Fibrinogen: A Clinical Update on Liver Transplantation

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ABSTRACT

Introduction. Hemostatic and coagulation disorders related to severe liver disease may cause massive bleeding beyond what can be expected from surgical trauma in liver transplantation. Fluid resuscitation and fibrinolysis may aggravate the problem, as plasma fibrinogen decreases in all patients. The objective of this review was to update the criteria for fibrinogen replacement in liver transplantation.

Methods. A PubMed and Scopus search from 1990 to 2015 was made. The following key words were used: fibrinogen, liver transplantation, coagulation, and blood product replacement. Controlled trials and observational studies were selected on the basis of clinical relevance.

Results. There is a scarcity of published controlled studies on perioperative fibrinogen replacement. Most articles refer to expert opinion; therefore, criteria for the administration of fibrinogen have been empirically established. The response to cryoprecipitate or fibrinogen concentrate administration in liver transplantation has not been established. Viscoelastic platelets free tests have been reported to have a good correlation with Clauss-measured plasma fibrinogen concentration. In surgical patients, the median increase in fibrinogen plasma level per gram injected has been determined in 0.2375 g/L. Alternatively, fibrinogen replacement can be guided based on viscoelastic hemostatic assays.

Conclusions. In liver transplantation, plasma fibrinogen levels are low in most patients during surgery. Fibrinogen administration to correct hypofibrinogenemia has a positive impact on surgical bleeding. However, there is a scarcity of literature about fibrinogen administration; therefore, administration should be adjusted to replace plasma fibrinogen levels in the range of normal and guided by thromboelastometry.

IN liver transplantation (LT) surgery, disease transfusion of red blood cells occurs in 20% to 86% of LT [1]. Risk of bleeding and transfusion in LT are determined by the preoperative hemoglobin value, the severity of liver disease expressed by the MELD score, donor characteristics, surgical technique, and anti fibrinolytic therapy [1].

After injury as occurs in LT, arteries constrict. This facilitates the adhesion of platelets to the site of injury, where they can join the extravascular matrix to form a platelet clot, followed by a chain of activation to produce a "burst" of thrombin. In advanced cirrhosis, thrombin generation is preserved in spite of low levels of hemostatic proteins [2]. As a result of thrombin action, large amounts of fibrinogen are captured by the platelet glycoprotein IIb-IIIa receptor and converted to fibrin, which is polymerized by thrombin-activated FXIII and simultaneously cross-linked by 2-antiplasmin to stabilize the thrombus [3]. Fibrinogen (coagulation factor I) is a plasma-soluble protein synthesized in the liver that decreases during the surgical procedure. The interaction between thrombin and fibrinogen affects both the thickness and the fibrinolytic resistance of fibrin fibers. The speed of these reactions is dependent on plasma

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0041-1345/15
http://dx.doi.org/10.1016/j.transproceed.2015.10.025

fibrinogen concentration. Failure of fibrin polymerization caused by a low level of fibrinogen facilitates the release of thrombin and factor X from the local thrombus to systemic circulation, promoting the factor consumption and surgical bleeding [4].

During hepatectomy and the anhepatic phase, coagulopathy is the result of decreasing clotting factors, caused by surgical bleeding, which is facilitated by the administration of high volumes of crystalloid, colloid, or blood products. In addition, platelets and clotting factors can be affected by acidosis, hypocalcemia, and hypothermia, as well as the fibrinolytic enzymes released from damaged cells, all of which can lead to increased fibrinolysis of already-formed blood clots. Preservation of vena cava (piggyback technique) helps to reduce bleeding during LT, possibly because it improves physiologic parameters: body temperature, cardiac output and tissue perfusion, gas exchange, acid–base status, and fluid–electrolyte balance [5]. At the time of graft reperfusion, further deterioration occurs and is characterized by global reduction of all coagulation factors, a decrease in antithrombotic factors (antithrombin III, protein C), a decrease of plasminogen activator inhibitor factors and other natural antifibrinolytics (α2 antiplasmin), and the simultaneous generation of tissue plasminogen activator. All can be accentuated if hemodynamic disturbances occur, with an enlargement of the clotting process, leading to massive bleeding [6]. In these cases, a flat line on heparinase thromboelastography (TEG) or thromboelastometry (Rotem) is found, which may indicate severe fibrinolysis as well as a heparin effect [7]. These circumstances require intensive treatment based on blood component administration (packed red cells, plasma, fibrinogen, and platelets), and antifibrinolytic drug therapy. The objective of this review was to update the criteria for fibrinogen replacement in LT.

METHODS

A Pubmed and Scopus search from 1990 to 2015 period was performed. The following key words were used: fibrinogen, liver transplantation, coagulation, and blood product replacement. Controlled trial and observational studies were selected on the basis of clinical relevance.

RESULTS

Correlation of Plasma Fibrinogen Levels and Clotting Tests and Bleeding During LT

Early detection of coagulopathy is crucial in preventing exacerbation of bleeding and the vicious cycle of coagulopathy during LT. Conventional coagulation tests: prothrombin time (PT), and partial thromboplastin time (PTT) do not provide information about the quality of the clot or the dynamics of its formation. The platelet count and plasma fibrinogen level indicate substrate exposed. Point-of-care monitoring based on thromboelastography or thromboelastrometry, which evaluates the viscoelasticity of whole blood and permits the assessment of the entire clotting process from clot initiation and formation to clot stability, may be used for decision-making because the risk of bleeding and thrombosis may coexist during LT surgery and when empirical treatments are applied [8]. In the cirrhotic patient, a Rotem pattern may be characterized by a decrease in maximum clot firmness (MCF) and an enlargement in clotting time (CT) and in clot formation time, with an acceptable correlation between MCF with fibrinogen and platelets but a weak correlation between the clotting time and PT [9]. During the surgical procedure, correlation between MCF with fibrinogen and platelets is maintained; on the contrary, correlation of PT and viscoelastic parameters is inconsistent [10].

At the time of a graft reperfusion, depending on quality and hemodynamic disturbances, further deterioration of coagulation occurs and is characterized by a global reduction of all factors and marked fibrinolysis. In terms of TEG pattern, an enlargement of clotting process and fibrinolysis and even a flat line can occur in nearly 30% of patients [7]. MCF is highly influenced by fibrinogen levels and platelet count [11]. To eliminate the contribution of platelets to clot strength, a glycoprotein-IIb/IIIa inhibitor is included in the lyophilized TEG functional fibrinogen test, whereas cytochalasin D is used in the Rotem–Fib-tem test. MCF in the presence of cytochalasin D (Fib-tem) correlates well with fibrinogen levels [12]. Other investigators have focused on the evaluation of both platelets and fibrinogen. The A10 of Ex-tem was shown to be rapid and valuable in predicting coagulation status, and also useful in assessing the need for perioperative transfusion of platelets and fibrinogen [13]. In a retrospective study in LT, the bias between A5 Fib-tem and MCF Fib-tem was quantified in 1.3 mm in patients with hypofibrinogenemia [14].

Even if a platelet-free test of TEG or Rotem has been reported to have a good correlation with Clauss-measured plasma fibrinogen concentration, the absolute values of MCF differ between the 2 tests, probably related to different degrees of platelet inhibition [15]. In surgical patients, the fibrinogen level may be overestimated when assessed using TEG [16]. Despite these limitations, in a series of LTs, cutoff values that best predicted the transfusion threshold for platelets and fibrinogen were A10 Rotem-Ex-tem of 35 mm and A10 Fib-tem of 8 mm [17]. In a large cohort of surgical patients, mainly LTs, the low values of clot firmness can identify patients with very early fibrinolysis [18].

Fibrinogen Replacement in LT

Normal plasma fibrinogen values are in the range of 2 to 4 g/L. The plasma fibrinogen concentration is influenced by the measurement method. A quantitative method relying on immunological binding of fibrinogen-antigen (the Clauss method) overestimates the value of fibrinogen, with greater interference with artificial colloid solutions [19]. Hypofibrinogenemia (fibrinogen $<$100 mg/dL), due to decreased synthesis, and dysfibrinogenemia are commonly found in candidates for LT [20,21]. In addition, fluid resuscitation and surgical bleeding in LT may result in extensive hemodilution