboembolic event, if the patient is hospitalized for surgery, or if an underlying inherited coagulation disorder is known to be present.

Heparin and drugs that specifically target platelets may play a role in the treatment of the inflammatory process *per se* owing to their anti-inflammatory properties^[27,28], but their precise role needs further evaluation in clinical trials. If thrombosis does supervene during the course of inflammatory bowel disease, management should not be different from treatment of patients without inflammatory bowel disease. However, acquired risk factors should be minimized and exclusion of genetic defects, if tests are available, should be considered. Clearly, additional fundamental studies are needed to further elucidate the role of this inflammatory process and its mediators in the pathogenesis of thromboembolism followed by large multicenter clinical studies that might define the role of emerging treatments, including newer biologic therapies.

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