Perioperative thromboprophylaxis in liver transplant patients

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Abstract

Improvements in surgical and anesthetic procedures have increased patient survival after liver transplantation (LT). However, the perioperative period of LT can still be affected by several complications. Among these, thromboembolic complications (intracardiac thrombosis, pulmonary embolism, hepatic artery and portal vein thrombosis) are relatively common causes of increased morbidity and mortality. The benefit of thromboprophylaxis in general surgical patients has already been established, but it is not the standard of care in LT recipients. LT is associated with a high bleeding risk, as it is performed in a setting of already unstable hemostasis. For this reason, the role of routine perioperative prophylactic anticoagulation is usually restricted. However, recent data have shown that the bleeding tendency of cirrhotic patients is not an expression of an acquired bleeding disorder but rather of coexisting factors (portal hypertension, hypervolemia and infections). Furthermore, in cirrhotic patients, the new paradigm of "rebalanced hemostasis" can easily tip towards hypercoagulability because of the recently described enhanced thrombin generation, procoagulant changes in fibrin structure and platelet hyperreactivity. This new coagulation balance, along with improvements in surgical techniques and critical support, has led to a
dramatic reduction in transfusion requirements, and the intraoperative thromboembolic-favoring factors (venous stasis, vessels clamping, surgical injury) have increased the awareness of thrombogenic complications and led clinicians to reconsider the limited use of anticoagulants or antiplatelets in the postoperative period of LT.

Key words: Anticoagulation; Liver transplantation; Antiplatelets; Thrombosis; Coagulation; Heparin; Thromboelastography; Thromboprophylaxis; Hepatic artery thrombosis; Portal vein thrombosis

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Core tip: The improvements in surgical and anesthetic techniques during liver transplantation (LT) have led to such a reduction in transfusion requirements that bleeding risk is no longer the major concern. The increased knowledge of coagulation balance and the reported incidence of thrombotic complications (hepatic artery and portal vein thrombosis, intracardiac thrombosis, pulmonary embolism) in the LT setting have brought attention to perioperative thromboprophylaxis in an attempt to decrease the morbidity and mortality associated with these complications. The major concern of thromboprophylaxis is the risk of bleeding complications in a setting of already unstable hemostasis. Hence, monitoring its administration and the careful selection of the patients to be treated are of great importance.

INTRODUCTION

Cirrhosis has been traditionally conceived as a hypocoagulable condition, and bleeding is a feared complication of any invasive procedure. In patients with end-stage liver disease, significant coagulopathy (as defined by routine coagulation tests) has historically led clinicians to consider cirrhosis to be the prototype of acquired bleeding disorders, thus supporting the common practice of empirically transfusing patients with blood products or prohemostatic agents to correct standard laboratory test values to reduce the risk of bleeding[1,2]. In this review, we underline the concept of rebalanced hemostasis typical of cirrhotic patients (both in patients with cirrhosis and in patients with acute liver failure), as obtained by the parallel declines in pro- and antihemostatic drivers, resulting in a net hemostatic balance[3]. We also discuss the paradoxical pro-thrombotic tendency of cirrhotic patients. The new hemostatic balance, in fact, is thought to be much less stable compared with that of healthy patients and can easily tip it towards bleeding or thrombosis.

Prophylactic anticoagulation represents a routine practice to prevent thromboembolic complications [deep vein thrombosis (DVT) and pulmonary embolism (PE)] that can be potentially life-threatening in the postoperative course. Although the utility of thromboprophylaxis after general surgery has been established beyond doubt, in liver transplantation (LT), this opinion is not uniformly shared and does not represent a routine practice. LT is considered an operation with major bleeding risks. Transplanted livers may have delayed primary function, and coagulation does not improve immediately after transplantation, making hemorrhagic complications and transfusions not uncommon[4,5]. In contrast, although intraoperative thrombotic phenomena are uncommon, they are associated with an elevated mortality (ranging from 45% to 68% for PE and 50% for early hepatic artery thrombosis (HAT) and from 32% to 60% for portal vein thrombosis (PVT))[6-9].

Here, we reviewed the literature assessing thrombotic risks in cirrhotic patients and in the post-transplant period and evaluated whether empirical pharmacological thromboprophylaxis strategies and the use of global hemostasis assays may play a beneficial role in reducing this procedure-related thrombotic complications. We do not cover mechanical prophylaxis (intermittent pneumatic compression) because it must be considered and adopted in all abdominal surgery patients who are at a moderate or high risk for venous thromboembolism (VTE), who are, in turn, at a high risk for major bleeding complications[10].

NEW CONCEPT OF REBALANCED HEMOSTASIS AND THE UTILITY OF STANDARD LABORATORY TESTS

A marked reduction of both procoagulant factors (factors II, V, VII, IX, X, XI, XII), anticoagulant factors (anti-thrombin III, protein C, and protein S), an increase in von Willebrand factor (vWF) and a reduced level of ADAMTS13, a vWF-cleaving protease, are the specific features of cirrhosis and bring the patient to a new hemostatic balance[11]. vWF performs its hemostatic functions by binding to factor VIII and to constituents of connective tissue and by promoting platelet adhesion to endothelial surfaces and platelet aggregation under high shear stress[11].

Thrombocytopenia, as a consequence of hypersplenism in patients with portal hypertension, abnormal thrombopoietin metabolism, increased platelet destruction mediated by antiplatelet antibodies, and bone marrow suppression caused by alcohol, antiviral and immunosuppressive therapies, is another clinical feature of chronic liver disease[12]. Unless the platelet...
count is severely low (< 50 × 10^9/L), thrombocytopenia does not represent an increased bleeding risk. Such a low platelet count is usually sufficient to guarantee a normal thrombin generation, and the low number of platelets is compensated by a higher level of vWF, which is responsible for greater platelet adhesion[13,14]. Hyperfibrinolysis is another described feature of end-stage liver disease, but its role in the coagulopathy of cirrhosis is still debated[15].

Elevated tissue plasminogen activator and a deficiency of thrombin-activatable fibrinolysis inhibitor have been associated with laboratory changes typical of hyperfibrinolysis and an increased risk of bleeding[16]. However, cirrhosis has also been associated with reduced fibrinolysis, as shown by the decreased plasminogen and increased plasminogen activator inhibitor. The contrasting results explain the ongoing debate regarding the absence or presence of a hyperfibrinolytic state in patients with liver disease, even if the balance of fibrinolysis is probably restored by the parallel changes in profibrinolytic and antifibrinolytic drivers[17]. The decreased synthesis of both procoagulants and anticoagulants typical of cirrhosis usually restores a normal hemostatic balance (Table 1), which is so fragile that it can easily become unbalanced in a hemorrhagic or prothrombotic sense, depending on the presence of renal failure, infection, or upper gastrointestinal bleeding. The complexity of hemostatic balance in end-stage liver disease comes from the fact that a patient with cirrhosis and sepsis can be equally at risk for thrombosis, as a result of inflammation[18], and for bleeding, as a result of the release of anticoagulant endogenous heparinoids[19]. The new equilibrium described in stable patients with cirrhosis makes bleeding episodes related more to portal hypertension and hypervolemia than to defective hemostasis.

Despite this “balanced” hemostatic condition, cirrhosis results in the prolongation of standard coagulation tests, which usually do not analyze the complex interplay between pro- and anticoagulants and thus do not provide an accurate evaluation of the alteration in the in vivo hemostatic balance[11,20]. Prothrombin time (PT), activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) provide only a measure of procoagulant factors and are insensitive to the plasma levels of anticoagulant factors, so they are unreliable to depict the hemostatic status of patients with end-stage liver disease. The lack of reliability of standard plasma coagulation tests, as underlined in the Baveno VI guidelines[21], comes from the fact they are performed without thrombomodulin addition, which is the main protein C activator, and they only detect the first 5% of whole thrombin formation. The normal to increased thrombin generation shown by thrombomodulin-modified thrombin generation tests has further confirmed the unreliability of standard coagulation tests. Therefore, PT, aPTT and INR are untrustworthy in predicting bleeding risk or thrombotic risk and guiding perioperative hemostatic therapy[22]. Platelet number also poorly represents hemostatic capacity in cirrhotic patients, and thrombocytopenia is usually balanced by a marked increase in the plasma level of von Willebrand factor[13]. The defects in antifibrinolytic proteins balanced by decreased plasminogen[23], the decreased fibrinogen partially balanced by prothrombotic changes in the structure of the fibrin clot[24], and the increased factor VIII and reduced antithrombin and protein C constitute the basis for the recently recognized normo- or hypercoagulable state of cirrhosis, with a consequent risk of thromboembolic events.

**Table 1  Balance of antihemostatic and prohemostatic drivers in the cirrhotic patient**

| Anti-hemostatic drivers | Pro-hemostatic drivers |
|-------------------------|------------------------|
| Primary hemostasis      |                        |
| Abnormal platelet function | Elevated vWF |
| Thrombocytopenia        | Reduced ADAMTS 13     |
| Decreased production of thrombopoietin | Platelet hyperreactivity |
| Coagulation             |                        |
| Reduced synthesis of factors II, V, VII, IX, X, and XI | Reduced anticoagulant protein C, protein S, antithrombin III |
| Vitamin K deficiency    | Procoagulant changes in fibrin structure |
| Hypo-dysfibrinogennemia |                        |
| Fibrinolysis            |                        |
| Low α2-antiplasmin, factor XIII, and TAFI | Low plasminogen |
| Low fibrinogenemia      | High PAI               |
| t-PA                    |                        |
| Elevated tPA            |                        |
| ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. |

vWF: Von Willebrand factor; TAFI: Thrombin-activatable fibrinolysis inhibitor; t-PA: Tissue plasminogen activator; PAI: Plasminogen activator inhibitor; ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.
bleeding complications. In 2006, Northup et al[25] found that approximately 0.5% of all admissions involving cirrhosis patients resulted in a new thromboembolic event. Thus, despite the endogenous coagulopathy of cirrhosis, some patients experience venous thromboembolism, such as DVT or PE. Subsequent studies noted that liver cirrhosis per se represents a risk factor for VTE and that all the conditions that can favor any thrombotic complication are frequent in patients with end-stage liver disease. Platelet hyperreactivity, normal or enhanced thrombin generation, as shown by the thrombin generation test, endothelial dysfunction, hyperdynamic circulation, which can bring to circulation stasis, and the reduced mobility of the fragile cirrhotic patient are recognized prothrombotic conditions. Other authors have shown that this thrombophilia seems to worsen as the liver disease progresses, exposing the cirrhotic patients with more severe disease to a greater risk for VTE[26]. Hypoalbuminemia, as an expression of the severity of liver disease and the degree of portal hypertension, has been associated with an increased rate of VTE[27].

Recently, Ambrosino et al[28] conducted a systematic review and meta-analysis to evaluate the risk of VTE associated with cirrhosis, which was 3.7%. They confirmed a significantly increased VTE risk in 695012 cirrhotic patients compared with 1494660 non-cirrhotic controls (OR: 1.703; 95%CI: 1.333, 2.175; \( P < 0.0001 \)). In particular, patients with cirrhosis experienced an increased prevalence of DVT compared to non-cirrhotic subjects. In contrast, more heterogeneity among studies has been found for PE risk, even if it has been shown to be higher in the cirrhotic population.

PVT, which is rare in the general population but relatively frequent in patients with cirrhosis, is another typical feature of chronic liver disease. Its prevalence increases with the severity of liver disease, ranging from 0.6% to 26%[29]. While patients with compensated cirrhosis are rarely affected, PVT is frequently detected in advanced stages, increasing to 25% in LT candidates and to 35% in cirrhotic patients with hepatocellular carcinoma (HCC)[30]. The main risk factors for PVT are the same as those described for thromboembolic disease in general: hypercoagulability, endothelial lesions, reduced portal blood flow and, when HCC is present, the neoplastic invasion of the portal vein. Because of the high prevalence of this thrombotic complication and the possible repercussions on LT[31], the available data suggest that prophylactic PVT treatment may be indicated in cirrhotic patients awaiting LT or after hepatic resection, even if this medical practice has not yet been included in international guidelines due to a lack of randomized controlled trials[32,33]. According to the Baveno VI consensus, anticoagulation should be considered in potential LT candidates with thrombosis of the main portal trunk or progressive PVT, with the goal of facilitating LT and reducing post-transplant morbidity and mortality[21].

## THROMBOEMBOLIC EVENTS IN SURGICAL LIVER TRANSPLANT PATIENTS

Traditionally, perioperative bleeding complications, attributed to the endogenous coagulopathy and thrombocytopenia, represented the major concern during LT. In recent years, thanks to improvements in surgical techniques and anesthetic care, hemorrhagic complications have become less frequent, making transplants without intraoperative transfusion more common. The awareness of the new hemostatic balance that characterizes cirrhotic patients, together with the reduced bleeding complications during surgery, has redirected the attention to perioperative thrombotic complications, making surgeons and anesthetists more aware of the possibility of systemic venous or arterial thrombotic events. Recently, the idea of the occurrence of thrombotic complications associated with liver transplant as a consequence of an uncontrolled activation of coagulation rather than of surgical complications has become more common. Usually, thrombotic events associated with LT can be divided into systemic thrombotic complications and regional vascular events (i.e., hepatic artery, portal vein, hepatic vein thrombosis). The incidence of early HAT, which may result in graft loss if arterial flow is not restored in the first 24 h after its occurrence, is approximately 3%-5% in adult patients, and the PVT incidence is approximately 2% in LT, with a very high mortality rate, ranging from 65% to 75%[34,35]. Hepatic vein thrombosis is instead considered a technical complication in case of a size mismatch of the grafts and in twisting and split liver transplant (i.e., reconstruction of the middle hepatic vein in extended right splits or insufficient drainage of the anterolateral sector in full-right grafts). Such dangerous complications can have surgical causes (for HAT: Difficult and prolonged arterial reconstruction, kinking of the artery, prolonged surgical time, prolonged cold or warmed ischemia times, the use of an aortic jump graft[36]; for PVT: Prior PVT or splenectomy, small portal vein size, use of venous conduits, insufficient portal flow due to large collaterals or systemic shunts[37]). Nevertheless, there are increasing data suggesting that changes in the hemostatic system (genetic factors, end-stage renal disease, diabetes, and history of prior DVT/PE) as well as intra- and postoperative blood products transfusion (increased transfusions of cryoprecipitate or fresh-frozen plasma and factor VII) may contribute to the development of HAT[37,38]. Interestingly Stine et al[39] have recently showed that pre-transplant PVT is associated with increased risk of early graft loss from HAT suggesting that hypercoagulability, besides surgical factors, could be involved in the post-transplant HAT occurrence[39].
DVT is a rare post-transplant complication that has a reported incidence between 3.5% and 8.6% in recent series [40]. Intraoperative systemic thrombotic complications, which mainly occur as acute PE or intracardiac right atrial thrombosis, are other dangerous events described in the perioperative period whose incidence of approximately 1%-4% seems to be higher than that reported in other surgical operations [41,42]. VTE is a well-documented postoperative complication, and PE is the most common cause of preventable death in surgical patients. Several risk factors for the development of PE during LT have been suggested, including vascular clamping, veno-venous bypass, central venous catheters, anti-fibrinolytic drugs, tissue injury/ischemia, venous stasis and etiology of liver disease.

In recent years, it has been shown that the cirrhotic patients are in a new hemostatic balance that undergoes new changes during liver transplant. During this surgical procedure, vWF remains elevated [43], and its functional capacity increases during surgery, probably due to an enhanced release of vWF from the activated endothelial cells. In association with that finding, the plasminogen concentration of ADAMTS13-cleaving protease decreases during transplant, leading to an imbalance between vWF and ADAMTS13, which is possibly responsible for the thrombotic risk.

Thrombocytopenia, which is typical of end-stage liver disease and potentially worsened by hemodilution and consumption during liver transplant, is not associated with a reduction in platelet function [44]. The preserved platelet adhesion, together with an imbalanced vWF/ADAMTS13 ratio, could somehow explain the increased incidence of thrombotic complications in the liver transplant perioperative period [45].

For secondary hemostasis, in cirrhotic patients, the parallel decline in pro- and anticoagulation proteins leads to a new balance characterized by normal thrombin generation. In the perioperative liver transplant period, the reduction of protein C, protein S, antithrombin III, and heparin cofactor II and the persistent increase in factor VIII lead to increased thrombin generation and to a hypercoagulable status [46]. During surgical procedures, the fibrinolytic system, which is normally in equilibrium in cirrhotic patients, can move temporarily towards hyperfibrinolysis in the anhepatic phase and after reperfusion [46]. However, at the end of surgery, a hypofibrinolytic condition, related to a massive increase in plasminogen activator inhibitor type 1 (PAI-1), develops and usually lasts up to 5 d after surgery [47]. Even if the reduction in the fibrinolytic activity can justify the occurrence of some thrombotic complication, such a causal relation has not been demonstrated by scientific works. The recent clinical literature seems to underline the role of the perioperative hypercoagulable status in the genesis of thrombotic complications such as HAT, PVT and other systemic thrombotic events.

Although perioperative bleeding complications occur more often than thrombotic ones, postoperative thromboses are associated with high morbidity and, in some cases, with mortality. Independent of the real origin of the prothrombotic status observed in cirrhotic patients who undergo LT, more efforts on the prevention of such complications by means of different prophylactic antithrombotic therapies are necessary. A prophylactic antithrombotic treatment to prevent these complications may be clinically relevant, and because of the fear of bleeding complications in the postoperative period, it could be useful to have an instrument that can reflect the coagulation status of the transplanted patient better than the routine laboratory tests can, which have been unreliable in reflecting the in vivo physiology.

### HEMOSTATIC STATUS IN THE TRANSPLANTED PATIENT AND DIAGNOSTIC TOOLS

**Standard coagulation tests**

Standard coagulation tests have long been the standard laboratory indicators of patients’ coagulation status. According to the cell-based model of hemostasis, these tests do not account for the important interactions between platelets, clotting factors, and other cellular components in the generation of thrombin or for the balance between coagulation and fibrinolysis. Furthermore, PT and PTT give only one piece of information, i.e., whether the thrombin generation has started, but they give no information of what occurs afterwards.

**Viscoelastic tests**

Because of the limits of conventional coagulation tests in recognizing significant coagulopathies or guiding transfusion, in recent years the viscoelastic tests has gained increasing importance. Viscoelastic tests give an "in vitro“ picture of the growth of the clot and a measure of its stability until its physiological or pathological lysis. These viscoelastic coagulation tests performed beside, including ROTEM® and TEG®, produce faster and more reliable results than conventional tests do. These two commercial devices function by slightly different mechanisms. The thromboelastometer (ROTEM-analyzer, TEM International, Munich, Germany) uses a fixed cup with a pin that rotates, while the thrombelastograph (TEG-analyzer, Haemonetics Corp., Braintree, MA, United States) uses a fixed pin and a rotating cup [48,49].

TEG and rotational ROTEM are technologies that were previously applied in different surgical fields and are now applied to cirrhosis physiology. A more dynamic and targeted approach to the overall hemostatic process is at the basis of their success. They provide visual information on the coagulation process in terms...
of maximal fibrin clot formation, fibrinolysis and tendency to hypercoagulability. These characteristics make these tests ideal for a rapid diagnosis of the type of coagulopathy and for an appropriate (and rational) choice of the therapeutic option in different fields, such as trauma care, cardiac surgery and LT. Several studies have evaluated the effect of using TEG and ROTEM during LT on perioperative blood product transfusions, suggesting that a transfusion algorithm based on viscoelastic tests leads to reduced transfusions, but no survival benefit has been observed to date.

Actually, recent studies have noted that bleeding is no more the unique feared risk in liver cirrhosis. In the setting of liver surgery, several risk factors in addition to those previously described (vascular clamping, veno-venous bypass, central venous catheters, anti-fibrinolytic drugs, tissue injury/ischemia, venous stasis, etiology of liver disease, endothelial damages, ischemia time and vWF/ADAMT13 ratio imbalance) can increase the probability of thrombotic complications.

End-stage liver disease per se is a risk factor for VTE, and liver transplant surgery can improve the thrombotic condition. When dealing with cirrhotic patients, a test that could give information on hemorrhagic risk and the presence of normal clot stability or on the tendency to hypercoagulability would offer physicians an indication for prophylactic treatment without creating too much fear of the bleeding complications often associated with liver transplant. In the setting of liver disease and liver surgery, conventional coagulation tests give no or wrong information about hemostatic conditions, indicating hypocoagulability; in contrast, global viscoelastic tests show an enhanced hemostatic capacity or hypercoagulability.

TEG and ROTEM are seemingly superior tests of coagulation function in cirrhotic patients undergoing LT compared with traditional measures, but their capacity to recognize hypercoagulation status has yet to be demonstrated beyond much doubt.

In surgical settings, the study by Hincker and colleagues showed the encouraging results that ROTEM can predict thrombotic complications after major non-cardiac surgery. Similarly, Kashuk and colleagues demonstrated that the presence of hypercoagulability identified by r-TEG is predictive of thromboembolic events in surgical patients. When comparing TEG to INR in living-donor LT, TEG has been a useful tool to monitor for hypercoagulability in the perioperative period among liver donors, detecting a hypercoagulable state in some patients in spite of an elevated PT-INR.

Mallet et al. reported that several of the 124 liver recipients with end-stage liver disease presented with or developed a hypercoagulable thromboelastogram during liver transplant. Nevertheless, the 6 patients who developed early HAT had some TEG signs of hypercoagulability (increased cloth strength, high G, or shortened reaction time), though it was not clear what kind of influence these alterations could have on thrombotic complication. The authors also showed that standard laboratory tests did not succeed in diagnosing any signs of hypercoagulability. Although hypercoagulability on a viscoelastic device can be associated with an increased risk of thromboembolic events in different surgical fields, trauma setting and critical care, the same association in cirrhotic patients seems more difficult to demonstrate. In these patients, the definition of hypercoagulability based on viscoelastic parameters is not unique, and it has included a shortening of reaction time (R time), an increase in maximal amplitude (MA), an increase in net clot strength (G), or a combination of these parameters. However, emerging evidence suggests that hypercoagulability detected by ROTEM or TEG can increase the probability of venous or arterial thrombotic complications in certain patients, such as those who undergo liver transplant. Lerner et al., in a review of 27 case reports of thromboembolic events during LT, showed that TEG profiles were hypercoagulable in more than 70% of cases. The study by Zanetto and colleagues showed that in cirrhotic patients with hepatocellular carcinoma, thromboelastometry could detect hypercoagulability, as identified by the presence of a shorter clotting time and higher maximum clot firmness, which was associated with PVT presence. In particular, an increased baseline MCF FIBTEM (> 25 mm) was associated with a 5-fold higher risk of developing PVT in cirrhotic Child A patients. Recently, Zahr and colleagues analyzed the native procoagulant state of 828 LT recipients by using pre-transplant thromboelastographic data to identify risk factors for early HAT and found that the MA value was significantly higher in patients diagnosed with early HAT compared with those who were not. Specifically, an MA value on preoperative TEG of 65 mm or greater was recorded in a total of 7% of patients who went on to develop early HAT (hazard ratio = 5.28; 95% CI: 2.10-12.29; P < 0.001), whereas only 1.2% of patients with an MA less than 65 mm experienced this complication. The authors concluded that preoperative TEG may reliably identify group of recipients at greater risk of developing early HAT. The use of viscoelastic tests in detecting any hypercoagulability condition during liver transplant seems helpful in better managing blood product transfusion or, hypothetically, prophylactic therapy, but it remains unclear whether these tests during the course of the surgery would be of additional outcome benefit, and several doubts remain about the reliability of their measures. Compared with the thrombin generation test (TGT), ROTEM and TEG may not be appropriate for hemostasis assessment in patients with liver cirrhosis, and it could lead to the unnecessary transfusion of fresh-frozen plasma or to the wrong administration of a thromboprophylactic drug. Even though Blasi et al.
reported that "parameters from the first derivative of the ROTEM are similar to the thrombin generation assay, which is considered the gold standard marker of hyper/hypocoagulability", several papers underline the lack of correlation between the ROTEM and TGT results. Lentschener and colleagues showed that while thromboelastometry detected a hypocoagulable profile in decompensated cirrhotic patients, TGT showed a normal to increased thrombin generation, suggesting a preserved hemostasis and/or a procoagulant state\[^{62}\].

In addition to the non-uniformity of results between thromboelastography and TGT, non-uniformity has been recorded within an individual test (ROTEM or TEG). Some of the discrepancies can be partially explained by the differences in test methods, the activators used and the lack of viscoelastic test reference ranges for cirrhotic patients. The current habit to define hypo- or hypercoagulability by referring to reference ranges obtained from healthy individuals may not provide a reliable estimation of the coagulation status and bleeding risks of cirrhotics\[^{63}\]. Other limitations of the use of ROTEM and TEG need to be considered when analyzing the information they give. Platelet dysfunction, either drug-induced or inherited, is not detected. These devices are insensitive to the effects of vWF and factor XII\[^{64,65}\], and they lack activation of the anticoagulant protein C system. Other shortcomings of TEG and ROTEM are the lack of adequate standardization, low reproducibility of the results and sensitivity to preanalytic variables\[^{66,67}\].

**Thrombin generation test**

TGT is a promising laboratory tool for investigating hemorrhagic coagulopathies, predicting the risk of recurrent VTE after a first event, and monitoring patients on parenteral or oral anticoagulants\[^{68}\]. In contrast to TEG and ROTEM, TGT can be performed with or without thrombomodulin, thus allowing us to analyze the natural anticoagulant protein C pathway. Furthermore, TGT offers more information on the hemostatic capacity in total because in contrast to viscoelastic tests, it assesses not only fibrin formation but the generation of thrombin, which does not stop when the fibrin clot has been generated\[^{69}\]. For this reason, TGT best mimics the *in vivo* balance of pro- and anticoagulant proteins in plasma and the dynamics of thrombin generated *in vivo*\[^{70}\].

TGT measures specific parameters such as the lag-time (time to start), the time to peak, the peak height, and the endogenous thrombin potential\[^{69}\], so when used to analyze cirrhotic patients, it has shown a preserved or even increased thrombin generation, indicating a normal or even increased coagulation capacity, while ROTEM, performed in the absence of thrombomodulin, has shown hypoocoagulation in proportion to the level of liver impairment\[^{62}\].

Although TGT seems to better describe the interactions between pro- and anticoagulant factors in the hemostatic process of patients with end-stage liver disease, this test is performed in platelet-poor plasma and/or platelet-rich plasma, which requires time to prepare and makes this method unsuitable for quick diagnosis and therefore impractical in a routine clinical setting.

Similar to TEG and ROTEM, this assay is not sufficiently standardized for broad clinical use, and the large variance of the preanalytic variables and the lack of standardized reference ranges prevent its routine clinical use\[^{68}\]. Thrombin generation assays, although they are not readily available today, could provide a more effective tool for assessing the hemostatic system in patients with cirrhosis, but until further studies are performed, viscoelastic tests could be helpful for the clinical conditions associated with increased thrombotic risks by avoiding the overcorrection of the coagulation defects detected.

**ROLE OF THROMBOPROPHYLAXIS**

**Review methodology**

A systematic literature search was performed independently by two of the authors (LDP and RM) using PubMed, and the Cochrane Library Central. The search was limited to humans and articles reported in the English language. No restriction was set regarding the type of publication, date or publication status. Participants of adult age and any sex who underwent living transplantation or living donor liver transplantation procedures were considered. The search strategy was based on different combinations of words for each database. For the PubMed database, the following combination was used: ("liver transplantation" OR "liver transplant" OR "hepatic transplantation" OR "hepatic transplant") AND ("thromboprophylaxis" OR "anticoagulation" OR "antiplatelets" OR "antithrombotic therapy" OR "antithrombotic prophylaxis" OR "prophylactic anticoagulation" OR "anticoagulants" OR "aspirin" or "heparin").

The same key words were inserted in the search manager fields of the Cochrane Library Central. The search was broadened by extensive cross-checking of reference lists of all retrieved articles fulfilling inclusion criteria. For all databases, the last search was run on March 28, 2018. The same two authors independently screened the title and abstract of the primary studies that were identified in the electronic search. The following inclusion criteria were set for inclusion in this systematic review: (1) studies reporting a thromboprophylactic therapy in liver transplant procedures; (2) studies reporting a description of the anticoagulation or antiplatelet therapy performed in liver transplant recipients; and (3) if more than one study was reported by the same institute, only the most recent or the highest quality study was included.
The following exclusion criteria were set: (1) letters, comments and case reports; and (2) studies where it was impossible to retrieve or calculate data of interest.

The same two authors extracted the following main data: (1) first author, year of publication and study type; (2) number and characteristics of patients; (3) effectiveness of the thromboprophylaxis performed in term of portal vein thrombosis, hepatic artery thrombosis, deep vein thrombosis and pulmonary embolism; and (4) complications of thromboprophylaxis. Bias of the individual studies was categorized based on study design. All relevant texts, tables and figures were reviewed for data extraction. Discrepancies between the two reviewers were resolved by consensus discussion.

The literature search yielded 634 articles; after the removal of all the articles that did not reflect the inclusion and exclusion criteria, a total of 11 articles published between 1997 and 2018 were included in this systematic review. Three studies were prospective[61,76,80], only one was a prospective case control study[73] while all the others were retrospective[61,72,74] and four of these had control group[73,77-79]. No papers reported multicentric data. All these studies included a total of 5192 patients (adult and children).

**Description of the studies**

Despite the altered coagulation tests and thrombocytopenia, patients with end-stage liver disease are at a risk for thrombosis[81]. Several authors suggested that routine thromboprophylaxis should therefore not be withheld from hospitalized patients with liver disease[81] unless risk factors for bleeding are present. Recent advances in the understanding of the coagulopathy in chronic liver disease have provided strong support for anticoagulation as a new therapeutic paradigm for patients with cirrhosis, which would be able to decrease the progression of the liver disease[81].

Although the incidence of venous thrombosis after LT is similar to that reported in other types of major surgery, the fact that these complications occur despite hypocoagulable routine laboratory tests in the first postoperative days indicates that these routine tests probably do not reflect the in vivo physiology. The lack of reliable laboratory tests and the contraindications to thromboprophylaxis in cases of high hemorrhagic risk, such as that recognized in LT, make the management of anticoagulants complex in this surgical setting. After LT, patients may be hypercoagulable because of an imbalance between coagulation and fibrinolytic mechanisms, tipping towards a prothrombotic state in the early postoperative phase[82]. It has been established as well that after LT and partial hepatectomy, patients are hypercoagulable because of enhanced thrombin generating capacity, despite prolongations in the PT[83,85]. Furthermore, postoperative immunosuppressive drugs may play a role in increasing platelet aggregation and thrombogenicity[86]. However, usually physicians find several difficulties in administering thromboprophylaxis because they do not know if, in the postoperative period, the coagulopathy persists or the coagulation balance reverts to normality. In the light of the above mentioned observation thromboprophylaxis should not be withheld on basis of post-operative prolonged PT values, as in reality coagulation is hyperactive and standard coagulation test are not truly representative of the real coagulation status in these patients. Other difficulties come from the lack of effective predictors of VTE. INR, MELD score and platelet number have been unreliable to predict thromboembolic complications[85]. Due to the risks of bleeding and coagulopathy in the postoperative LT period, antithrombotic prophylaxis to prevent VTE is not routinely used, and no consensus exists.

Recently, Mukerji and colleagues advised delaying anticoagulation until the post-transplant INR was above 1.5 to 2.0 and the platelet count was below 50000[9]. Similarly, Blasi and colleagues suggested administering thromboprophylaxis with low-molecular-weight heparin to patients with Child A cirrhosis and in patients who undergo intraoperative thrombectomy, avoiding its administration if the platelet count is under 30 x 10^9/L or in cases of significant intraoperative blood loss[81].

Even if thromboprophylaxis in the early postoperative period of cadaveric liver transplant recipients is not routinely administered and the reports on the usage of heparin are very limited, more surgeons have begun to implement thromboprophylaxis therapy to reduce the risk of vessel thrombosis (Table 2). Most liver transplant centers have developed their own protocols for heparin infusion and the monitoring of its activity, even though bleeding remains the most feared complication associated with anticoagulation therapy, especially in cases of delayed graft function and marginal graft. For instance, Kaneko et al[71] reported a high incidence (9%) of surgical revision for hemorrhagic complications in their living related liver recipients who received unfractionated heparin (UFH). They suggested that the dose of heparin should be adjusted to maintain activated clotting time (ACT) levels lower than the previously settled ones during the early postoperative period. Mori et al[80] declared that their basic protocol after living donor LT for the patients who underwent portal reconstruction for PVT did not include anticoagulation therapy. Only patients with good coagulation (PT-INR < 1.5) or slow portal flow were administered intravenous heparin at the dose of 5 U/kg/h during the first week after the LT and only then shifted to warfarin[86]. Similarly, Stange and colleagues suggested to administer low-dose heparin as a continuous infusion of 5.000 IE over 24 h, beginning 6 h postoperatively, for 14 d only in case of split-liver transplantation or complex arterial reconstruction[70].

In contrast to Kaneko and Mori, Yip and colleagues[73] implemented a standardized prophylactic regimen in LT recipients with subcutaneous heparin.
| Authors         | Type of study | Drug used                                      | Target population | Number Pts | PVT | HAT | Bleeding | Observations                                                                 |
|-----------------|---------------|-----------------------------------------------|-------------------|------------|-----|-----|---------|------------------------------------------------------------------------------|
| Blasi 2016[61]  | Retrospective study No controls                  | Enoxaparin not routinely, unless intraoperative. thrombectomy or the patient was under anticoagulant treatment before LT. No thromboprophylaxis if the platelets are under $30 \times 10^9/L$. | Adult LT        | 328        | 8 (2.4%) | NA  | Not reported | 5/8 patients with PVT did not receive prophylaxis, and the other 3 received it days after LT or in only a few doses |
| Kaneko 2005[71] | Prospective study No controls                    | Dalteparin administration adjusted with reference to the ACT (130-160 s) | Adult Living-donor LT | 128        | 1 PVT (0.78%) and 1 (0.78%) PVT + HAT | 2 HAT (1.5%) and 1 HAT + PVT (0.78%) | 11 (8.5%) surgical revisions and 8 (6.25%) patients with hemorrhages complications treated conservatively | High hemorrhage complication rate in this series indicates that a lower target ACT range may be preferable in the second post-operative week. |
| Gad 2016[74]    | Retrospective study No controls                   | Heparin infusion up to 180-200 units/ kg/day adjusted with reference to the ACT (target levels, 180-200 s) and/or the aPTT (target levels, 50-70 s). | Adult and pediatric living-donor LT | 186        | 5 (2.3%) | 4 HAT (1.8%) | 4 HAT and PVT (1.8%) | Pre-LT PVT may deserve more intensive anticoagulation therapy |
| Sugawara 2002[76] | Prospective study No Controls                    | LMWH, ATIII, prostaglandin E1 (0.01 g/kg/h) and a protease inhibitor | Adult Living-donor LT | 172        | 4 (2.3%) both PVT + HAT | 7 (4.0%) | Not considered | The authors’ strategy against HAT is aimed to correct the imbalance between the coagulation and anticoagulation systems |
| Mori 2017[80]   | Prospective study No controls                    | Heparin infusion at the dose of 5 U/kg/h during the first week after LT | Adult Living-donor LT | 282 total patients; 48 patients with pre-existing PVT; number of patient with thromboprophylaxis not cited | 8 (17%) | NA  | Not considered | The basic protocol after LDLT does not provide anticoagulant therapy. Only patients with good coagulation (INR < 1.5 or slow portal flow (velocity < 10 cm/s) and intraoperative portal reconstruction for PVT were administered intravenous heparin. The aim of this study was to determine the risk factors that influence the incidence of DVT/PE and the effectiveness of prophylaxis |
| Yip 2016[73]    | Retrospective case control study                 | Subcutaneous heparin (5000 U) every 8 h | Adult LT         | 999 total patients; 288 patients with thromboprophylaxis from 2011 | Not considered | Not considered | NA | The aim of this study was to determine the risk factors that influence the incidence of DVT/PE and the effectiveness of prophylaxis |
(5000 U) every 8 h, demonstrating that this therapy significantly reduces VTE events without increasing bleeding risks. In support of this kind of thromboprophylaxis, other studies have found that unfractionated heparin did not increase the risk of bleeding in patients with cirrhosis[74,77]. Gad and colleagues[77], in a retrospective work on 222 adult and pediatric living-donor LTs, reported their standard prophylactic therapy (heparin infusion up to 180-200 units/kg per day adjusted with reference to the ACT and/or the aPTT) and concluded that a more intensive anticoagulation therapy could be one option, especially when dealing with preoperative PVT. Uchikawa et al[75], fearing bleeding complications associated with UFH administration, proposed a thromboprophylactic regimen with dalteparin, a relatively selective inhibitor of factor Xa activity. In their prospective case-control group, they showed that anticoagulation therapy, based on ACT, reduces thrombotic complications without increasing bleeding[75]. Similarly, Sugawara et al[76] demonstrated the efficacy of intensive anticoagulation obtained with low-molecular-weight heparin (LMWH) administration.

In addition to LMWH and UFH, antiplatelet drugs have been proposed for prophylaxis after LT because of the important role of platelets in thrombotic complication. Wolf and colleagues in 1997 showed no benefit of prophylactic low-dose aspirin therapy in the prevention of early HAT after liver transplantation[77]. Differently, Vivarelli et al[78], in a single-center retrospective study, examined the effect of long-term aspirin administration (100 mg) on the incidence of late HAT in a large number of patients. They found a relative risk reduction of 82% without any recorded bleeding episodes throughout the follow-up period. Unfortunately, one of the major limitations of the

| Study | Study Type | Intervention | Patient Group | ACT Target | n | ACT Measurement | Incidence (%) | Incidence Comparison | Incidence Comment |
|-------|------------|--------------|---------------|------------|----|-----------------|---------------|---------------------|------------------|
| Uchikawa 2009[75] | Prospective case control study | Continuous i.v. Dalteparin infusion administered in the anhepatic phase to maintain the ACT levels from 140 to 150 seconds (Gr.A) vs continuous i.v. Dalteparin infusion administered immediately after the operation and adjusted depending on clinical findings (Gr.B) | Adult Living-donor LT | 42 total patients (10 vs 32) | 0 % in Gr. B | 0 % in Gr. B | 0 % in Gr. B 5 (15.6 %) in Gr. A | The study evaluated the advantage of ACT as a reliable tool for bedside monitoring of LMWH anticoagulant effects during and following LDLT |
| Stange 2003[76] | Retrospective study | UFH 5000 IU over 24 h beginning 6 h postoperatively, for 14 d | Adult Living-donor LT | 1192 Not evaluated | 14 (1.17 %) | 3 (0.2%) bleeding episodes not apparently related to UFH | The authors analyzed the incidence, clinical presentation, therapeutic options, and outcome of hepatic artery thrombosis (HAT) |
| Wolf DC, 1997[77] | Retrospective case control study | 81 mg oral aspirin in adult and 40 mg in children from postoperative day 1 | Adult and pediatric LT | 499 total patients (354 vs 175) | Not evaluated | 10 (2.9 %) vs 6 (3.6 %) in the not treated group | 89 (16.8 %) gastrointestinal bleeding 66 treated vs 23 not treated patients | The spontaneous or invasive maneuver-related bleeding episodes were more frequent in the treated group |
| Vivarelli 2007[78] | Retrospective case control study | 100 mg aspirin | Adult LT | 838 total patients (236 treated vs 592 not treated) | Not evaluated | 1/236 (0.4 %) treated patients vs 13/592 (2.2 %) not treated patients | 15/304 patients (4.9 %) vs 5/165 (3 %) patients overall HAT (early and late) in the control and treated group | The aim of this study was to determine the safety and efficacy of aspirin therapy on late HAT |
| Shay 2013[79] | Retrospective case control study | 325 mg aspirin | Adult LT | 469 total patients (165 treated vs 304 not treated) | 6/304 (2 %) not treated patients vs 1/165 patients treated (0.6 %) | Similar bleeding rates between the two groups | The aim of this study was to determine the safety and efficacy of early aspirin therapy on clinical outcomes |

| Abbreviations | Description |
|---------------|-------------|
| LT | Liver transplant |
| PVT | Portal vein thrombosis |
| HAT | Hepatic artery thrombosis |
| ACT | Activated clotting time |
| aPTT | Activated partial thromboplastin time |
| DVT | Deep vein thrombosis |
| PE | Pulmonary embolism |
| LMWH | Low-molecular-weight heparin |
| UFH | Unfractionated heparin |

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| PE | Pulmonary embolism |
| LMWH | Low-molecular-weight heparin |
| UFH | Unfractionated heparin |
of anticoagulation in these patients must be carefully undergone liver transplant, and the risks and benefits thromboprophylaxis administration. Therefore, several most physicians to a more frequent postoperative of the “auto-anticoagulated patient”, has oriented normal or even increased coagulation status in patients The growing evidence from clinical studies of the after LT with mechanical prophylaxis alone ≥ 9% given to using both mechanical and chemical prophylaxis efficacy standpoints. However, consideration should be valued. Some of these warnings regard the chosen drug. Unfractionated heparin and LMWH are the most frequently used drugs, although there are several concerns and a lack of consensus on the required doses, the efficacy of treatment and the best way to monitor the pharmacologic effects achieved.

Unfractionated heparin
Heparin is used to reduce the incidence of HAT after liver transplantation. The anti-coagulatory effect of UFH comes mainly from its capacity to enhance the endogenous anticoagulant antithrombin III activity, from its effects on platelets, platelet factor 4, the fibrinolytic system and thrombin[82,83]. In liver cirrhosis or liver failure, the hepatic synthesis of coagulation factors, including antithrombin, is impaired, affecting anti-Xa testing and the predictability of UFH’s anticoagulation effect[84]. In cirrhotic patients, a discrepancy has been reported between the anti-Xa level and the activated partial thromboplastin time while monitoring UFH therapy[85]. The anti-Xa tests underestimate the UFH levels, whereas the aPTT gives an overestimation[86]. Neither of these tests assesses drug levels directly; rather, they estimate the drug levels starting from the anticoagulant action of the drug.

When monitoring unfractionated heparin’s effects by aPTT modifications, physicians must address an already prolonged aPTT value in many patients with cirrhosis, making the aPTT target ranges for these patients unclear. The aPTT test has not been assessed in cirrhotic patients, and its targeted range is unclear given that aPTT is prolonged at baseline in patients with cirrhosis. In this case, the level of ant-Xa is usually decreased, and that of aPTT is increased. This condition brings into question whether the augmentation of UFH doses based on anti-Xa level could expose patients to a higher risk of bleeding or if decreasing the UFH dose based on aPTT values could predispose patients to subtherapeutic therapy.

The fluctuating liver graft synthetic capacity and the consequently variable antithrombin level in the plasma of the transplanted patients make the heparin anticoagulation activity extremely variable during the postoperative period, requiring continuous monitoring and dose adjustment. Thus, understandable fears of bleeding are common in the post-liver transplant period.

Hemorrhagic complication can occur with the poorly monitored use of heparin. Kaneko et al[81] reported that 9% of their living related liver recipients who used UFH developed hemorrhagic complications that required surgical treatment. Other authors[87] noted the safety profile of heparin infusion in a liver transplant setting, underlining the necessity to obtain several samples to monitor its activity.

The ACT monitors the activity of the intrinsic pathway in the coagulation system and has been used after liver transplant to assess heparin anticoagulation.

### Table 3 Possible conditions warranting thromboprophylaxis in the postoperative period of liver transplant recipients

| Condition                                                                 |
|---------------------------------------------------------------------------|
| Living-donor liver transplant and split liver                             |
| Surgical difficulties and complex vessel reconstruction                  |
| Presurgical portal vein thrombosis                                        |
| Intraoperative portal or hepatic artery thrombectomy                      |
| Hypoplastic portal vein                                                  |
| Jump graft artery reconstruction                                          |
| Cholestatic recipient diseases and Budd-Chiari disease                    |
| Non-alcoholic fatty liver disease/non-alcoholic steatobesity              |
| Small or multiple recipient arteries                                      |
| Low portal or arterial blood flow intraoperatively                        |

study was the inability to verify the effect of aspirin on early HAT because of authors’ inability to start aspirin immediately after LT in all patients with known impaired coagulative function or with a high risk of bleeding[78]. In contrast to Vivarelli, Shay et al[79] showed that aspirin prophylaxis is safe and effective in decreasing early HAT in adult recipients, making the HAT incidence decrease from 3.6% to 0% in the treated group. There was no difference in bleeding complications between the groups, regardless of the dosage of aspirin (325 mg) used.

There are emerging data on the safety of anticoagulants in patients with cirrhosis[81,89]. Several groups recommend thromboprophylaxis in the absence of clear contraindications in the clinical, but not surgical, setting[90,96]. A different situation is represented by LT, where guidelines for VTE prophylaxis are lacking from both safety and efficacy standpoints. In this setting, a careful risk stratification, a wise drug choice and a reliable monitoring of drug effects may orient the choice on whether cirrhotic patients could benefit from prophylaxis (Table 3).

### DRUG CHARACTERISTICS AND MONITORING ASSAY

In general, liver transplant surgery guidelines regarding VTE prophylaxis are lacking from both safety and efficacy standpoints. However, consideration should be given to using both mechanical and chemical prophylaxis after LT. Some studies, in fact, have reported rates as high as 79.6% of transplants being undertaken without transfusion[91] and a risk of developing a DVT after LT with mechanical prophylaxis alone ≥ 9%[40]. The growing evidence from clinical studies of the normal or even increased coagulation status in patients with cirrhosis, which has replaced the old dogma of the “auto-anticoagulated patient”, has oriented most physicians to a more frequent postoperative thromboprophylaxis administration. Therefore, several warnings must be considered before implementing a more liberal use of anticoagulants in patients who have undergone liver transplant, and the risks and benefits of anticoagulation in these patients must be carefully assessed.
Different target levels, depending on the clinical study, have been described and range from 130-160 s [71] and 180-200 s [72]. Most liver transplant centers have developed their own protocols for heparin infusions and heparin activity monitoring based on empirical rules. Because of the lack of consensus on the target ranges to be reached to obtain anticoagulation without increasing the hemorrhagic risk too much, authors have chosen the target limit arbitrarily, and surprisingly, the same target range has been both associated and not associated with bleeding complications in different clinical papers.

Another limit of UFH administration is heparin-induced thrombocytopenia (HIT), which is an adverse immune-mediated reaction to heparin that results in platelet count decreases of more than 50% within 5 to 10 d after heparin administration. The prevalence of HIT or HIT antibody in the liver recipient population seems to be very low [97], with the exception of Budd-Chiari syndrome patients, in whom the HIT prevalence is significantly higher than the general population [98]. Nevertheless, the careful monitoring of platelet count and possible thrombosis is necessary when heparin therapy is prolonged or patients have a history of heparin therapy.

Despite these limitations, UFH pharmacokinetics, especially if administered at low doses, characterized by a rapid short-term action, poor bioavailability, and a rapidly reversible anticoagulant effect in case of hemorrhagic complications, makes UFH a good anticoagulant in liver transplant patients with concomitant renal failure. Because of the limitations of both anti-Xa and aPTT tests in estimating the drug levels in plasma, thrombin generation testing could represent a valid alternative that offers information about the true anticoagulant effect of this drug; unfortunately, this test is not available for routine clinical use [96].

**Low-molecular-weight heparin**

LMWH selectively inhibits clotting factor X and, augments antithrombin III activity [73]. Despite being considered a drug with less risk of bleeding [99] than unfractionated heparin due to its selective inhibition of coagulation factor X, and because of its reduced ability to bind to platelet factor 4 and von Willebrand factor, its anticoagulation activity may be difficult to predict [99]. The anticoagulation efficacy in the presence of both graft and renal dysfunction may be extremely variable, and a reduction in the dosage of LMWH is recommended because it has increased anticoagulant potency in patients with cirrhosis [100]. Hence, in patients with impaired renal function, which is commonly seen following LT, monitoring and dose adjustments according to the degree of renal injury are required. For this reason, in patients with a high bleeding tendency, such as liver transplant recipients, an adjustable continuous infusion of LMWH may be recommended to avoid peak plasma levels and to better manage the continuous changes in the coagulation cascade related to the graft functionality [75].

While LMWH reduces ischemia-reperfusion-associated liver damage, which may make it more advantageous than UFH for intraoperative and postoperative anticoagulant therapy in LT, continuous monitoring and dose adjustments according to the degree of renal function are required. The most widely used test that correlates with the administered LMWH dose is the anti-FXa activity in plasma, which measures the inhibitory activity of LMWH-antithrombin (AT) complexes towards FXa. However, the assay is prone to several pitfalls that need to be considered when it is used to monitor the cirrhotic patient [101]. The low levels of antithrombin typical of cirrhotic patients limit the formation of LMWH-AT-FXa complexes and lower the ability of the anti-FXa activity assay to guide LMWH dosage [96]. Potze and colleagues found that the anti-FXa assay underestimated the LMWH dose administered in vitro to plasma of cirrhotic patients and had dangerous clinical consequences [96]. The low reliability of the anti-FXa assay, which underlines a persistently low anti-FXa activity, can lead to dangerous LMWH dose escalation in the postoperative period in liver transplant recipients [103]. To overcome this limitation of the assay at low AT levels, some authors propose the addition of AT before monitoring LMWH, which is not the standard practice in most routine diagnostic laboratories [81]. Another alternative could be represented by the ACT, which is the most commonly used and sensitive monitoring method to verify UFH’s effects. Some reports have documented that ACT is not reliable in monitoring LMWH’s effects [103,104], and the ACT cannot usually monitor the activity of factor Xa. However, in other clinical papers, ACT did monitor the anticoagulatory effect of LMWH in coronary intervention procedures [105] and in living-donor LT [75]. Uchikawa et al [75] showed that ACT measurement is a simple, reliable method for bedside monitoring of LMWH’s (dalteparin’s) anticoagulant effects for living-donor LT.

The usefulness of the conventional ACT for LMWH monitoring is still under debate. TGT could represent a valid alternative [106]. However, this test is still impractical in a routine clinical setting, as it requires time to prepare and is not suitable for quick diagnosis.

**Antiplatelet**

The constant activation of platelets in the perioperative period of liver transplant, which can lead to platelet consumption and sequestration in the liver following graft reperfusion, has been associated with the occurrence of arterial thrombosis and graft failure [46]. Because of the significant role of platelets in the development of thrombosis, antiplatelet therapy has come to be seen as an attractive preventive therapy. Aspirin’s ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of
the cyclooxygenase (COX) enzyme, which leads to an interference with platelet aggregation and to an endothelial cell-mediated inhibition of the coagulation cascade\cite{107}. Although the widespread use of aspirin seems attractive, the traditional fear of hemorrhagic complication in the postoperative period of the liver transplant patient is responsible for the general avoidance of anticoagulant medication in these patients and for the very few studies performed on the efficacy and safety of antiplatelet drugs after liver transplantation. The literature on antiplatelet administration in the post-transplant period is controversial. Wolf and colleagues (1997) found no benefit of prophylactic low-dose aspirin therapy in the prevention of early HAT after liver transplantation, and even if aspirin administration did not seem to be associated with postoperative bleeding complications, a trend toward an increased incidence of gastrointestinal bleeding was seen\cite{77}. In contrast, Vivarelli et al\cite{78}. reported the efficacy and safety of long-term aspirin administration for the occurrence of late HAT, without hemorrhagic complications associated with aspirin administration. Similarly, Shay et al\cite{79}, who used a higher dosage of aspirin immediately after surgery, showed that aspirin prophylaxis was safe and effective in decreasing early HAT in adult recipients, with no evidence of significant bleeding. These recent works seem to suggest that thromboprophylactic anticoagulation with aspirin in selected high-risk LT patients may be considered carefully.

Antiplatelet agents, in contrast to other anticoagulants, could offer the advantage of not requiring laboratory monitoring for dose adjustments. No tests are usually performed to avoid excessive inhibition of platelet function, and the issues regarding monitoring in the use of other anticoagulants cannot be applied to antiplatelet drugs. Unfortunately, laboratory tests of platelet function are frequently abnormal in patients with cirrhosis, and it may be challenging to detect the efficacy of anti-platelet agents in a category of patients with thrombocytopenia and platelet function alterations\cite{108}. Furthermore, despite the clinical evidence for the efficacy of aspirin for early and late HAT, the use of aspirin has been associated with an increased risk of a first variceal bleeding in patients with established varices\cite{109} and with acute renal failure, hyponatremia, and diuretic resistance in patients with ascites\cite{110}, occasionally making preventive aspirin administration in liver recipients difficult.

**Clopidogrel**

P2Y12 blockers such as clopidogrel, which has an active metabolite that irreversibly inhibits the ADP P2Y12 receptor, have been proposed to prevent post-transplant arterial thrombosis, but the risk of thrombosis vs bleeding must be wisely considered when choosing this drug in the postoperative period\cite{77}.

Perioperative management of antiplatelet therapy in patients who undergo surgery with a high hemorrhagic risk is difficult and should be formulated by a team of experts (surgeon, anesthesiologist), who should weigh the relative risk of bleeding with that of thrombosis. The risk of bleeding complications in the perioperative period has been increased 1.5-fold under low-dose aspirin\cite{111}, and when clopidogrel is not discharged within 7 d prior to the operation, this risk increases to 30%\cite{112}. Clopidogrel is correlated with increased bleeding and is usually interrupted in the postoperative period until the risk has been reduced. Clopidogrel's hemorrhagic risk, the lack of established reversal agents, the fact that it is widely metabolized by the liver and excreted in urine, and the risk of excessive anticoagulation in the immediate postoperative period have made this drug barely manageable and, thus, not indicated for postoperative antithrombotic prophylaxis.

**Direct oral anticoagulant agents**

Direct oral anticoagulant agents (DOACs) have been proposed as an attractive alternative to heparin and LMWH for the prevention of post-transplant thrombotic complications. Moreover, preliminary data show that the use of DOAC is safe in cirrhotic\cite{113}. These drugs have the advantages of oral administration, fixed dose and no need for laboratory monitoring. Moreover, their mechanism of action is independent of antithrombin, which is necessary for LMWH to be effective but may be severely impaired in cirrhosis patients. However, we know of no DOAC study in postoperative liver transplant patients. The experience with DOACs is still limited, their anticoagulation effect is not quickly reversible, their elimination route is through the kidney and liver, and excessive drug accumulation could be associated with bleeding issues in the postoperative period. In liver transplant recipients, renal and liver function are often impaired, and excessive anticoagulation effects could develop, making DOACs of scarce interest for postoperative thromboprophylaxis.

**CONCLUSION**

The widespread fear of postoperative bleeding after LT has been partly reduced by the awareness of the real coagulation balance of cirrhotic patients and by the increasing number of transplants performed without the need for transfusion. The old concept of the cirrhotic patient as an anticoagulated patient and the idea that the normal coagulation tests are able to represent the real coagulation balance of the patient have now been replaced. With this new knowledge, the attention towards thromboembolic complications of the liver transplant patients has become increasingly pressing. An unbalanced coagulation system toward hypercoagulability may persist for a variable period of time after the liver transplant. The delayed recovery of the anticoagulant factors and the reaching of normal activity among almost all of the procoagulant proteins not before day 1 to 3 postoperatively have been
widely described[82]. The increasing awareness that hypercoagulability can represent a serious risk in the perioperative period of the liver recipient, together with the lack of reliable tests to verify the presence of this condition, should increase the awareness of physicians of the need for adequate thromboprophylaxis therapy. Literature on this matter is scarce, and the degree of anticoagulation to be achieved or the tests to monitor anti-coagulation are not the result of common consensus.

Thromboprophylaxis should be used more often. From the literature available, we infer that the most commonly used drugs for antithrombotic purposes in patients undergoing LT are UFH, LMWH and cardioaspirin. The use of DOAC and clopidogrel in this category of patients is still limited, due in particular to their slowly reversible effect and the excessive anticoagulation effect they can cause because of their elimination route. Likewise, the possibility of hemorrhagic complications in transplanted patients remains a real fear. Pharmacological prophylaxis is probably beneficial in reducing the incidence of thromboembolic complications in the perioperative period, but a careful patient selection and a reliable coagulation test to monitor the pharmacological prophylaxis are needed. Thrombin-generation assays are the most reliable tests to represent the net amount of thrombin that can be generated as a result of the pro- and anticoagulant drivers and is a promising laboratory tool for investigating hemorrhagic and thrombotic coagulopathies. However, this test is still impractical in a routine clinical setting because it requires time to prepare and is not suitable for quick diagnosis. While waiting for this test to be readily available for bedside testing, viscoelastic tests, with all their limitations, could be helpful for the clinical conditions associated with increased thrombotic risks by avoiding the overcorrection of coagulation defects.

Unfortunately, because of the lack of a coagulation test that reliably predicts the risk of bleeding or thrombosis in the perioperative LT period, strong recommendations on thromboprophylaxis in this setting cannot be made, in particular in patients with delayed graft function. More well-designed clinical studies on the efficacy, safety, and tolerability of anticoagulant drugs for the prevention of thrombotic events in transplanted patients are needed.

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