Fresh frozen plasma in treating acute variceal bleeding

Lisman, Ton; Procopet, Bogdan

Published in:
Liver International

DOI:
10.1111/liv.14988

Publication date:
2021

Received: 1 June 2021 | Accepted: 4 June 2021

DOI: 10.1111/liv.14988

EDITORIAL

Liver INTERNATIONAL WILEY

Fresh frozen plasma in treating acute variceal bleeding: Not effective and likely harmful

Patients with end-stage liver disease are at risk for both bleeding and thrombotic complications.[1] Although the paradoxical risk for both bleeding and thrombotic events has been ascribed to the complex haemostatic changes that occur in patients with cirrhosis, this explanation may be wrong. It is now well accepted that patients with end-stage liver disease largely remain in a haemostatic balance due to simultaneous changes in pro- and antihaemostatic pathways.[2] The increased thrombotic risk is likely related to specific prothrombotic changes in the haemostatic system such as an imbalance in the von Willebrand factor/ADAMTS13 axis, decreased hepatic production of the natural anticoagulants associated with enhanced thrombin generating capacity, a prothrombotic clot structure and resistance to fibrinolysis in the sickest patients.[3–5] In contrast, the spontaneous or procedure-related bleeding risk of patients with end-stage liver disease is at least in part unrelated to the haemostatic changes in these patients.[1] For example, multiple lines of evidence suggest that variceal bleeding, one of the most common bleeding complications, is fully unrelated to haemostatic failure but is altogether attributable to portal hypertension and local vascular abnormalities. Indeed, the cornerstone of the prevention and variceal bleeding treatment consists of medication (nonselective beta-blockers, vasoactive drugs) or procedures (TIPS) that decrease portal pressure. Prohaemostatic therapy, either with blood component transfusion or by infusion of pharmacological agents, is therefore not indicated.

Nevertheless, despite clear expert opinion[6] and societal recommendations,[1,7] patients with variceal bleeding frequently receive blood products or other prohaemostatic therapy during initial resuscitation in line with general recommendations on treatment of massive bleeding. Although societal guidance documents indicate that transfusion of fresh frozen plasma (FFP) or platelet concentrate likely is ineffective in acute variceal bleeding and is associated with adverse events such as infection, transfusion-related acute lung injury or transfusion-associated circulatory overload, the risk/benefit of blood component transfusion in acute variceal bleeds has not been formally assessed. In this issue of Liver International, Mohanty and coworkers provide compelling evidence that transfusion of FFP during acute variceal bleeding is ineffective and does harm.[8] Specifically, in multivariable analysis, FFP transfusion was associated with an increased risk of failure to control bleeding at 5 days and with mortality at 42 days.

Why is FFP still commonly given to patients with cirrhosis and acute variceal bleeding, even though societal guidelines advise against this treatment? First, in the setting of acute variceal bleeding, red blood cell (RBC) transfusion might become necessary either because of anaemia or because of the development of hypotension, with evidence from randomized trials favouring a low haemoglobin threshold for RBC transfusion (7 g/dL).[9] When RBCs are transfused, clinicians are inclined to transfuse balanced amounts of FFP and platelet concentrate as per general major bleeding protocols. Indeed, in the study by Mohanty, almost all patients that received FFP had also received RBC transfusion. Secondly, patients with advanced chronic liver disease frequently have a prolonged prothrombin time or associated International Normalised Ratio (INR), and it is (at least at first sight) a logical clinical response to try to correct a prolonged INR in a bleeding patient. Interestingly, a proportion of patients in the Mohanty study received FFP in the absence of a substantially prolonged INR (<1.5), suggesting that these patients were given FFP not to counteract their coagulopathy but as a general response to RBC transfusion.

Why is FFP ineffective as a haemostatic agent in the setting of acute variceal bleeding? The most likely explanation is that variceal bleeding is truly a nonhaemostatic bleed.[1] The risk of variceal bleeding is not enhanced by anticoagulant therapy,[10] and the severity and outcome of variceal bleeding are not worse in patients using anticoagulant drugs at the time of the bleed.[11] If anticoagulants do not make variceal bleeding worse, it seems plausible that it is unlikely that procoagulants are effective in stopping the bleed. Indeed, recombinant factor VIIa, a low volume prohaemostatic, had little effect in randomized studies on variceal bleeding.[12] In addition, the coagulation system in patients with end-stage liver disease is intact, or even hypercoagulable,[2] and one study published only in abstract form has demonstrated intact thrombin generating capacity even in patients during an acute variceal bleed.[13] The 'don't fix anything that isn't broken' principle is another reason why FFP is likely ineffective during bleeding in patients with end-stage liver disease. In vitro and ex vivo studies have shown that although FFP improves the INR, it hardly enhances thrombin generating capacity,[14–16] although one recent study suggested FFP to have prothrombotic effects in a real-life clinical setting by increasing the thrombin generation to levels higher than healthy controls and by demonstrating an increase in levels of markers of coagulation activation.[17] Importantly, the number of units

of FFP transfused was relatively modest at 2 units (range 0-22), and the expected improvement in INR (particularly in a bleeding patient) by 2 units of FFP in a patient with advanced chronic liver disease will be limited. Two recent studies showed a reduction in INR of 33% and 18% by a mean of 4 units of FFP.[16,17] It is thus questionable whether the FFP transfused in the Mohanty study had any meaningful effect on haemostasis.

Why might FFP do harm during acute variceal bleeding? The data in the Mohanty study show a clearly increased rate of failure to control bleeding at five days. This may very well be explained by volume overload leading to exacerbation of portal hypertension. Thus, although FFP may be administered in an attempt to improve the coagulopathy and decrease the bleed, the effects of FFP on portal pressure achieve the exact opposite. Moreover, RBC transfusions were more frequent in the FFP transfusion group, which would have a synergistic effect on portal pressure increase. In addition, FFP administration was associated with a profoundly increase risk of 42-day mortality in the Mohanty study, which may not only in part be explained by sequelae of the variceal bleed but may also in part be related to side effects of the FFP. However, given the retrospective design, the proper explanation for the difference in survival is difficult to establish. The adjustments for MELD or Child-Pugh score are probably not enough since INR, which would eventually trigger the indication of transfusion, is among the score's variables. Indeed, in the FFP group, the patients had more advanced liver disease (more ascites and hepatic encephalopathy), and, eventually, that would be enough to explain the difference in prognosis.

Nails in the coffin of prohaemostatic therapy in managing variceal bleeding? Three prohaemostatic approaches have shown a lack of benefit with evidence of harm in variceal bleeding. Notwithstanding the limitations of the retrospective analyses by Mohanty and coworkers, there are multiple clear signals that FFP is ineffective in patients with advanced chronic liver disease and may do harm.[1] In addition, large, randomized studies on the effect of recombinant factor VIIa and tranexamic acid in patients with acute variceal bleeding have been performed, and studies with both agents had unfavourable outcomes.[12,18] Thus, the mainstay of treatment of variceal bleeding is endoscopic evaluation and treatment combined with pharmacological approaches to reduce portal pressure.[19] Restrictive RBC transfusion is indicated in the resuscitation of patients that are bleeding extensively. However, the addition of FFP or platelet concentrate to these RBC transfusions should be avoided, as improvement of haemostatic status is not required. FFP and platelets do not or only marginally improve haemostasis, and blood products may do harm by exacerbation of portal hypertension and general transfusion-related side effect. Although recombinant factor VIIa and tranexamic acid are low-volume products and therefore lack volume overload issues, these prohaemostatic interventions are also not indicated as they are ineffective and associated with thrombotic risk.[18,20] It seems plausible that patients with acute variceal bleeding and modest RBC transfusion requirements do not need FFP and platelet transfusion. What needs to be done in case of massive bleeds requiring generous amounts of RBCs requires further study. In these patients receiving massive RBC transfusions, some sort of fluid needs to be supplemented in conjunction with the RBCs. Importantly, in these massively bleeding patients, the haemostatic system may become dysfunctional due to consumption and hemodilution, and patients with a coagulopathy associated with massive bleeding on top of the preexisting coagulopathy of end-stage liver disease may eventually lead to 'coagulopathic' bleeding, and these patients may benefit from some sort of prohaemostatic therapy.

The message that patients with acute variceal bleeding should not be treated as a general patient with massive blood loss should be more extensively communicated among hepatologists, haematologists, emergency specialists and intensive care specialists, for example, by 'Choosing Wisely' campaigns (https://www.choosingwisely.org/).

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

Ton Lisman[1]
Bogdan Procopet[2]

[1]*Surgical Research Laboratory and Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*
Email: j.a.lisman@umcg.nl
[2]*Regional Institute of Gastroenterology and Hepatology "Octavian Fodor", Hepatology Department and "Iuliu Hatieganu" University of Medicine and Pharmacy, 3rd Medical Clinic, Cluj-Napoca, Romania*

Handling Editor: Virginia Hernandez-Gea

ORCID

Ton Lisman https://orcid.org/0000-0002-3503-7140
Bogdan Procopet https://orcid.org/0000-0001-8118-1760

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How to cite this article: Lisman T, Procopet B. Fresh frozen plasma in treating acute variceal bleeding: Not effective and likely harmful. *Liver Int*. 2021;41:1710–1712. https://doi.org/10.1111/liv.14988