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Review Article

Bleeding and thrombosis in cirrhotic patients: What really matters?

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ABSTRACT

Bleeding complications, particularly in the gastro-intestinal tract, may complicate the clinical course of liver cirrhosis. Coexistence of abnormal global tests exploring the platelet and clotting systems generated the hypothesis that cirrhotic patients have "coagulopathy" predisposing to bleeding complications. Using more sophisticated laboratory methods this hypothesis has been partly confuted as cirrhotic patients actually disclose an ongoing prothrombotic state in the portal and systemic circulation that could predispose to thrombosis. Recent data of the literature support this hypothesis as portal vein thrombosis and peripheral thrombosis are frequent features of cirrhosis. We reviewed the literature data to assess the prevalence of bleeding and thrombotic complication in cirrhosis and the role of clotting activation in precipitating them. Whilst it appears scarcely relevant the interplay between the so called "coagulopathy" and bleeding, the interplay between clotting activation and thrombosis seems to be relevant but needs more accurate investigation in larger study populations.

1. Introduction

Bleeding complications, particularly in the gastro-intestinal tract, may complicate the clinical course of liver cirrhosis. The liver synthesizes almost all coagulation factors with the exception of factor VIII, which is synthesized by stellate and endothelial cells [1]. Coagulation factors are usually reduced coincidentally with liver failure with the exception of factor VIII, which is, on the contrary, increased [2]. For many years the reduced synthesis of clotting factors has been thought to be responsible for abnormal laboratory tests exploring global clotting activation, such as prothrombin time (PT) and activated partial thromboplastin (aPTT), and for potentially favouring bleeding precipitation. Recent studies from Tripodi et al. [3] demonstrated that such changes may not reflect clotting activation in vivo as they did not take into account the concomitant reduction of anticoagulant factors such as Protein C and S, which are also synthesized by liver [4]. Therefore, it is becoming evident that in cirrhosis coagulation system activation is haemostatically balanced with a paradoxically trend to hypercoagulation. Thus, we have previously shown that cirrhotic patients have an ongoing prothrombotic state that was documented by an enhanced rate of thrombin generation [5]. Such change of clotting activation typically occurred in peripheral as well as in the portal circulation of patients with severe liver failure [6]. An enhanced ratio factor VIII/natural anticoagulants has been suggested to play a role [7]. However it is still to be clarified if the increase of factor VIII is dependent upon an enhanced synthesis or reflects an impaired clearance secondary to the increase of von Willebrand factor (vWf) [8,9]. Previous studies from our group may help to elucidate some of the above reported changes of clotting system in cirrhosis. Thus, we have previously shown that cirrhosis is associated with enhanced levels of endotoxemia particularly in case of severe liver failure [5]. Endotoxemia may activate clotting system with different mechanisms. Thus it may release vWf from endothelial cells so favouring a reduced clearance of factor VIII [10]. Also, endotoxemia may elicit a procoagulant state with an alternative mechanism as it enhances the expression of tissue factor with ensuing clotting activation in monocytes from cirrhotic patients [11]. Such effect is more pronounced in the portal circulation of cirrhotic patients where endotoxemia could be a trigger for thrombosis [6]. Treatment of cirrhotic patients with non-absorbable antibiotics resulted in simultaneous reduction of endotoxemia, vWf and clotting activation [5,10], suggesting that this treatment may counteract the procoagulant state in cirrhosis.

Even if these data are profoundly attacking the existence of coagulopathy in liver cirrhosis, there is still need of implementing this concept into clinical practice. An important matter of discussion is whether markers of coagulation activation may help identify cirrhotic patients who are prone to spontaneous or procedure-related bleeding. Discrimination between these two types of bleeding is of particular relevance to deeply understand the role, if any, of "coagulopathy" in cirrhosis [2].

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Bleeding, however, is not the only haemostatic disorder occurring in cirrhosis. Likely for the reasons above reported, cirrhotic patients experience thrombosis of the portal vein, which, paradoxically, may precipitate bleeding in the gastrointestinal tract. Identification of risk factors for portal vein thrombosis (PVT) could be useful to reduce the negative impact of this event on gastrointestinal bleeding and on the selection of candidates for liver transplantation [12].

For these reasons cirrhosis is a unique clinical setting where bleeding and thrombosis coexist. In this review we investigated whether data present in the literature may help to identify those patients who are more prone to bleeding (spontaneous or surgical) or to thrombosis.

2. Spontaneous bleeding

2.1. Gastrointestinal bleeding

In patients with advanced liver disease, the most frequent and potentially life-threatening site of bleeding is the gastrointestinal tract. In the majority of cases it originates from specific sites such as oesophageal or gastric varices, peptic ulcer and gastric mucosa. In about two-thirds of patients they form in oesophagus and pose a high risk for rupture [13]. Variceal bleeding occurs in 20–30% of cirrhosis patients and accounts for 80–90% of bleeding episodes in these patients. Up to 30% of initial bleeding episodes are fatal and as many as 70% of survivors have recurrent bleeding after two weeks from the first episode [13]. Gastrointestinal bleeding is mainly haemodynamic in its mechanisms and is related to portal hypertension, which is a major determinant of variceal rupture. Advanced Child-Pugh class of cirrhosis, large varices and the presence of red wale markings correlate highly with the risk of a first episode of bleeding. Constipation, vomiting, severe coughing, and excessive consumption of alcohol may precipitate variceal bleeding [13]. Bacterial infections have also been associated with an increased risk of early recurrent bleeding in many cirrhotic patients. Indeed, antibiotic prophylaxis to prevent bacterial infection in patients presenting with a variceal bleed has been demonstrated to reduce the risk of re-bleeding [14].

Clinical evidence indicates that variceal bleeding is more severe, more difficult to control and more likely to recur in patients with advanced liver failure. However, the role played by the coagulopathy of cirrhosis in gastrointestinal bleeding is still unclear. In fact, more prolonged PT and lower platelet counts have only a limited predictive value for variceal bleeding.

The most widely used indicator of risk for variceal bleeding is the NIEC Index of the North Italian Endoscopic Club for the study and Treatment of Esophageal Varices [15], which results from the combination of size of oesophageal varices, severity of red wale markers and Child-Pugh class. Its prognostic efficiency was further improved by a large multicenter prospective study of first variceal bleeding in cirrhosis. In this study a much larger importance of variceal size was found and the relative weight of more severe liver dysfunction according to Child-Pugh score was rather limited [16].

In a recent study performed in 240 patients with liver cirrhosis and acute variceal bleeding and 240 matched patients without bleeding, Valsalva manoeuvre-related activities such as straining on defecation, vomiting, and severe cough, which all can cause an abrupt increase in intra-abdominal pressure, were independent determinants of first oesophageal bleeding. The number of patients with prolonged prothrombin time was not different between the two groups [17]. However, a prospective cohort study is required to clarify the causal relationship between potential precipitating factors and variceal bleeding.

The role of coagulation status to predict ulcer bleeding after oesophageal variceal band ligation was assessed by a prospective study of 150 patients with cirrhosis. There was no difference in any of the coagulation parameters, including PT, PTT, platelet count and overall thromboelastography, between patients who did or did not bleed [18].

An association between markers of hyperfibrinolysis and risk of variceal bleeding was described in a cohort of 61 patients with cirrhosis. High levels of D-dimer and tissue plasminogen activator (t-PA) were found to be the only significant laboratory marker of risk of variceal bleeding, independent of other laboratory markers and severity of liver disease. Apart from the intrinsic bias related to the small sample size of the study, it should be considered that increased t-PA and D-dimer may also reflect the systemic proteolysis that may occur in cirrhosis [19].

On the basis of these data any conclusion regarding the relationship between “coagulopathy” and gastro-intestinal bleeding cannot be drawn. A major issue regards the methodology of the reports, which are mainly retrospective, included a small sample size and did not distinguish between patients who bled for the first time or re-bled. This last point is of particular relevance taking into account that mechanism of bleeding or re-bleeding may be potentially different.

2.2. Intracerebral haemorrhage

In a series of 4515 hospitalized cirrhotic patients in Taiwan, the occurrence of spontaneous intracerebral haemorrhage was a rare complication (0.8%), and was more strongly related to the aetiology of the disease (0.3% in virus-related cirrhosis and 1.8% in alcohol-related cirrhosis), rather than to the severity of liver disease. Indeed, no statistical differences were observed with respect to Child-Pugh score and prolonged PT. [20]. In addition, in a retrospective review of brain imaging studies and medical records of patients admitted with chronic liver disease and coagulopathy who presented with acute mental status changes, no incidence of spontaneous intracranial haemorrhage was found even in individuals with severe coagulopathies [21].

Conversely, in a Danish population-based case-control study, patients with liver cirrhosis and non-cirrhotic alcoholic liver disease had a substantially increased risk for intracranial haemorrhage [22]. The effects of alcohol were particularly important, with the shortest time interval between the diagnosis of liver disease and hospitalization for brain haemorrhage found amongst patients with alcoholic cirrhosis (2.3 years versus 6.2 years in non-alcoholic cirrhosis). In a further study performed in patients with mild liver disease admitted to a General Hospital in Taiwan, heavy drinkers had a significantly higher risk of haemorrhagic stroke than non-heavy drinkers [23]. In some cases, cerebral metastasis is the initial manifestation of hepatocellular carcinoma (HCC) and cirrhotic patients may develop cerebral haemorrhage and have a stroke-like presentation [24,25].

According to the above conflicting findings, it is unclear whether cirrhotic coagulopathy is associated with an increased risk for spontaneous haemorrhagic stroke. However, an increased risk of intracerebral haemorrhage appears to be present in patients with mild-to-moderate alcoholic liver cirrhosis.

3. Bleeding related to invasive procedures

3.1. Liver biopsy

Percutaneous liver biopsy is associated with a 0.08–0.7% risk of major intraperitoneal bleeding, with an overall mortality rate secondary to haemorrhage of 0.01–0.4% based on different hospital series.

In an extensive study performed in three Medical Centres in California bleeding occurred in 22 out of 3080 patients with suspected