REVIEW ARTICLE

Bleeding Risk and Management in Interventional Procedures in Chronic Liver Disease

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ABSTRACT

The coagulopathy of liver disease is distinctly different from therapeutic anticoagulation in a patient. Despite stable elevated standard clot-based coagulation assays, nearly all patients with stable chronic liver disease (CLD) have normal or increased clotting. Common unfamiliarity with the limitations of these assays in CLD may lead to inappropriate and sometimes harmful interventions, including blood product transfusions before a procedure. Knowledge of the distinct hemostatic alterations in CLD can allow identification of the small subset of patients with clinically significant coagulopathy who can benefit from hematologic optimization before invasive procedures.

ABBREVIATIONS

AASLD = Association for the Study of Liver Disease, ACLF = acute-on-chronic liver failure, AICF = accelerated intravascular coagulation and fibrinolysis, ALF = acute liver failure, aPTT = activated partial thromboplastin time, CLD = chronic liver disease, DDAVP = desmopressin acetate, DIC = disseminated intravascular coagulation, FFP = fresh frozen plasma, HVPG = hepatic venous pressure gradient, INR = international normalized ratio, rFVIIa = recombinant factor VIIa, TF = tissue factor, vWF = von Willebrand factor

MECHANISMS OF HEMOSTASIS AND BALANCED ALTERATIONS IN CHRONIC LIVER DISEASE AND ACUTE LIVER FAILURE

Patients with chronic liver disease (CLD) have compensated and decompensated disease. In decompensated disease, decreased vascular resistance can no longer maintain a normal hepatic venous pressure gradient (HVPG) of < 5 mm Hg, and clinically evident complications of portal hypertension occur. Even with elevated standard coagulation assays, nearly all patients with CLD have adequate hemostasis as a result of proportionately decreased hepatic synthesis of both procoagulants and inhibitors and compensatory antifibrinolytic abnormalities.

Primary Hemostasis

In primary hemostasis, injured endothelium releases von Willebrand factor (vWF), an adhesive protein that preferentially binds and activates platelets traveling in high shear force flow of the microcirculation (Fig 1). Bound platelets deform to maximize surface area and rapidly form a thrombus of aggregated platelets by interlinking adjacent platelets between the long-length serum fibrinogen and vWF strands. The short fibrin degradation products bind the same receptors resulting in poor platelet aggregation and fibrin polymerization (Fig 1).

Primary hemostasis-type bleeding predominantly involves skin and mucosa given their inherent fibrinolytic properties and greater reliance on vWF in binding

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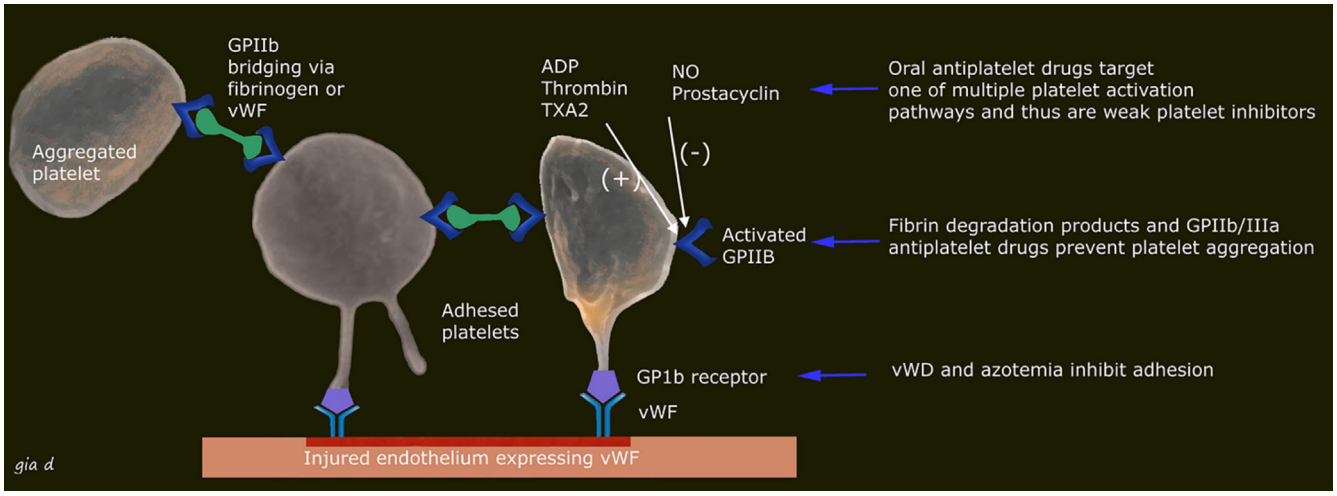

Figure 1. Platelet adhesion and aggregation. Endothelial exposed vWF binds platelets traveling in high sheer force via their GP1b receptors. The bound GP1b receptors cause release of granules containing mediators (ADP, thrombin, TXA2) that activate the GPIIb receptors. The activated GPIIb receptors of adjacent platelets bind the long-length fibrinogen or vWF strands resulting in interplatelet aggregation. Antiplatelet drugs (abciximab, tirofiban, eptifibatide) blockade GPIIb receptors preventing platelet adhesion. Fibrin degradation products similarly can occupy these receptors, but their short length does not effectively allow antiplatelet linking and can result in bleeding. Azotemia inhibits vWF. ADP = adenosine diphosphate; GP = glycoprotein; NO = nitric oxide; TXA2=thromboxane A_2.

platelets. Mucocutaneous bleeding includes easy or recurrent nose and gingival bleeding, petechia or small ecchymoses, melena, frequent hematuria, and oozing from needle-sticks. Immediate and prolonged bleeding after minor cuts or venipuncture is characteristic. Most body cavity fluids, which include saliva, urine, and ascites, have high fibrinolytic activity and more commonly hemorrhage (1–3).

In CLD, thrombocytopenia and platelet dysfunction are offset by increased platelet adhesion secondary to elevated endothelial production of vWF (4). Progressive CLD tends toward a procoagulant state by increased endothelial synthesis and decreased hepatic clearance of factor VIII and vWF and decreased synthesis of inhibitors (protein C, protein S, and antithrombin) (5–7). Splanchnic and peripheral deep venous thrombosis is common in hospitalized patients and is diminished with anticoagulation (8–11) despite elevated standard clotting assays.

Secondary Hemostasis

In secondary hemostasis, the coagulation cascade occurs on the aggregated platelet surfaces, stabilizing the platelet plug through fibrin formation. In the initiation phase, a small clot of thrombin rapidly forms and serves as the endpoint for the clot-based assays (prothrombin time, international normalized ratio [INR], and activated partial thromboplastin time [aPTT]). In stable CLD, prolongation results from reduced hepatic synthesis of coagulation factors that are not counterbalanced by reduced inhibitors, as inhibitors do not have a role in this early phase. INR is prolonged before aPTT because of the short half-life of factor VII.

In the amplification phase, the early thrombin rapidly generates the bulk of the thrombin on platelet surfaces in a positive feedback loop (the thrombin burst). In this physiologically important phase, a balanced reduced hepatic synthesis of procoagulants and inhibitors results in normal thrombin generation (**Fig 2**) (12–18). Finally, thrombin initiates the conversion of fibrinogen to a stable cross-linked fibrin clot.

These clot-based assays were designed to quantify the anticoagulant effects of heparins and vitamin K antagonists and indirect factor Xa inhibitors (heparin group) but are invalid in stable CLD, as they do not take into account the balanced reduction of inhibitors that results in normal clot formation in the physiologically important amplification phase. An assay that includes thrombomodulin (a protein C activator) reflects the balanced reduction of both procoagulants and inhibitors (19) in advanced CLD and shows similar thrombin generation in patients with and without prolonged assays.

Secondary hemostasis-type coagulopathic bleeding typically results from congenital or acquired factor deficiencies or dysfunction. In contrast to the slow oozing primary hemostasis-type bleeding of platelet dysfunction, factor-type bleeding is usually profound deep tissue bleeding, such as large subcutaneous hematomas, muscle and joint hematomas, and bleeding into body cavities. Its infrequent occurrence in CLD is usually due to vitamin K deficiency (poor oral intake or biliary dysfunction). It should always be considered in fulminant ALF and ACLF, as profound uncompensated clotting factor depletion may acutely occur in either.

Fibrinolysis

After hemostasis is established, fibrinolysis naturally resorbs the clot. Fibrinolysis is also balanced in stable CLD (**Fig 2**) (20). Advancing severity of liver disease,