

Venous thromboembolism in cirrhosis: A review of the literature

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Although hemorrhage has traditionally been regarded as the most significant hemostatic complication of liver disease, there is increasing recognition that hypercoagulability is a prominent aspect of cirrhosis. Identifying markers of coagulability and monitoring anticoagulation therapy in the setting of cirrhosis is problematic. The bleeding risk of venous thromboembolism (VTE) prophylaxis and treatment in patients with chronic liver disease is unclear and there are currently no recommendations to guide practice in this regard. In the present report, the mechanism of coagulation disturbance in chronic liver disease is reviewed with an examination of the evidence for an increased VTE risk in cirrhosis. Finally, the available evidence is assessed for prophylaxis and therapy of VTE in chronic liver disease, and the role it may play in decreasing clinical decompensation and improving survival.

Key Words: *Cirrhosis; Venous thromboembolism*

Venous thromboembolism (VTE) in patients with cirrhosis is an increasingly recognized clinical problem, and ideal methods of prophylaxis, treatment and monitoring of VTE in this patient population have not yet been determined. Although bleeding has traditionally been regarded as the most frequent and severe hemostatic complication of liver disease, there is increasing awareness that an elevated international normalized ratio (INR) in patients with cirrhosis and 'autoanticoagulation' may not be protective from thrombosis. Indeed, hypercoagulability is now a recognized aspect of liver disease. Furthermore, there is considerable difficulty in identifying markers of coagulability in the setting of cirrhosis, and the bleeding risk of VTE prophylaxis and treatment remains unclear. Monitoring of therapy continues to be problematic, and there are few expert recommendations guiding VTE prophylaxis and treatment in patients with chronic liver disease (CLD) (1,2). In the present article, we review the mechanism of coagulation disturbance in CLD and evaluate the utility of alternative clinical markers of coagulation. We examine the evidence for increased VTE risk in these patients and discuss possible confounding risk factors. Finally, we consider the recently available evidence for prophylaxis and therapy of VTE in chronic liver disease, and their role in preventing progressive liver decompensation and improving survival.

MECHANISM OF COAGULATION DISTURBANCE

Hemostasis is altered in cirrhosis and the global effect is complex, with the possibility of both bleeding and thrombotic complications. For example, a reduction in the synthesis of procoagulant factors, including factors II, V, VII, X, XI, XII and XIII, has been documented in CLD leading to elevations in INR. Fibrinogen synthesis and platelet numbers are also reduced. However, more recent studies indicate that cirrhosis is also associated with a decrease in the production of anticoagulant factors, such as antithrombin (AT) and proteins C and S, of

La thromboembolie veineuse en cas de cirrhose : une analyse bibliographique

Même si l'hémorragie a toujours été considérée comme la pire complication hémostatique de la maladie hépatique, on convient de plus en plus du caractère primordial de l'hypercoagulabilité en présence de cirrhose. Il est difficile d'obtenir des marqueurs d'identification de la coagulabilité et de surveiller l'anticoagulothérapie en cas de cirrhose. On ne connaît pas vraiment le risque de saignement lié à la prophylaxie et au traitement de la thromboembolie veineuse (TEV) chez les patients atteints d'une maladie hépatique chronique, et il n'existe pas de recommandations pour orienter la pratique à cet égard. Dans le présent rapport, les auteurs analysent le mécanisme de perturbation de la coagulation en cas de maladie hépatique chronique et examinent les données probantes d'accroissement du risque de TEV en cas de cirrhose. Enfin, ils examinent les données probantes disponibles sur la prophylaxie et le traitement de la TEV en présence d'une maladie hépatique chronique et le rôle qu'ils peuvent jouer pour réduire la décompensation clinique et améliorer la survie.

potentially equal or greater magnitude (3-6). Other factors that may increase coagulation in cirrhosis include decreased production of fibrinolytics such as plasminogen, increased thrombin generation, increased endothelial derived procoagulant factors, such as factor VIII and von Willebrand factor (7-10), as well as hyperhomocysteinemia secondary to vitamin B and folate deficiencies (11). Elevated levels of antiphospholipid antibodies have been found in some patients with cirrhosis and may be a risk factor for thrombosis (12). In addition, traditional risk factors for VTE are often present in cirrhotic patients, including advanced age, hospitalization, immobility, inflammation, elevated estrogen levels, surgery and cancer.

In cirrhotic patients, biochemical changes that lead to hypercoagulability are not measured by conventional parameters such as INR or partial thromboplastin time. For example, reagents that are used to measure the prothrombin time do not contain thrombomodulin and, thus, do not adequately reflect reduced levels of anticoagulant factors such as protein C, which relies on thrombomodulin for activation (13,14). Furthermore, the INR may not be an accurate measure of bleeding tendency in cirrhosis because calibration of the thromboplastin test reagent uses plasma obtained from patients taking vitamin K antagonists, and this method has not been validated in liver disease. Indeed, variation in laboratory methodologies for determining prothrombin time in patients with cirrhosis leads to significant differences in INR values (15,16).

Traditional anticoagulant therapies for VTE may be poor treatment options for cirrhotic patients. The vitamin K antagonistic effects of warfarin reduce protein C and protein S production, which are already decreased in CLD, leading to increased thrombotic risk. Warfarin-based anticoagulation is also difficult because of the variability in baseline INR in CLD and, thus, unclear targets of therapy. Using low molecular weight heparin (LMWH) is also problematic because there is some suggestion that low AT levels in liver disease may cause

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TABLE 1
Summary of key studies of venous thromboembolism (VTE) risk in cirrhosis

| Author (reference), year | Study design | Patients, n/controls, n | Main results |
|---------------------------|----------------------|-------------------------|--|
| Heit et al (21), 2000 | Case control | 625/625 | Reduced risk of VTE (OR 0.10) in chronic liver disease |
| Ali et al (22), 2011 | Case control | 8248/441,551 | VTE incidence 1.8% in cirrhotic patients compared with 3.7% in overall hospitalized patients |
| Aldawood et al (23), 2011 | Retrospective cohort | 226 | VTE incidence 2.7% in hospitalized cirrhotic patients |
| Huerta et al (24), 2007 | Case control | 6550/10,000 | Increased risk of VTE (OR 1.65) in chronic liver disease |
| Gulley et al (25), 2008 | Case control | 963/12,405 | VTE incidence increased in cirrhosis 1.8% versus 0.9% in controls (P=0.007). Low albumin was predictive of VTE |
| Sogaard et al (26), 2009 | Case control | 67,519/308,614 | Relative risk for VTE is 2.06 for liver cirrhosis and 2.10 for noncirrhotic liver disease |
| Wu and Nguyen (27), 2010 | Case control | 640,000 /575,000 | Increased risk VTE in cirrhosis: OR 1.23 in compensated cirrhotic patients; OR 1.39 in decompensated cirrhotic patients |
| Northup et al (28), 2006 | Case control | 113/113 | 0.5% of hospitalized cirrhotics had first VTE. Low albumin was predictive of VTE |
| Dabbagh et al (30), 2010 | Retrospective cohort | 190 | VTE incidence in hospitalized patients with chronic liver disease was 6.3%. Prolonged international normalized ratio was not protective from hospital-acquired VTE |

CLD Chronic liver disease

resistance to this agent. For instance, in cirrhotic patients being treated with LMWH, AT levels as well as antifactor Xa (anti-Xa) activity, are low. Furthermore, both AT levels and anti-Xa activity are negatively correlated with the severity of liver disease, suggesting that reduced hepatic synthesis of AT may be the cause of this phenomenon. The decreased anti-Xa activity of LMWH in cirrhotic individuals with poor liver function limits the use of anti-Xa assays in monitoring anti-coagulation (3,17). Thrombin generation (TG) is increased in CLD as discussed above, and can be measured using specific assays. Studies have shown a relationship between this parameter and a hypercoagulable profile in cirrhosis. However, TG assays are not widely available and TG needs to be explored further as a clinical marker of coagulation (18). New therapies with direct AT or anti-Xa activity are currently under investigation. These agents may be attractive because they do not reduce protein C levels and their mechanism of action is independent of AT. Furthermore, they are administered orally and do not require regular laboratory monitoring (19,20).

RISK OF VTE IN CIRRHOSIS

Several single-centre and population-based studies have attempted to assess the risk of VTE in patients with cirrhosis but the reported results were often conflicting. Key studies are described below and are summarized in Table 1. The incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE) in hospitalized patients with cirrhosis ranged from 0.5% to 6.3%. Although most studies suggested an increased risk of VTE in cirrhosis, the OR varied among studies and most suggested a nonstatistically significant relationship. The majority of these studies could not control for VTE prophylaxis.

Only two studies showed a reduced risk of VTE in liver disease. One case-control study compared 625 patients with their first VTE to 625 matched patients without VTE, and identified independent risk factors for VTE (21). In the multivariate analysis, the authors determined that in patients with liver disease, the risk of VTE was reduced, with an OR of 0.1 (21). This finding is of unclear clinical relevance because the study was not designed to examine the risk of VTE associated with liver disease, but rather to determine general risk factors for VTE. Indeed, the authors could only identify 11 patients with 'serious' liver disease and could not characterize this condition further. Furthermore, it was not specified whether these patients were hospitalized.

Another retrospective study identified 449,798 cirrhosis-related hospitalizations using hospital administrative data (*International Classification of Diseases, Ninth Revision [ICD-9]*) codes and identified patients with concomitant diagnosis codes for VTE or PE. Patients with cirrhosis but without VTE were used as the control group, and factors independently associated with VTE were identified. The

authors found that VTE was prevalent in cirrhotic patients (1.8%), although the frequency was significantly lower than in noncirrhotic patients with hepatitis C (2.1%) or overall in hospitalized patients (3.7%). Compared with cirrhotic controls, patients with VTE were more likely to be older and had more comorbidities. Malnutrition and black race were also independently associated with VTE (22).

In contrast to these two studies, other studies found that the risk of VTE was not reduced in cirrhotic patients compared with controls and, indeed, was increased in some. One recent retrospective cohort study (23) found a VTE rate of 2.7% in hospitalized cirrhotic patients. Another cohort study found that the OR for VTE in CLD patients was 1.65, although this did not reach statistical significance (95% CI 0.97 to 2.82) (24). In a case-control study, Gulley et al (25) identified 963 hospitalized patients using biopsy, imaging and clinical evidence of cirrhosis, and matched these with 12,405 controls without evidence of cirrhosis. DVT or PE events were identified using ICD-9 codes and confirmed with imaging. The incidence of DVT/PE was significantly higher in cirrhotic patients than in controls (1.8% versus 0.9%) but was lower than that in patients with other medical illnesses (7.1% in chronic kidney disease, 7.8% in congestive heart failure and 6.1% in solid organ cancers). The difference in VTE incidence between cirrhotic patients and controls was lost in the multivariate analysis, leading the authors to conclude that the risk of VTE was not lower than in controls without significant comorbidity.

Two additional studies showed an increased risk of VTE in liver disease. A nationwide Danish case-control study (26) identified 67,519 patients with unprovoked VTE using a national registry, along with 308,614 population controls. Logistic regression was used to compute the RR of VTE in patients with CLD. This study found that the RR of VTE was significantly higher in patients with liver disease, ranging from 2.06 (95% CI 1.79 to 2.38) for liver cirrhosis to 2.10 (95% CI 1.91 to 2.31) for noncirrhotic liver disease. Finally, a retrospective population-based study from the United States (27) investigated the incidence of VTE in 400,000 compensated cirrhotic patients, 240,000 decompensated cirrhotic patients and 575,000 controls who were admitted to hospital for non-VTE-related reasons. They found an increased risk of VTE in the first two groups (ie, patients with cirrhosis) compared with controls (OR 1.23 in compensated and OR 1.39 in decompensated cirrhotic patients). Interestingly, this difference was only apparent in patients <45 years of age, with no difference in VTE incidence after that age. The authors hypothesized that younger patients with cirrhosis may not have received VTE prophylaxis, and proposed that the lack of difference in VTE incidence after 45 years of age was due to a predominance of non-cirrhotic-related risk factors.

Several studies found that cirrhotic patients with conventional markers of bleeding tendency (elevated INR) were not protected from VTE. A retrospective case control study included more than 21,000 patients with cirrhosis admitted to a tertiary-care hospital and found 113 patients with documented new VTE. They compared these data with 113 cirrhotic patients without VTE and determined the risk factors for thrombosis. They found that 0.5% of all hospitalized patients with cirrhosis experienced a VTE despite having an elevated INR. Indeed, INR and platelet count were not found to be predictive of VTE, but a low serum albumin level was an independent predictor. The authors suggested that serum albumin deficiency may mirror low levels of endogenous anticoagulants (28). Serum albumin was also found to be an independent predictor of DVT/PE in cirrhotic patients in the study by Gulley et al (25).

Similarly, a cohort study found that INR prolongation was not protective against VTE. The authors found 190 patients admitted to a tertiary care hospital with a primary diagnosis of CLD and divided these patients into quartiles according to highest admission INR. The overall incidence of VTE was 6.3%, which is a rate similar to other hospital admitted patients (25,29). There was no significant difference in VTE between INR quartiles, and one-half of the VTE cases occurred in patients with an INR >1.6. Indeed, there was a risk of VTE even with an INR >2.2. The majority of patients who developed VTE were classified as Child-Turcotte-Pugh (CTP) class C. The authors concluded that the notion of 'autoanticoagulation' being protective against VTE was unfounded, and that patients with elevated CTP scores were at higher risk (30).

VTE PROPHYLAXIS AND THERAPY

Overall, the use of VTE prophylaxis is not widespread in hospitalized patients with CLD, likely due to concerns of increased bleeding risk in patients with elevated INR. One recent study (23) found that 76% of the cirrhotic patients admitted to hospital received neither pharmacological nor mechanical DVT prophylaxis. This was supported by another study (30) that found pharmacological prophylaxis for VTE was used in only 9% of patients, while mechanical compression devices were used in 16%.

The safety of VTE prophylaxis or treatment in cirrhosis is unclear, and there are no randomized controlled trials to guide practice in this regard. Patients with abnormal coagulation profiles, such as an elevated INR, were excluded in the landmark clinical trials studying VTE, and the utility of lower extremity compression devices has not been studied in patients with cirrhosis. However, one retrospective study evaluated the risk of bleeding or VTE associated with postoperative LMWH prophylaxis in 229 patients with cirrhosis and hepatic resection for hepatocellular carcinoma (31). The study reported that 68.5% of patients received VTE prophylaxis with LMWH while 31.5% did not. Of the group receiving prophylaxis, 0.63% developed VTE postoperatively compared with 1.38% of patients not receiving prophylaxis; this was not a significant difference. The rate of postoperative hemorrhage was also not statistically different between the two groups. The authors noted that only one patient in each group developed VTE but that the patient in the no-prophylaxis group died of hepatic failure secondary to portal venous thrombosis (PVT). Six episodes of bleeding were documented, five of which were in the prophylaxis group. Three consisted of oozing from surgical drains requiring blood transfusion, two patients had intraperitoneal collections and one experienced a gastric bleed. Only one required intervention consisting of percutaneous drainage of an intraperitoneal collection. The authors also examined multiple other risk factors including age, CTP class and Model for End-stage Liver disease scores, platelet count and intraoperative transfusion requirements. None of these affected the risk of VTE or bleed. Only the presence of varices was associated with increased risk of bleeding ($P=0.05$) (31).

One study examined 84 patients with cirrhosis who were treated with LMWH for either prophylactic or therapeutic indications (17).

The authors noted that seven patients experienced an episode of variceal bleeding (8.3%), a rate comparable with the baseline rate in patients with advanced cirrhosis. There were no deaths or thromboembolic events during the observation interval. The authors concluded that the use of LMWH in patients with cirrhosis appeared to be safe, but acknowledged that their study was underpowered to definitely establish the safety of LMWH treatment in these patients.

The literature related to anticoagulation in patients with acute and chronic PVT may provide insight into the safety of therapeutic anticoagulation in cirrhosis. PVT is encountered in 10% to 25% of cirrhotic patients, but optimal management in cirrhosis was only recently addressed in expert consensus guidelines. The American College of Chest Physicians 2012 guidelines on antithrombotic therapy and prevention of thrombosis (2) recommend that patients with symptomatic splanchnic or hepatic vein thrombosis undergo anticoagulation therapy. They also recommend no anticoagulation if these conditions are incidentally found. Retrospective studies have shown that anticoagulation therapy is associated with improved rates of recanalization in acute PVT (32). One study investigating cirrhotic patients with chronic PVT treated with therapeutic enoxaparin found no significant bleeding complications after complete eradication of varices using band ligation despite 50% of patients having presented with variceal bleeding (33). Furthermore, therapeutic anticoagulation in patients with splanchnic venous thrombosis awaiting liver transplantation were not found to experience excess bleeding complications and, in fact, anticoagulation was associated with an overall survival benefit (34). Another study also did not detect excess bleeding events attributable to anticoagulation therapy in patients with PVT (35). This was true even in the presence of esophageal varices, as long as patients received appropriate prophylactic measures (ie, beta blocker or endoscopic therapy).

Finally, a recent abstract presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases, held in San Francisco, California (USA), examined the use of enoxaparin in preventing PVT in patients with advanced stages of cirrhosis (36). Villa et al (36) performed a prospective, randomized controlled study among 70 patients with CTP class B-C cirrhosis. The primary end point was portal vein or mesenteric vein thrombosis, and secondary end points included overall survival and clinical decompensation. The authors also investigated the occurrence of bleeding and thrombocytopenia as safety end points related to anticoagulation. Participants received either enoxaparin 4000 IU daily or placebo for 12 months, followed by a 12-month observation period. No hemorrhagic events attributable to the active drug were evident at 24 months, although one patient developed thrombocytopenia secondary to the enoxaparin. In the first year, a significant reduction in the occurrence of PVT was apparent in the enoxaparin group compared with the placebo group (0% versus 16.7%). During the follow-up year, this effect was lost, with three PVTs occurring in the enoxaparin group (two to six months after discontinuation of the drug) and four in the placebo group. Of note, clinical decompensation was significantly less frequent in the enoxaparin arm and this effect was only partially lost after discontinuation of the active drug. Survival was also significantly increased in the enoxaparin arm. These findings are consistent with human and animal studies that suggest that a procoagulant imbalance in CLD favours progression of liver fibrosis and, conversely, that anticoagulant therapy can slow this process (4).

CONCLUSION

The risk of VTE in cirrhosis is an emerging concern and the notion of 'autoanticoagulation' appears to be unfounded. Currently, no clear evidence-based recommendations can be made with respect to VTE prophylaxis and therapy in patients with end-stage liver disease. Further investigation is needed to determine the utility of novel methods assessing coagulability and monitoring anticoagulation therapy in patients with CLD, as does the possible role for the new antithrombotic drugs with direct action on factor Xa or thrombin.

Overall, the safety of prophylactic or therapeutic anticoagulation in selected patients with cirrhosis, but without the presence of high-risk esophageal varices, appears to be comparable with other general medical patients. The most recent clinical practice guidelines from the American College of Physicians recommend pharmacological VTE prophylaxis with heparin or a related drug for hospitalized medical patients unless the assessed risk for bleeding outweighs the likely benefits. The guidelines also recommend against the use of

mechanical prophylaxis with graduated compression stockings (37). Clinical practice must be individualized in this complex patient population. Based on the available evidence, it can be concluded that VTE prophylaxis is, overall, safe in selected patients. Importantly, all patients with cirrhosis should undergo periodical screening endoscopy to assess varices and the risk of bleeding. VTE treatment should be used in patients with minimal varices, no evidence of clinical bleeding and with an appropriate clinical indication.

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