Anemia – The overlooked factor in bleeding related to liver disease

To the Editor:
Several elegant studies, summarised in their review by the Coagulation in Liver Disease Study Group, have helped in changing the paradigm of bleeding related to liver disease, from abnormal coagulation profile to haemostatic alterations secondary to portal hypertension, endogenous heparinoids, sepsis, and renal failure [1]. However, one of the key omissions in this respect is the role of anemia in worsening the haemorrhagic tendency of liver dysfunction. Anemia is common in individuals with chronic liver disease and is likely to be of multifactorial etiology including folate deficiency, hypersplenism, hemodilution, haemolysis, bone marrow suppression due to viruses or ethanol, renal insufficiency, and, most importantly, variceal bleeding. How anemia would worsen the bleeding tendency in these patients has not been directly studied but several factors are responsible.

Firstly, anemia worsens the hyperdynamic circulation, the key pathogenetic feature of portal hypertension [2]. This is possibly due to the reduction in blood viscosity but some evidence for the role of the vasodilator nitric oxide (NO) has also been suggested [3]. As demonstrated in experimental animals, NO may also play a central role in the systemic and splanchic vasodilation associated with portal hypertension with increased vascular responses to specific inhibitors of NO biosynthesis [2]. Secondly, there is evidence that red blood cells not only have passive, rheological effects on blood coagulation but also actively stimulate thrombin generation [4]. The best example of the haemostatic role of red cells is represented by the increased thrombotic tendency of polycythemia and erythropoiesis-stimulating agents. Interestingly, a small prospective study of 42 patients with chronic anemia (unrelated to liver disease) shown an unexplained improvement in the activated partial thromboplastin time with transfusion of packed red cells [5].

By far, the most likely explanation for the bleeding tendency with anemia is the effect of red cells on platelet function. Red cells release adenosine diphosphate which promotes platelet aggregation and also stimulates platelet synthesis of thromboxane A2, a key platelet activator during vessel injury. Haemoglobin in anemia, activates guanylyl cyclase and further impairs platelet aggregation. Moreover, in normal physiological states, red cells, being the largest cells, tend to occupy the central part of the vasculature, pushing the platelets nearer to the vessel wall, where they are poised to respond to injury. In anemic states, the concentration of platelets in proximity to the endothelium is reduced thus affecting the haemostatic process. The beneficial effect of red cells on platelet function was first reported by Duke in 1910 but was conclusively proved by Hellem who examined anemic patients with bleeding defects showing a decrease in bleeding time (BT) upon transfusion of washed red cells [6]. This observation has been more recently confirmed, when improved BT after red cell transfusions were observed in experimental and clinical subjects with continued thrombocytopoenia and in uremic patients with bleeding tendency and normal platelet counts [7,8].

One of the possible negative arguments for these studies would be the assessment of BT rather than further bleeding episodes, with red cell replacement. BT is prolonged in cirrhotics to variable extent, although the exact cause for this phenomenon has never been explained, especially when there was no negative correlation between platelet counts and BT, and an abnormal VonWillebrand factor was not seen in these patients [9]. In this context, it is useful to remember that BT is not just a measure of platelet function but is also influenced by red cell volume, blood urea concentration, and strength of the vascular connective tissue. Although platelet dysfunction in liver disease has been experimentally shown to be balanced by increased highly active VonWillebrand factor multimers, the aforementioned remaining factors (especially correctable anemia), have not been considered [1].

Studies on a favourable outcome on bleeding with treatment of anemia in liver disease are worthwhile, especially as similar measures have hugely benefited patients with renal impairment treated with erythropoietin and intravenous iron. Homoncik and colleagues have conducted a randomized, double-blind, placebo-controlled trial of erythropoietin in 22 thrombocytopenic patients with alcoholic liver cirrhosis and have found higher platelet counts and platelet reactivity by flow cytometry in these patients with a more pronounced effect in presence of lower platelet counts [10].

In summary, although “blood component” (plasma products) transfusion may indeed be harmful in liver patients with bleeding tendency, strong consideration should be made for “blood” transfusion, despite its rare adverse effects. It is also worthwhile assessing the response to iron replacement and/or erythropoietin administration in selected patients (bearing in mind thrombotic potential) on the bleeding risk associated with liver disease.

Conflict of interest
The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References
Letters to the Editor

Reply to Dr. Tachil:
We appreciate the interest of Dr. Thachil in our recently published meeting report on coagulation disorders in patients with liver disease [1]. Dr. Thachil states that the anemia of liver disease may be important in the bleeding manifestations in these patients, with which we fully agree. The role of anemia was simply not discussed during the 3rd International Symposium on Coagulopathy and Liver disease, highlights of which were summarised in the meeting report. Whereas the omission of the role of anemia in the conference programme is the responsibility of us as conference organisers, we have made a case for the role of anemia in the coagulopathy of liver disease in previous publications [2,3]. We fully agree that red cells are important in the hemostatic process, in particular due to the effects of red cells on platelet attachment to the damaged vasculature in flowing blood. In fact, experimental evidence from us and others has indicated that anemia is a key factor in platelet hypofunction studied in ex vivo experimental models [2,4]. Furthermore, as also mentioned by Dr. Thachil, correction of anemia in patients with renal disease by red cell transfusion or administration of erythropoietin appears to reduce uremic bleeding. Nevertheless, we do believe clinical evidence supports the concept of ‘rebalanced hemostasis’ in liver disease [5]. More and more centers report that a large proportion of patients can undergo a liver transplantation without any requirements for blood product transfusion despite persistent perioperative anemia (reviewed in [5]).

The rebalanced hemostasis theory explains these observations by the presence of compensatory factors for thrombocytopenia (high levels of von Willebrand factor) and decreased levels of procoagulant and antifibrinolytic proteins (i.e., decreased levels of anticoagulant and profibrinolytic proteins). No compensatory factor for anemia appears present, although as mentioned in our meeting report, platelet function in vivo could be promoted by a reduced glycolcalix on the vascular endothelium. To our knowledge experimental data on a possible role of reduced endothelial glycolcalix in promoting platelet function in the anemic and thrombocytopenic patient with cirrhosis are not available, but experiments testing this hypothesis would be of interest.

As discussed in the meeting report, bleeding episodes do occur in patients with liver disease, and also during liver transplantation severe bleeding can on occasion be encountered. Reversal of anemia may thus be of benefit for the patient with liver disease by reducing bleeding risk, and we agree with Dr. Thachil that clinical studies on this issue are worthwhile. We have recently proposed outlines for clinical studies on the prevention of bleeding or thrombosis in patients with liver disease [5] and agree that randomised controlled studies on reduction of bleeding during invasive procedures by red cell transfusion or administration of erythropoietin and intravenous iron would also be of interest. These studies, however, should carefully assess potential risks associated with these therapeutic strategies. We and others have recently demonstrated that transfusion of red cell concentrates during liver transplantation is associated with increased morbidity and mortality [6]. Accumulating clinical and laboratory evidence suggests that a restrictive transfusion policy, which includes acceptance of a low hematocrit, during liver transplantation is safe and effective (reviewed in [5]). Transfusion of red cell concentrates to patients with liver failure may result in aggravation of portal hypertension, which may even paradoxically induce or facilitate bleeding. These effects demonstrated both experimentally and clinically (reviewed in [7]) led to recommendations that red cell transfusions be limited in variceal bleeding with a target hemoglobin between 7 and 8 g/dl in the Baverno V criteria [8]. One could argue that a slightly higher value or use of a hematocrit target of 25% might better balance between effective platelet rheology and portal pressure as the initial platelet plug probably plays some role in variceal bleeding cessation, although pressure effects dominate.

The effects of red cell transfusion on hemostasis in the patient with liver failure and portal hypertension are thus complex, and clinical studies should therefore assess both efficacy and safety. In our opinion, current evidence suggest that a restrictive transfusion policy, which includes restrictive use of red cell concentrates should be standard of care until randomised clinical studies suggest otherwise. Administration of erythropoietin may be a more attractive therapeutic strategy in patients with liver disease, as an unwanted volume expansion is avoided.

Reply to Dr. Tachil:

Anemia as a potential contributor to bleeding in patients with liver disease – Neglected but not forgotten


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