Re: Bleeding Risk and Management in Interventional Procedures in Chronic Liver Disease

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Editor:

With interest I have read the debate between DeAngelis et al (1) and Sarode et al (2) on prophylactic administration of platelet concentrates in patients with cirrhosis before invasive procedures. Although I agree with both debaters that we lack high-quality clinical evidence in support of a certain threshold below which prophylactic platelet transfusion may be beneficial, I think the argument by DeAngelis et al (1) is based on a substantial overinterpretation of a laboratory study (3).

DeAngelis and coworkers (1) suggest that the finding that thrombin generation in platelet-rich plasma is impaired, particularly at platelet counts below 50,000–60,000/μL, justifies prophylactic platelet transfusion in patients with profound thrombocytopenia. However, the laboratory test referred to by DeAngelis and coworkers (1) assessed thrombin generation under static conditions with platelet activation occurring solely by in situ-generated thrombin. In vivo, support of coagulation reactions occurs on platelets adhered to and aggregated at the site of vascular injury. Platelet adhesion and aggregation may be preserved under thrombocytopenic conditions by the highly elevated plasma levels of the platelet adhesive protein von Willebrand factor (4), as Sarode and coworkers (1) indicate.

In addition, platelet adhesion in vivo may be enhanced by a procoagulant state of the vasculature, which may include endothelial activation and decreased integrity of the glycocalix. The thrombin generation test does not take into account the capacity of platelets to adhere and aggregate. Moreover, the role of platelets extends far beyond their capacity to support thrombin generation, and therefore a recommendation for a minimal platelet count based on a thrombin generation test alone puts disproportional emphasis on one of the many functions of platelets in hemostasis. Also, in vivo, platelets are likely activated by multiple agonists, including thrombin and collagen, and it has been well established that the procoagulant capacity of platelets markedly increases under stimulation by collagen and thrombin compared with thrombin alone (5,6). Importantly, within a platelet thrombus, distinct platelet subpopulations exist, notably a population that is procoagulant and a population that lacks procoagulant activity but is involved in clot retraction (7). Therefore, a thrombin generation test in platelet-rich plasma likely poorly reflects the true procoagulant capacity of platelets.

In addition, experimental animal studies have indicated that other cellular surfaces, notably endothelial cells, may be much more relevant than platelets in providing a procoagulant lipid surface (8). Additionally, the role of red blood cells in hemostasis is increasingly recognized, and anemia (which is frequent in cirrhosis) may impair hemostasis by multiple mechanisms, including decreased platelet adhesion to the damaged vessel wall, alterations in fibrin structure, and decreased red cell–mediated inhibition of fibrinolysis (9). The biochemical arguments in support of a 50,000/μL threshold for platelet transfusion therefore appear inadequate.
I disagree with DeAngelis and coworkers (1) that viscoelastic testing may better define hemostatic status, as viscoelastic tests do not take into account the highly elevated levels of von Willebrand factor, other effects of flow on hemostasis, and the defects in the protein C system in patients with cirrhosis. In addition, it has been demonstrated that platelet transfusion hardly improves the results of global tests of hemostasis (10), which may be partly related to the poor recovery of transfused platelets eluded to by Sarode et al (2). Finally, although there is evidence that thrombocytopenia increases the risk for procedural bleeding in cirrhosis, there is also published evidence that bleeding risk is unrelated to platelet count (11).

Given the uncertain benefits, poor recovery of platelet transfusion, potential side effects such as volume overload and general transfusion reactions, and costs of platelet transfusion, I would argue against routine prophylactic correction of thrombocytopenia before invasive procedures, particularly in patients with a low bleeding risk. Well-designed clinical studies comparing restrictive versus threshold-based platelet transfusions with bleeding and complications as endpoints will be required to settle the uncertainty regarding the relevance of a preprocedural platelet count in cirrhosis. Until these studies have been performed, local practices will inevitably vary, but arguments in favor or against certain platelet thresholds should not be driven by published laboratory data based on tests that do not allow or justify clinical extrapolation.

REFERENCES


Drs. DeAngelis et al respond:

We appreciate the correspondence (1) regarding our paper (2); it reflects a shared recognition of the need for more definitive studies, as we noted. The authors appropriately note that patients with advancing chronic liver disease may exhibit a procoagulant state. However, this may not ensure adequate hemostasis after a sudden procedural-related endothelial injury. Within seconds of injury, adequate numbers of platelets are required to adhere to injured endothelium and aggregate to form a sufficient hemostatic plug. Although the authors note Lismann’s well-known work regarding increased von Willebrand factor activity (3), there is also evidence that platelet adhesion and aggregation is impaired in cirrhosis as a result of changes in platelet composition inherent to cirrhosis (4,5). Decreased platelet activation results from impaired thromboxane production, calcium transport and release of platelet granules, and upregulated inhibitory pathways. Plasma factors also limit platelet function and include elevated levels of plasma apolipoprotein E, bile salts, and elevated levels of fibrin split products. The study of Tripodi et al (6) in human liver disease showed impaired thrombin production as platelet levels decrease to less than approximately 50,000/mm³; this constitutes the best available human data to support a target platelet count in the interest of minimizing bleeding risk in increased-risk procedures. Whether that level can always be achieved or can be used as a marker for greater caution in clinical situations constitute related but different issues. These may well be answered with the emergence of safer thrombopoietin agonists.

The authors (1) base their critique on interesting literature that may be significantly less relevant to human liver disease. One study demonstrated that factor Va and factor Xa after a laser injury in a mouse arteriole may extend beyond the location of the aggregated platelets (7). Its authors posited that endothelium itself may serve as a substrate for the coagulation cascade. The other quoted studies (8,9) theorize that collagen and thrombin together active platelets more than either alone. These reports suggest that an in vitro test with thrombin alone is not sufficient to access platelet function. We acknowledge these points, but the studies are far removed from an understanding of the complexity and challenges of studying platelet activity in human chronic liver disease (10).

Clearly, much has yet to be learned in this field, and there is wide interest in improving our understanding of this.

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