Digestive and Liver Disease 48 (2016) 455–467

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Position Paper

Hemostatic balance in patients with liver cirrhosis: Report of a consensus conference

Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI)

ARTICLE INFO

Article history:
Received 27 January 2016
Accepted 18 February 2016
Available online 27 February 2016

Keywords:
Bleeding
Cirrhosis
Hemostasis
Thrombosis

ABSTRACT

Patients with cirrhosis present with hemostatic alterations secondary to reduced availability of pro-coagulant and anti-coagulant factors. The net effect of these changes is a rebalanced hemostatic system. The Italian Association of the Study of the Liver (AISF) and the Italian Society of Internal Medicine (SIMI) promoted a consensus conference on the hemostatic balance in patients with cirrhosis. The consensus process started with the review of the literature by a scientific board of experts and ended with a formal consensus meeting in Rome in December 2014. The statements were graded according to quality of evidence and strength of recommendations, and approved by an independent jury. The statements presented here highlight strengths and weaknesses of current laboratory tests to assess bleeding and thrombotic risk in cirrhotic patients, the pathophysiology of hemostatic perturbations in this condition, and outline the optimal management of bleeding and thrombosis in patients with liver cirrhosis.

1. Introduction

Hemostatic alterations are common in patients with cirrhosis. For a long time it was believed that a defective synthesis of pro-coagulant factors together with thrombocytopenia increased the risk of bleeding but protected against thrombosis in these patients. Accordingly diagnostic and therapeutic invasive procedures in patients with cirrhosis were considered risk factors for bleeding. However, this belief has been challenged by evidence of a concomitant decrease of anti-coagulant factors. The net effect of these changes is a rebalanced hemostasis. However, this hemostatic profile is unstable, and patients can be tipped toward both bleeding and thrombosis under certain conditions [1–5]. Thus, there is growing evidence that proper understanding of the hemostatic pathways in liver disease requires a global perspective which account for the complexity of hemostasis, with dynamic interactions between pro-coagulant and anti-coagulant factors.

2. Methods

A consensus meeting promoted by the Italian Association for the Study of the Liver and the Italian Society of Internal Medicine was held to discuss limitations of current laboratory tests for the assessment of bleeding and thrombotic risk, and to review the management of bleeding and thrombosis in patients with cirrhosis. A scientific board of experts was initially appointed to identify relevant topics relating to alterations of coagulation in cirrhotics. Subsequently, relevant literature data pertaining to each of the 5 identified major topics was conducted by several ad hoc subcommittees of experts with the aim to highlight areas with high-quality and/or uncertainty; the sub-committee work ended with the formulation of several statements. The process ended with a formal consensus meeting held in Rome in December 5 and 6, 2004, when the statements were finalized, graded according to quality of evidence and strength of recommendations, and finally approved by an independent jury. The quality of evidences and strength of

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http://dx.doi.org/10.1016/j.dld.2016.02.008
1590-8658/

recommendations were graded according to the GRADE system (Table S1).

3. Laboratory tests to assess bleeding

3.1. Bleeding time

In patients with cirrhosis, bleeding time is prolonged [6], but the clinical meaning of this laboratory alteration is uncertain as values were not predictive of bleeding secondary to liver biopsy [7] or esophageal variceal rupture [8]. Even in settings other than cirrhosis, the test had no predictive value for bleeding [9]. Furthermore, a randomized clinical trial on patients with variceal bleeding aimed at testing the efficacy of desmopressin (a drug known to shorten the bleeding time) combined with terlipressin, was interrupted prematurely because of excess hemorrhagic events in the desmopressin arm [10].

Statement. ***Bleeding time should not be used in patients with cirrhosis as a screening test to predict the risk of esophageal varices bleeding or bleeding following invasive procedures (A2).***

3.2. Platelet count

Patients with cirrhosis present with variable degrees of thrombocytopenia [11] and increased levels of the adhesive protein von Willebrand factor (VWF) which facilitates in vitro platelets to adhere and aggregate normally [2]. When the platelet count was adjusted to a standard value of 100×10^9/L, platelet-rich plasma from patients with cirrhosis generated in vitro as much thrombin as that of healthy subjects [12]. Although the benefit of platelet infusion to avoid bleeding in cirrhotics has never been assessed in clinical trials, counts of 60×10^9/L are considered sufficient to secure in vitro thrombin generation at the lower reference limit [12]. In hepatitis C-related cirrhosis, platelet numbers of $\leq 60 \times 10^9$/L were associated with an increased risk of procedure-related bleeding [13]. The practice of transfusing one single adult platelet dose only to patients with cirrhosis and counts $<50 \times 10^9$/L undergoing variceal banding elevates circulating platelet counts only marginally, with no or little effect on thrombin generation and thromboelastometry [14].

Statement. ***Platelet counts $\geq 50 \times 109$/L are considered to ensure normal primary hemostasis (B).***

3.3. Prothrombin time

The prothrombin time (PT), with results expressed as international normalized ratio (INR), is the standard test to monitor therapy with vitamin K antagonists (VKA). In cirrhosis, PT prolongation parallels impairment of the synthetic capacity of the liver has been used to assess bleeding risk. However, increasing evidence suggests that PT (and other congener tests) poorly reflects the hemostatic balance in cirrhosis. In these patients, reduced levels of pro-coagulants are counteracted by a parallel reduction of their anti-coagulant counterparts [4]. The paradoxical prolongation of the PT, in spite of normal thrombin generation, stands to the fact that the PT is more sensitive to the reduction of pro-coagulants than to the reduction of anti-coagulants, especially of protein C. Protein C, which is reduced in cirrhosis, must be activated to express its full anti-coagulant activity. In addition, its main physiological activator, thrombomodulin, is located in endothelial cells but not in plasma nor in reagents used to estimate the PT. Previous observations are in line with the long lasting evidence that the PT is a poor predictor of peri- or post-operative bleeding in cirrhosis [15–22]. Furthermore, a powerful pro-hemostatic agent, such as recombinant activated factor VII (rFVIIa), although capable of considerably shortening the PT [23], proved to be ineffective to stop esophageal bleeding [23,24], or to reduce bleeding at surgery [25,26].

Statement. ***Current evidence does not support the use of PT values as predictors of bleeding or to monitor the effectiveness of hemostasis-modifying therapy in patients with cirrhosis (A2).***

3.4. Thromboelastometry/thromboelastography

Whole blood viscoelastic tests evaluate the kinetics of coagulation, from initial clot formation to final clot strength. The viscoelastic properties of blood components are assessed in vitro by the thromboelastometry/thromboelastography (ROTEM/TEG) techniques. Due to the reagents used for testing (i.e. citrated whole blood, which includes plasma, erythrocytes, leukocytes and platelets), these tests should, at least in principle, reflect the global coagulation occurring in vivo better than other conventional plasma-based tests. Although data from clinical trials are lacking, these tests are widely used in the setting of liver transplantation to manage major hemorrhage or to trigger blood transfusion. Even in this setting, the threshold values of ROTEM/TEG parameters for triggering transfusion of hemostatic agents (such as fresh frozen plasma), remains to be determined [27], even though in a randomized study significantly fewer units of fresh frozen plasma (FFP) or blood were needed at the time of liver transplantation in patients monitored by TEG [28]. These promising results warrant larger confirmatory studies.

Statement. ***The use of algorithms based on thromboelastometry/thromboelastography (ROTEM/TEG) may facilitate targeted transfusions with hemostatic agents, such as fresh frozen plasma, in patients undergoing liver transplantation or in those with severe bleeding (C2). However, the threshold values of these tests to target transfusion requirement need to be established in appropriate clinical trials.***

3.5. Thrombin generation assays

Thrombin generation assays (TGA) assess the time course of thrombin generation and its decay when plasma is triggered by small amounts of tissue factor and phospholipids. Because of their design, TGA approximate the in vivo coagulation balance better than conventional coagulation tests (PT/activated partial thromboplastin time [APTT]). When evaluated by TGA, patients with cirrhosis have the potential to generate as much thrombin as healthy subjects after thrombomodulin addition [1,4]. Patients with cirrhosis and relatively high levels of thrombin generation present with a hypercoagulable state in vitro [29] and may be at risk of thrombotic events. By the same token, patients with relatively low levels may be at increased hemorrhagic risk. However, clinical trials are warranted to test this hypothesis.

Statement. ***Thrombin generation assays are promising laboratory tools which may help stratify patients with cirrhosis at risk for hemorrhage or thrombosis (C2). Before their implementation in clinical practice is recommended effectiveness should be tested in clinical trials.***

3.6. Fibrinolysis

Under physiological conditions, plasminogen-to-plasmin conversion is regulated by profibrinolytic drivers [i.e., tissue plasminogen activator [t-PA], urokinase plasminogen activator and activated factor XII]. These effects are opposed by antifibrinolytic drivers (i.e., t-PA inhibitors (PAI-1), plasmin inhibitor (PI) and thrombin-activable fibrinolysis inhibitor (TAFI)]. Perturbations of this balance