Monitoring and Treatment of Coagulation Disorders in End-Stage Liver Disease

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Hemostasis in Cirrhosis

Hemostasis is a very complex system which is based on the interaction of platelets, endothelial cells, and plasmatic coagulation factors as well as their inhibition loops [1, 2]. Hemostasis can be stratified into primary and secondary hemostasis [3]. Under physiologic conditions, endothelium and platelets are negatively charged and repulse each other. As soon as a vessel wall is damaged, subendothelium, which is positively charged, attracts the negatively...
PT assay was developed for the follow-up of patients therapeutically anticoagulated with oral vitamin K antagonists [10]. This test is performed by using a blood sample which is centrifuged, with the plasma being subsequently removed. The time between the addition of TF and calcium and the occurrence of fibrin leafs (start of coagulation) is measured. The main drawback of this coagulation assessment is that only the procoagulant but not the anticoagulant activity is being measured, as in the case of protein C and S activity [4]. Thus, the interaction between procoagulant (factors II, VII, IX, X) and anticoagulant hemostatic components (protein C and S) and platelets cannot be assessed with this standard laboratory analysis. In liver cirrhosis, both pro- and anticoagulants are decreased. An increased international normalized ratio (INR) suggests a higher risk of bleeding, although the anticoagulants are also decreased, thus forming a new hemostatic balance. Many studies indicated that SLT do not reflect the actual risk of bleeding [11–14]. Ewe et al. [12] conducted a very interesting study more than 30 years ago. They evaluated the correlation between PT and spontaneous bleeding time in cirrhotic patients undergoing a laparoscopic liver biopsy. Their data clearly demonstrated that there was no correlation between actual liver bleeding time and PT. Around 40% of the patients with a PT of 100% experienced a prolonged bleeding, while patients with a PT of 15–20% had a normal liver bleeding time. Tripodi et al. [7] conducted another cornerstone study in which they demonstrated that both parts of the coagulation system, i.e. pro- and anticoagulants, showed the same level of decreased activity. These data are in line with the study of Lisman et al. [15] who measured a normal ETP during liver transplant procedure when compared to ETP in healthy controls, despite prolonged conventional coagulation tests in liver transplant patients.

A recent meta-analysis evaluated the value of SLT in terms of bleeding risk [16]. The authors analyzed more than 1,100 publications and retrieved 53 publications as well as 11 guidelines addressing this topic. They found only 3 prospective trials with altogether 108 patients, and none of these studies was a prospective randomized trial. The authors concluded that there is no scientifically based proof that SLT provide reliable data for predicting bleeding during invasive procedures.

**Viscoelastic Tests (Thrombelastography/ROTEM)**

Currently, two main viscoelastic tests (VETs) are being clinically used. One is thrombelastography (TEG™; Haemonetics, Niles, IL, USA), which was developed by the German physician Hartert in 1948 [17]. The other one is thrombelastometry (TEM) (ROTEM™ Delta; TEM International GmbH, Munich, Germany), being a technical modification of TEG. In the following, we will only briefly describe the two methods, as it is beyond the scope of this article to analyze them in detail.

The advantage of both methods is based on clot assessment in whole blood, thus taking into consideration the interaction of the pro- and anticoagulants, as well as the importance of platelets [4]. Both VET methods provide a graphic presentation of the clot for-
Fig. 1. On the left side, the ROTEM device is depicted. The coagulation assessment is performed in the whole blood in which an oscillating (4.75°) pin is submerged. A mirror which reflects a beam of the light is mounted on the upper part of the pin. The reflected light is processed by a computer and a graphic according to the coagulation status is printed. When there is no coagulation (the pin can oscillate freely), there is a flat line. When clot formation occurs, the oscillation is impaired and the shape of the graphic changes, i.e. the higher the amplitude of the graph, the higher the clot strength.

**Thrombelastography**

For clot assessment the blood is placed in a cup and a pin is submerged in the blood. It is then activated by kaolin, and the cup starts to rotate. Initially, since there is no clot formation, the cup rotates freely. As the clot formation develops, the resistance to the cup rotation increases and the dynamics of this increase in resistance is being recorded.

Kang et al. [18] evaluated the blood coagulation system of 66 consecutive patients undergoing liver transplantation by means of TEG or SLT monitoring and assessed the first clinical use of TEG in liver transplantation. The use of TEG contributed to a 33% reduction of red blood cells (RBC), fresh frozen plasma (FFP), and platelet transfusion, whereas blood loss was comparable in all patients. Despite these very encouraging results, physicians are very reluctant to use VETs in liver transplantation.

**Thrombelastometry-ROTEM Delta**

TEM consists of 4 analytic channels. They are activated with 4 different substrates. Within these 4 channels, one is able to diagnose whether a patient requires platelets, fibrinogen concentrate, prothrombin complex (PCC), or antifibrinolytic treatment (e.g. tranexamic acid (TXA)) (fig. 1, 2; table 1).

Several studies indicated that TEM can be used to guide coagulation management in liver transplantation. The study conducted by Blasi et al. [19] indicated that when the amplitude (clot strength) is greater than 35 mm after 10 min (A10 (EXTEM)), the patients are unlikely to bleed to a degree that would require transfusion. Two other studies [20, 21] illustrated that the amplitude after 10 min and even after 5 min shows an excellent correlation with maximum clot firmness (MCF), which enables the physician to reach an
adequate treatment decision within 7–12 min. Another study indicated significantly lower transfusion requirements if the coagulation management was performed based on the analysis of coagulation factors and TEM. Using these tests reduced the transfusion requirement to a median of 2, 0, and 0 units for RBC, FFP, and platelets, respectively. Almost 40% of transplantations were performed without any kind of blood product, 85.3% without FFP, and 71.4% without platelets.

Depending on the new coagulation model [3], thrombin generation is a physiological process which consists of three stages: initiation, propagation, and amplification. Following a burst of thrombin activation, fibrin is being produced from fibrinogen to build a clot which will be strengthened by factor XIII.

SLT assess only the initial 10% of thrombin generation whereas VETs will assess the whole clot formation, including the first 10%, the clot strength, and fibrinolysis (fig. 3).

However, the whole coagulation process (initiation, propagation, and amplification) is followed by VETs.

### Bleeding Management in Patients with End-Stage Liver Disease Undergoing Invasive Procedures

During the process of bleeding management it is important not only to control the bleeding but also to prevent the development of thrombosis.

### Coagulation Management in Patients with Cirrhosis Scheduled for Invasive Procedure

The traditional approach for the management of the hemostatic system has consisted of proactive transfusion based on SLT values in order to try to prevent a bleeding complication [4]. However, based on the aforementioned studies which used VETs as a guiding parameter, the newly developed concept of balanced coagulation suggests that proactive coagulation treatment is not necessary unless excessive bleeding develops [1].

#### Table 1. Possible hemostatic disorder correlated with pathological ROTEM values

<table>
<thead>
<tr>
<th>Measurements</th>
<th>ROTEM</th>
<th>Hemostatic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clot initiation</td>
<td>CT in s</td>
<td>enzymatic coagulation factors, antiocoagulants, fibrin degradation products, tissue factor expression</td>
</tr>
<tr>
<td>Clot kinetics</td>
<td>CFT in s; α-angle in degrees</td>
<td>enzymatic coagulation factors, antiocoagulants, fibrinogen, platelets</td>
</tr>
<tr>
<td>Clot strength</td>
<td>A5/A10 in mm; MCF in mm</td>
<td>platelets, fibrinogen, factor XIII</td>
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<tr>
<td>Clot stability (lysis)</td>
<td>L160 in % of MCF; ML during run time in % of MCF</td>
<td>fibrinolytic enzymes, fibrinolysis inhibitors, factor XIII</td>
</tr>
</tbody>
</table>

CT = Clotting time; CFT = clot formation time; A5/A10 = amplitude 5/10 min after CT; MCF = maximum clot firmness; L160 = lysis index 60 min after CT; ML = maximum lysis.

#### Bleeding Management in End-Stage Liver Disease

According to the concept of a new rebalanced hemostasis, it includes a more conservative attitude towards transfusion of RBC, FFP, or platelets. Unnecessary transfusion of these blood components should be avoided since we do not have any scientific proof of a benefit associated with these SLT-guided transfusions [22]. Two major randomized controlled trial (RCT) studies in patients with end-stage liver disease (ESLD) explicitly demonstrate that the use of VETs can significantly reduce the amount of transfusion without an increase of bleeding events. Wang et al. [23] conducted an RCT study in which 28 patients were assigned to VET- versus SLT-guided hemostatic management. In patients monitored via TEG, significantly less FFP was transfused (mean: 12.8 vs. 21.5 units). Importantly, the 3-year survival in both groups did not differ.

De Pietri et al. [24] conducted an RCT in 60 patients with ESLD who were scheduled for various invasive surgical interventions (laparoscopy, liver biopsy, liver resection). The patients were randomly assigned to VET and SLT groups in a ratio of 1:1. Coagulopathy was defined as INR ≥ 1.8 and platelet count ≤ 50/nl. These values acted as a trigger for FFP or platelet transfusion. TEG was used as a VET method. If the reaction time (i.e. time required from clot initiation to form 2 mm deviation, expressed in min, equals clotting time (CT) in ROTEM) was pathological, FFP were transfused to correct the hemostasis; if the maximum amplitude was...
≤ 40 mm, then platelets were transfused. In the control group, 100% of the patients received at least one of the blood components (RBC, FFP, and/or platelet), as compared to only 16% in the TEG group. Clinically significant bleeding episodes were more frequently observed in the SLT group; however, their number did not reach statistical significance.

Leon-Justel et al. [25] conducted a prospective trial in 200 liver transplantation patients. The first 100 patients were treated with an SLT-guided hemostatic management protocol while the other 100 patients received ROTEM-guided hemostatic management. The study results indicated a significant reduction of transfused RBC, FFP, and platelets in the ROTEM group. Moreover, the number of blood-product-free transfusions increased from 5 to 24% (p < 0.001), and secondary endpoints like reoperation for bleeding, acute kidney failure, or hemodynamic instability were significantly lower in the ROTEM group.

In a prospective study, Bedreli et al. [26] showed that compared with SLT-guided hemostasis treatment, ROTEM-guided coagulation management for minimally invasive procedures can reduce the use of coagulation factors without increasing bleeding complications, providing further support for VET-guided hemostatic management.

**Treatment of Thrombin Generation Impairment**

Thrombin generation is the basic step in clot formation. According to the classic model of the physiology of coagulation, the coagulation cascade is divided into extrinsic and intrinsic pathways. Both pathways lead to an activation of coagulation factor X. Following the activation of the factor X, a common pathway of activation of coagulation factors is initiated, leading to the conversion of prothrombin into thrombin. Thrombin activates the fibrinopeptids A and B which break down fibrinogen into fibrin which in turn forms a fibrin net. This fibrin net is then stabilized by factor XIII. The new model of coagulation system functioning presumes that the coagulation system consists of three phases: initiation, propagation, and amplification [3]. At the end of the amplification phase, a thrombin burst occurs, which induces formation of the fibrin net and cross-linking with factor XIII to enhance the clot strength. The activation of coagulation depends on the factors II, V, VII, IX, and X. Deficiency of these factors is detected as a propagation/major parameters (CT, MCF) obtained from these two ROTEM channels give us information whether the patient requires treatment/major parameters (CT, MCF) obtained from these two ROTEM channels give us information whether the patient requires treatment.

Two alternatives for the treatment of an impaired thrombin generation are available, namely the administration of FFP or of PCC. There are two special requirements for a drug, i.e. efficacy and safety. Abdel-Wahab et al. [28] evaluated the efficacy of FFP in critically ill patients with moderate coagulopathy (1.1 ≤ INR ≤ 1.85). The authors calculated an INR decrease which correlated with the number of transfused FFP. Transfusion of FFP resulted in normalization of PT-INR values in only 0.8% of the patients. Even transfusion of 4 units of FFP and more did not improve hemostasis. Sarani et al. [29] evaluated the safety of FFP transfusion in critically ill patients. Nosocomial infections occurred three times more often in patients who received FFP transfusions. In this multivariate analysis, the infection rate per transfused FFP unit was 1.039.

Stanworth et al. [30] conducted a multicenter coagulopathy study in which they analyzed the utilization of FFP in intensive care unit patients. There was a wide range of futile FFP transfusion. Based on their results, the authors concluded that in a high number of patients who received FFP a beneficial effect could not be seen. In this context, a study is of interest in which 4-factor PCC (4-F-PCC) was administered to successfully control acute bleeding in patients following/during surgery [31]. The authors administered a dose of 25 IU/kg body weight (BW) when CT EXTEM was greater than 75 s and of 40 IU/kg BW when CT EXTEM was greater than 100 s. No major side effects or complications were reported. The used 4-F-PCC preparations (BeriplexTM; CSL Behring, Marburg, Germany, or OctaplexTM; Octapharma, Lachen, Switzerland) contain vitamin K-dependent procoagulants (factor II, VII, IX, and X) as well as vitamin K-dependent anticoagulants (protein C and S) and are considered to be safe regarding the risk of thrombosis [32]. The first publication reporting the use of 4-F-PCC in ESLD dates back to 1994 [33]. Initially, 4-F-PCC was applied together with antithrombin 3 (AT III) to minimize the risk of thrombosis. However, if PCC is only being used in bleeding patients and the usage is guided by TEG and with high concentration of protein C and S in the vials, the use of AT III might not be necessary. In our opinion, PCC administration should be guided by TEG to avoid overtreatment and thrombosis. A recent case-control study in 256 liver transplant patients indicated that the use of coagulation factors, including 4-F-PCC, did not increase the rate of thrombotic events compared with patients receiving no coagulation factors [31].

**Management of Clot Firmness Impairment**

Clot firmness depends on the interaction of fibrinogen and platelets. Fibrinogen is the most important coagulation factor. More than 90% of the coagulation factors are mapped from fibrinogen, which is the only coagulation factor to be kept within a normal range to build a stable clot. The interaction between platelets and fibrinogen should be thought of as a brick wall, whereas the bricks are supposed to be the platelets and the fibrinogen is the cement which keeps the bricks together [34]. The most valuable diagnostic method for clot firmness assessment is ROTEM. The MCF in the EXTEM channel provides the best information about the interaction of platelets and fibrinogen. The FIBTEM channel offers information on the sole fibrinogen contribution to the whole clot formation. The values/graphic presentation/major parameters (CT, MCF) obtained from these two ROTEM channels give us information whether the patient requires fibrinogen and/or platelets [35]. In case of excessive bleeding and low MCF in EXTEM and FIBTEM, fibrinogen should be applied; if MCF in FIBTEM is within the normal range, then platelets should be replaced.

A recent study from our group indicated that an MCF ≥ 40 mm in EXTEM and an MCF ≥ 9 mm in FIBTEM are safe margins to avoid bleeding in liver transplantation [31].
There are some recent studies which showed that already after 10 or even 5 min, an MCF value can be used to decide about administering fibrinogen or platelets. Görlinger et al. [21] showed that early values of clot firmness in EXTEM and FIBTEM (after 5, 10, and 15 min) allow for a fast and reliable prediction of ROTEM MCF in non-cardiac surgery patients. Song et al. [20] reported that in liver transplant patients, ROTEM parameters are sufficient to assess the requirement of platelet transfusion and/or hypofibrinogenemia as soon as 5 min after starting the test. Blasi et al. [19] showed in their study that the clot formation amplitude after 10 min in EXTEM (A10 (EXTEM)) is a specific and reliable parameter for coagulation management. Patients with A10 (EXTEM) > 35 mm – with A10 indicating the clot amplitude 10 min after the end of CT – are unlikely to suffer from excessive bleeding caused by a disruption of hemostasis.

Detection and Management of Fibrinolysis

The gold standard for the assessment of fibrinolysis are VETs [36]. Figure 4 presents fibrinolysis as detected by the ROTEM method. In the EXTEM, INTEM, and FIBTEM, graphic presentation of clot stability depicts fibrinolysis (after reaching the maximum amplitude the clot breaks down and, consequently, the am-
plitude on the graph is smaller). The ratio (MCF-Amplitude At time-point of maximum lys) 𝑀/𝑀𝐶Ｆ expressed as %) is called maximum lysis (ML). Excessive fibrinolysis is assumed when ML is ≥ 15%.

Hyperfibrinolysis in liver transplantation has been reported to occur very frequently (range 5–84%), mainly during reperfusion of the transplanted liver [37, 38]. However, most of the fibrinolysis is self-limiting and should only be treated when it occurs concomitantly with excessive bleeding [38]. The most commonly used anti-fibrinolytic drug is TXA. When fibrinolysis in combination with excessive bleeding occurs, TXA (30 mg/kg) should be administered, and ROTEM control should be performed 30 min after the administration of TXA.

**Conclusion**

Hemostasis in ESLD is a very complex system in a new rebalanced homeostasis. If patients do not bleed acutely, prophylactic coagulation management should be avoided, especially since available data indicate a higher risk of thrombosis in cirrhotic patients as compared to the normal population.

Coagulation management should be based on VET analysis because this kind of coagulation analysis reflects coagulation dynamics better, enables a faster reaction to an imbalance in the coagulation system, and is the gold standard for detecting fibrinolysis.

Based on the current data, hepatic coagulopathy should be managed with coagulation factors rather than with FFP, as they are more effective and have fewer side effects in terms of potential infection and/or patient volume overload.

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