Transfusion strategies in patients with cirrhosis: less is more

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List of abbreviations in the order of appearance:

PT: prothrombin time, FFP: fresh frozen plasma, RBC: red blood cell, AUGIB: acute upper gastrointestinal bleeding, UK: United Kingdom, TEG: thromboelastography

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The implementation of transfusion guidelines in patients with cirrhosis remains challenging, as the over-permissive practice of decades conflicts with emerging clinical data on the need and efficacy of both prophylactic and therapeutic transfusions.

Our understanding of coagulopathy in cirrhosis has significantly changed in the last decade and landmark publications have proved that cirrhosis is not a hypocoagulable state (1). Indeed, both pro- and anticoagulant factors are decreased and the haemostatic balance, although maintained, is set at a lower point (2). The relative deficiency of both coagulation system drivers results in a fragile balance that is easily tipped towards haemorrhage or thrombosis, depending on circumstantial risk factors such as bleeding, infection or renal failure (3). Patients with cirrhosis are not "auto-anticoagulated" but on the contrary have an increase risk of unprovoked venous thromboembolism compared to general population controls (4).

In vitro studies have shown that thrombin generation is impaired in patients with cirrhosis only when the platelet count drops to $<50x10^9$/L (5). Therefore conventional coagulation tests, such as prothrombin time (PT), do not reflect the bleeding tendency in such patients and cannot be used to guide transfusion decisions. A meta-analysis of the prophylactic use of fresh frozen plasma (FFP) prior to invasive procedures, showed that red blood cell (RBC) transfusion requirements are not reduced in patients with chronic liver disease (6).

Moreover, even in the setting of variceal bleeding, over-transfusion of RBCs is associated with a worse outcome, probably due to an increase in the portal pressure and further bleeding. In a randomised controlled trial of 921 patients with severe acute upper gastrointestinal bleeding (AUGIB), a restrictive transfusion strategy (transfusion when the haemoglobin <7 g/dl) was associated with reduced further

bleeding, fewer adverse events and improved survival compared to a liberal strategy (transfusion when the hemoglobin <9 g/dl) (7). Remarkably, the probability of survival was higher with the restrictive strategy than with the liberal strategy in the subgroup of patients with Child–Pugh class A or B cirrhosis (hazard ratio 0.30), while the portal-pressure gradient increased significantly in those patients assigned to the liberal but not in those assigned to the restrictive strategy (7). Following the results of this study, the recent Baveno VI (8) and United Kingdom (UK) guidelines (9) for the management of variceal bleeding recommend that red blood cells transfusion should be done conservatively at a target haemoglobin level between 7 and 8 g/dl, although transfusion policies in individual patients should also consider additional factors such as cardiovascular disorders, age, hemodynamic status and on-going bleeding. Although no recommendation was made for the management of coagulopathy, the Baveno VI guidelines state that PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis (8).

Despite these advances in our understanding of coagulopathy and bleeding risk in cirrhosis, there is a significant lag in clinical practice as evidenced by the nationwide UK audit by Desborough and co-authors (10). Data on 1313 consecutive patients with cirrhosis were collected from 85 hospitals in a 28-day period. In the entire cohort, 391/1313 (30%) of patients were transfused at least one blood component during their admission, which is a striking figure and is comparable to cohorts admitted in intensive care or undergoing major surgical procedures. Of these, 61% received transfusion for treatment and 39% for prophylaxis of bleeding. For those transfused with RBCs for treatment of AUGIB, the pre-transfusion threshold was >80g/L in 48/185 (26%) cases and >70g/L (restrictive threshold used in the Barcelona trial of transfusion strategies for AUGIB (7)) in 82/185 (44%). Transfusion

for prophylaxis in the absence of bleeding was given in 153/1313 (12%) of patients; in this category, 20/101 (20%) of patients had a pre-transfusion haemoglobin >80g/L and 58/101 (57%) had a pre-transfusion haemoglobin >70g/L. For patients transfused with FFP, 32/81 (40%) had a pre-transfusion INR of <1.5, which represents an arbitrary cut-off level for high-risk procedures. Of particular concern is the fact that a minority of patients received FFP and platelets empirically, in the absence of a planned procedure or bleeding. Thrombosis or thromboembolic disease occurred in 35/1313 (3%) cases including deep vein thrombosis, splanchnic vein thrombosis and pulmonary embolism and were the same in transfused and non-transfused patients.

This nationwide audit convincingly demonstrates that a very significant proportion of blood transfusions in patients with cirrhosis are unjustified and potentially harmful. The potential reasons and solutions for this differ between therapeutic and prophylactic transfusions. As far as the management of transfusion requirements in upper GI bleeding is concerned, this study has demonstrated that the adherence to existing national and international guidelines is poor. This could be due to the fact that patients with cirrhosis who bleed present to emergency departments and are initially treated by the acute medical team with delayed input from hepatology. Acute bleeding in patients with cirrhosis and coagulation abnormalities still triggers massive transfusion protocols that can actually do more harm than good. The British Association for the Study of the Liver recently issued a decompensated cirrhosis care bundle with a checklist to be completed within the first 6 hours of admission (11). Similar guidelines from international societies could inform other specialties and improve the acute care of liver patients.

As far as the prophylactic use of products is concerned, there are no evidence-based guidelines, as the in vitro data of thrombin generation in cirrhosis have not been translated in clinical trials to date. The wide variation in clinical practice reflects the need for further studies on coagulation in cirrhotic patients in various clinical settings with multiple co-factors taken into account, in order to identify accurate markers to predict the status of the coagulation imbalance in these patients. A recently published pilot randomised study examined the efficacy and safety of thromboelastography (TEG) in guiding the use of FFP or platelet transfusion before invasive procedures in patients with cirrhosis and impaired traditional coagulation tests (12). Despite the use of a conservative TEG threshold, only 5/30 patients in the TEG group received blood product transfusions as compared to all patients (30/30) in the standard of care group. Most notably, post-procedure bleeding occurred in only one patient in the standard of care group and none in the TEG group. Although most patients had low risk procedures and these results will require further validation, this study addressed an unmet clinical need and provided important proof-of-concept insights. Further adequately powered studies are warranted, potentially using thrombin generation assays, in order to conclusively identify the subgroup of patients with cirrhosis who need prophylactic administration of blood products prior to an invasive procedure.

It is therefore time that the liver community sufficiently communicates that cirrhosis is not an acquired bleeding disorder. Robust internationally accepted guidelines on transfusion policies in cirrhotic patients will result in this increased awareness, will identify areas of uncertainty and facilitate trials to resolve them.

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