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Editorial

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Nails in the coffin of fresh frozen plasma to prevent or treat bleeding in cirrhosis?

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Patients with chronic liver disease (CLD) have complex changes in their haemostatic system. These changes often include thrombocytopenia, low levels of coagulation factors and inhibitors, low levels of fibrinolytic proteins and elevated levels of endothelium-derived haemostatic proteins, including the platelet adhesive molecule von Willebrand factor. Patients often have prolongation of conventional coagulation tests (prothrombin time and associated international normalised ratio [PT/INR] and activated partial thromboplastin time [aPTT]), interpreted as indicating an increased risk of bleeding complications, particularly from planned invasive procedures. It has thus been a common practice to try to improve haemostasis both in bleeding patients and prophylactically prior to invasive procedures by infusion of blood products, particularly fresh frozen plasma (FFP). '*Two units of FFP and an INR of less than 1.5*' has been a frequent instruction when procedures are planned.

However, in many patients with CLD the haemostatic system appears to be in balance even when conventional tests are abnormal, due to the concomitant decline in both pro- and anti-haemostatic drivers.[1] Viscoelastic or 'functional' tests of coagulation such as thrombin generation tests are increasingly used as measures of haemostatic potential in patients with CLD, and there is now extensive data from studies using these techniques to suggest that in many patients coagulation potential is already normal or even supra-normal.[2]

Thus, although the administration of FFP aims to improve coagulation potential, it may not be necessary and indeed may well be ineffective and even detrimental in terms of the effects of volume expansion on portal pressure. In addition, other side effects of FFP transfusion can cause harm and there is evidence that patients with liver disease and patients who are critically ill are particularly susceptible to transfusion-related complications, such as transfusion-related acute lung injury.[1,3] Moreover, there is little clinical evidence that FFP is an effective pro-haemostatic, not only in patients with liver disease but also in the general population.[4] *In vitro* experiments have indicated that FFP does not increase coagulation potential in patients with cirrhosis as it supplies both pro- and anticoagulant proteins in equal amounts.[5] As a result, although plasma levels of individual coagulation factors increase and as a consequence the prothrombin time and INR may decrease, actual thrombin generating capacity does not change or may even decrease. Further, in many procedures undertaken in patients with CLD, procedural risk appears lower than generally appreciated.[6] Nevertheless, FFP continues to be widely used both in treatment and prophylactic settings.[7]

An important study by Rassi and colleagues in this issue of the *Journal*[8] demonstrates for the first time that administration of clinically relevant doses of FFP in both prophylactic and treatment 'real world' settings does not improve *ex-vivo* coagulation potential in patients with cirrhosis. This study therefore suggests that the common use of FFP in these settings is likely to be ineffective. Importantly, nearly 10% of the patients studied here had acute adverse reactions to transfusion, emphasising that FFP transfusion is not a benign intervention.

It is also notable that *ex vivo* thrombin generation decreased in more than a third of patients after infusion of FFP. As the authors speculate, this may be the result of the replenishment of protein C and its braking effect on the clotting cascade. In addition, replenishment of antithrombin and attenuation of factor VIII levels (which are higher in cirrhosis than in FFP) may also play a role.[9,10] A decrease in thrombin generation has not been demonstrated in experiments in which FFP was added *in vitro*,[5] and it may be that the decrease observed in the Rassi study is a chance finding. It needs to be noted that the analytical variation of the thrombin generation test is relatively high, and that some of the decreases observed are in fact within this analytical variation.

As we feel there is substantial evidence that FFP is ineffective in patients with cirrhosis and may do harm, we propose that FFP or other pro-haemostatics should not be used prophylactically in most routine settings in which bleeding risk is low. Indeed,

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it has been previously stated in "Choosing Wisely" campaigns by the American Association of the Study of Liver Disease (http://www.choosingwisely.org/societies/american-association-for-the-study-of-liver-diseases/) and Canadian Association for the Study of the Liver[11] that prophylactic FFP should not be used prior to minor procedures, and we propose to expand these statements. In addition, we propose that alternative prohemostatics should be studied for prohemostatic effects in the prophylactic setting in which anticipated bleeding risk is high, and in patients with active bleeding – particularly when this is unrelated to portal hypertension. These alternative strategies may include prothrombin complex concentrates, cryoprecipitate, and fibrinogen concentrate, all of which improve haemostatic potential *in vitro*[5] and appear effective in liver transplantation.[12] Recombinant factor VIIa has been extensively studied clinically, with mostly negative results.[13] Also, this drug does not appear to improve coagulation *in vitro*[5] and therefore seems unlikely to be of benefit.

Although this trial provides more nails in the coffin of the too often used practice of 'give 2 units FFP and don't worry' or the use of a spurious INR 'target', high quality clinical evidence for the inefficacy of FFP transfusion for prophylaxis or treatment of bleeding is lacking. Ideally, randomised studies should be performed to compare liberal FFP use with no FFP or with an alternative prohemostatic agent in both prophylactic and treatment settings. In addition, other issues in the clinical management of coagulation disturbance in CLD need to be addressed. For example, we need to better understand how the nature of coagulation changes across the spectrum of CLD and how it is impacted by the complications of CLD. Notably, relatively few patients in Rassi *et al.*'s study had the most severe forms of acute-on-chronic liver failure. This sub-population clearly needs to be further studied. We also need to know how to utilize the clinical laboratory to best evaluate these complex coagulation changes in the clinical setting – if we are not to rely on the INR or prothrombin time to guide our interventions, what tests should we trust? It is likely not helpful to perform haemostasis tests in patients with (anticipated) low bleeding risk, for example prior to procedures.[14] In those patients, a wait-and-see policy in which testing is only performed when active bleeding occurs is likely indicated. In case of active bleeding, laboratory testing, particularly with more advanced viscoelastic or thrombin generation tests is likely to be helpful to guide treatment. However, 'prophylactic' laboratory testing has little clinical use, as none of the tests we are currently using are able to indicate which patients are at a clearly increased risk of bleeding,[14] and there is ample evidence from studies in the general population that preprocedural haemostasis screening is not helpful and is associated with significant healthcare costs.[15] We need to be choosing wisely both in terms of diagnosis and treatment. Clearly, we need more studies to provide better guidance, but it is also clear that FFP does not have a role in routine management of bleeding in patients with CLD.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors drafted the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.09.024.

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