Editorial

Outcomes in patients with venous thromboembolism: does cirrhosis matter?

Carmen B. Smith, Erin K. Hennessey

Pharmacy Practice, St. Louis College of Pharmacy/Mercy Hospital St. Louis, St. Louis, Missouri, USA

Correspondence to: Carmen B. Smith. Assistant Professor of Pharmacy Practice, St. Louis College of Pharmacy/Mercy Hospital St. Louis, 4588 Parkview Place, St. Louis, Missouri 63110, USA. Email: Carmen.B.Smith@stlcop.edu.

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The total incidence of venous thromboembolism (VTE) in the United States is unknown, but it is thought to affect approximately 300,000–600,000 people each year (1). The incidence of VTE in patients with chronic liver disease (CLD) or cirrhosis has been reported to be anywhere from 0.2% to 6.3% (2-10). The liver plays a key role in the coagulation process by synthesizing both procoagulant and anticoagulant factors. Thus, coagulation abnormalities are to be expected in cirrhosis. Over the last ten years, a shift in the understanding of the hemostatic balance has occurred and it is now well known that patients with cirrhosis are not protected from VTE as once was thought (11,12). Knowing that VTE increases morbidity and mortality, as well as increased cost to the healthcare system (1), the recent study by Zhang *et al.* sought to evaluate how cirrhosis impacts VTE outcomes (13).

Zhang *et al.* matched patients with a diagnosis of VTE, defined as deep vein thrombosis (DVT) or pulmonary embolism (PE), with cirrhosis (case group) and without cirrhosis (control group). Matching was based on age, sex, and Charlson Comorbidity Index score. A total of 16 patients had a VTE with cirrhosis over the course of five years (13). Though the incidence of VTE in the cirrhotic population was not specified in this study, the low number of case patients appears to correlate with a previous study by Zhang *et al.* that took place in the same hospital over a similar time period. In that study, the authors found the incidence of VTE to be 0.2% (7).

Despite the known occurrence of VTE in patients with cirrhosis, we continue to see hesitation in utilization of anticoagulation in this patient population. Multiple studies have documented that only 17–43% of patients with cirrhosis receive pharmacologic prophylactic therapy (9,10,14,15). Information regarding the number of patients who receive treatment doses for VTE in cirrhosis is scarce. Rather, most data available regarding VTE treatment in cirrhosis revolves solely around the safety and efficacy of treatment. Zhang *et al.* found that only 50% of case patients received anticoagulation compared to 90.6% of control patients (P<0.001) (13). This is further data to emphasize that anticoagulation is underutilized in patients with cirrhosis not only for VTE prophylaxis, but also for treatment.

The disparity in treatment with anticoagulation is likely in part due to the challenge of accurate monitoring in these patients. Coagulation studies, such as international normalized ratio (INR), anti-factor Xa (anti-Xa) and activated partial thromboplastin time (aPTT), are all affected by the cirrhotic disease process (16). Another plausible reason is the known increased bleeding risk in patients with cirrhosis (17). Though the decreased production of both anticoagulant and procoagulant factors that occurs in cirrhosis puts patients at risk of thrombosis, it also contributes to an increased bleeding risk. Additionally, patients with cirrhosis may have other risk factors for bleeding such as thrombocytopenia and the presence of varices (16). The balance between thrombus development and bleeding is tenuous and it is difficult to predict which side of the scale patients will fall.

Several studies have indicated that use of pharmacologic prophylactic agents for the prevention of VTE in patients with cirrhosis is safe and results in no more bleeding than is experienced by patients with cirrhosis who receive no

chemoprophylaxis (9,10,18). Therapeutic anticoagulation for portal vein thrombosis (PVT) has been shown to be safe as well (11,19), possibly due to the resolution of thrombosis resulting in a reduction in portal pressures and thus lower incidence of variceal bleeding (11). Less is known regarding treatment of DVT/PE. Fuentes *et al.* looked at patients with cirrhosis being treated with unfractionated heparin (UFH) for VTE, defined as DVT, PE, or PVT. They found that cirrhotic patients treated with UFH required significantly more blood transfusions than those without cirrhosis (33% *vs.* 18%, P=0.002). However, it was noted that UFH use was based on an anti-Xa protocol rather than aPTT. Therapeutic anti-Xa, known to be low at baseline in patients with cirrhosis, resulted in supratherapeutic aPTT values which could account for the increased bleeding events observed (20). Bechmann *et al.* evaluated VTE (undefined) treatment and prophylaxis in the cirrhosis population. In this study, a total of nine patients received treatment doses of low molecular weight heparin (LMWH). Two of the nine experienced a gastrointestinal bleed (GIB); however, both patients were found to have subtherapeutic anti-Xa levels. The authors note that while there was no relation between bleeding and anti-Xa activity, the study was underpowered to determine safety (18).

Zhang *et al.* found a significantly higher incidence of bleeding in the case versus the control group (43.8% *vs.* 13.8%, P=0.006). This result was largely driven by variceal bleeding as evidenced by no difference between groups found when variceal bleeding was excluded (6.2% *vs.* 13.8%, P=0.698). Furthermore, the incidence in major bleeding was not different in the case group among those who received anticoagulation therapy and those who did not (25% *vs.* 62.5%, P=0.315) (13). These results indicate that bleeding outcomes are related to the disease rather than anticoagulation. Zhang *et al.* hypothesized that bleeding risk is mainly due to portal hypertension and not necessarily due to an imbalance in hemostasis (13). Given that variceal bleeding is dependent on variceal size and variceal size is increased with elevated portal pressures (21), this theory is almost certainly true. In fact, the presence of varices alone is known to increase the risk of bleeding (16,22). Cerini *et al.* evaluated patients with cirrhosis on anticoagulation admitted for an upper GIB and found that the etiology of the bleed was portal hypertension in 63% of patients. They also found that anticoagulation did not affect outcomes, further strengthening this theory (23).

In-hospital mortality was another outcome evaluated by Zhang *et al.* (13). Cirrhosis is known to be a disease that is associated with high mortality regardless of development of VTE. Currently, it is the fifth leading cause of death among adults (24). When looking specifically at variceal bleeding, 6-week mortality can be anywhere from 15–25%, with 5-year mortality ranging from 20–80% (21). The rate of variceal bleeding in the study by Zhang *et al.* was 37.5% in the case group, which constituted the majority of major bleeding reported in this cohort (6 of 7 events). Therefore, it is not surprising that the authors found a higher mortality rate in the case group versus the control (37.5% *vs.* 7.5%, P=0.002) (13). This is consistent with a nationwide U.S. study which also found that VTE was associated with increased mortality in both compensated and decompensated cirrhosis (25). But like bleeding rates, this result appears to be largely driven by the disease itself and not a result of VTE or anticoagulant therapies as the mortality rates were not statistically different between case patients who received anticoagulation and those who did not (25% *vs.* 50%, P=0.608). The authors note that the lower in-hospital mortality seen in those who received anticoagulation may reflect the benefit of anticoagulation (13). While this could be true, one must also consider the possibility of selection bias; that patients who were predicted to be at higher risk of mortality did not receive anticoagulation as a result of that risk. Additionally, it should be noted that the number of patients included in this study was small, so non-statistically significant results should be interpreted with caution due to potential lack of power.

In summary, liver cirrhosis increases the incidence of major bleeding and in-hospital mortality; however, the association is likely independent of the presence of VTE or use of anticoagulation, thus making it difficult to truly draw conclusions on the effects cirrhosis has on VTE outcomes. The recent study by Zhang *et al.* provides further insight into the controversy of the safety of anticoagulation in this patient population and provides more evidence that anticoagulation should not be withheld in patients with cirrhosis when the indication for its use is present.

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