What happens to coagulation-thrombosis mechanism in liver diseases?

Tülin Tiraje Celkan

Cerrahpaşa Medical Faculty, Department of Pediatrics, Division of Pediatric Hematology-Oncology, İstanbul, Turkey

Summary

Children with liver disease present complex and varied acquired coagulation abnormalities. Liver is the place where clotting factors are produced as well as inhibitors of coagulation and fibrinolytic system components. Although 75-85% of patients with liver disease show abnormal laboratory values, only 10-15% will have clinical bleeding symptoms, as liver has a large factor reserve capacity.

This paper will review acute and chronic liver disease and the hemostatic alterations. Treatment of the coagulopaty of liver disease is usually replacement of lacking factor and supportive care. Liver transplantation, which is very common recently, and its affects on hematological balance will also summarized. *(Turk Arch Ped 2013; 48: 94-101)*

Key words: Hemorrage, liver disease, thrombosis, treatment

Introduction

The liver is the place where all coagulation factors are produced. In 75-85% of the children with liver disease, abnormal results are obtained in laboratory tests (1-4). In addition, proteins which inhibit coagulation and the elements of the fibrinolytic mechanism are also produced in the liver. At the same time, the liver is the place where coagulation factors which are activated in the circulation are reserved and eliminated. Conclusively, 10-15% of the patients with liver disease display hemorrhage findings clinically (3). The liver has a wide reserve in terms of coagulation factors.

Causes of hemorrhage in liver diseases

The relation between hemorrhage and liver diseases has been known for a long time. In children, hemorrhage only arising from liver diseases is very rare clinically, but each pediatrician should consider this disease group in a patient who presents with hemorrhage in the differential diagnosis.

Although hemorrhage in liver diseases has many different causes, the main cause is deficiency of coagulation factor (Table 1). The liver is the place where all factors are produced. Fibrinogen, prothrombin, prekallicrein, HMWK (high molecular weight kininogen) and factor V, VII, VIII, IX, X, XI, XII and XIII are produced in the liver. Plasminogen, AT3, protein C and S, alpha-2 antiplasmin and alpha-1 antitrypsin are also produced in the liver. However, qualitative and quantitative disorders of platelets may also be detected in this group of patients. Another important factor is the insufficiency of the pathological liver tissue to eliminate activated factor and fibrinolytic factors from the circulation (5-7). In addition, disseminated intravascular coagulation (DIC) and increased fibrinolysis create predisposition to hemorrhage (8). Coagulation tests are helpful in showing hepatic reserve and in the diagnosis and prognosis of the underlying liver disease. For example, a factor V level below 20% indicates end-stage liver disease.

Presence of esophageal varices in patients with liver disease is an important cause of hemorrhage (9). Sinusoidal endothelial cells (SEC) are important for intrahepatic vascular resistance. Thromboxane A2 which is released from these cells leads to portal hypertension by causing increased intrahepatic resistance. Hypoactivity of these cells increases production of nitric oxide (NO) and leads to "hyperdynamic tissue syndrome" by causing to splenic and systemic pressure changes and endothelial

relaxation. Variceal hemorrhage, hepatorenal syndrome and hepatopulmonary syndrome may develop in this syndorme (10). New vessels which develop secondary to portal hypertension tend to bleed. Again, gastritis which occurs commonly in these patients is also a cause of hemorrhage.

Presence of cholestasis accompanying liver disease leads to a clinical picture of hemorrhage related with vitamin K deficiency by causing to insuffcient absorption of vitamin K. In this condition, both PT and aPTT are prolonged. For the diffferential diagnosis clinical response to vitamin K is evaluated or the level of factor V is determined to eliminate liver disease (11).

Clinically, presence of inhibitor which develops following infections which occur commonly in the childhood should be considered primarily in deficiency of multiple factors. Mixing study with 1/1 normal plasma is applied to investigate the presence of inhibitor. If the abnormal test does not improve with addition of normal plasma, the presence of inhibitor developed against the factors which are present in the plasma of the patient is confirmed. If the mixing study improves with the added plasma, factor deficiency should be considered. In deficiencies of multiple factors, liver diseases should absolutely be excluded.

Laboratory

In hemorrhage related with liver diseases, various laboratory tests may be helpful and the results may be variable with a great extent (Table 2).

In mild liver diseases, no significant finding is observed in the laboratory tests; the best example for this is viral and toxic hepatitis.

In patients with liver disease, the bleeding time is abnormal in 40% of the patients (12-14). In these patients, the bleeding time improves with DDAVP (desmopressin)

(15). However, decrease in hemorrhage in patients with liver disease or in transplant receivers with use of DDAVP could not be demostrated in randomly selected studies (14). Therefore, it is not useful to improve the bleeding time in these patients. In recent years, it was shown that bleeding control could be provided more easily with a hematocrite (Hct) of >25-30 in studies in which PFA-100 was used. Therefore, keeping Hct at 25-30% after excluding the possibility of thrombosis by providing sufficient circulation may decrease the risk of bleeding.

In children with liver disease, the most common disorder is prolonged PT (12-14). Prothrombin time is a more sensitive test compared to ALT and AST in showing hepatic functions (the factor which disrupts firstly is factor VII, since the half-time is 6 hours). However, there is generally no relation with a prolonged PT and bleeding risk. In patients with liver disease, bleeding generally occurs in presence of a triggering factor including mostly trauma, surgical intervention or infection. In a study performed in adults, the risk of bleeding was found to be 4% in patients with liver disease who had a PT of >15 s in procedures including paracenthesis, thoracenthesis, lumbar puncture and surgical interventions (16).

In presence of chronic liver disease, no relation could be demostrated between coagulation tests and cholesterol, albumin, transaminase levels and clinical status in most studies. Although the most common test which is found to be abnormal is PT, the level of factor V can be used as the best indicator of prognosis. However, this is also not specific for the differential diagnosis of the underlying primary disease. As stated, all factors are found to be decreased in liver diseases, but the level of factor VIII may be normal and even high. The reason for this is the fact that factor VIII can also be synthesized in the endothelium outside the liver. It is known that the ratio of FVIII/ vWF

Table 1. Conditions which cause to hemorrhage in liver diseases and compensation of this in the body (3)	
Hemorrhagic diathesis	Mechanism which inhibits hemorrhage
Thrombocytopenia	Increased vWF
Thrombocyte dysfunction	Decreased ADAMTS-13
Increased NO and prostacycline production	Increased factor VIII level in the blood
Decreased factor II, V,VII, IX, X and XI	Decreased Pr C, Pr S, AT, alpha-2 macroglobulin and heparin cofactor II
Vitamin K deficiency	
Disfibrinogenemia	
Increased fibolysis and t-PA	Decreased plasminogen level in the blood
Decreased ALFA-2 antiplasmin, factor XIII and TAFI	Increased PAI-1

TAFI: trombin activated fibrinolysis inhibitor, NO: nitric oxide, ADAMTS-13: a disintegrin and metalloproteinase with a thrombospondin type 1, von Willebrand factor-cleaving protease, t-PA: tissue plasminogen activator, PAI-1: plazminogen activator inhibitor-1

is increased in patients with cirrhosis (17,18). Especially the level of vWF is known to increase 10-fold. Although the level factor XIII is found to be within normal limits in studies performed, it is evaluated to be relatively deficient, since there is a problem in activation (17). While the level of FXIII decreases in hepatocellular diseases, it is found to be normal in obstructive jaundice. When fibrinolysis is disrupted and DIC develops, FXIII also decreases as all factors do. Factors are found with a rate of 50-150% in the plasma. However, a level of 20-50% for most factors can allow sufficient hemostasis. This is an evidence of the reserve of these factors.

Antithrombin-3 is the most important physiological inhibitor of coagulation. It inhibits other serine proteases (factor VII, IX, X, XI and XII) in addition to thrombin. It is synthesized in the liver and has a half-life of 48-58 hours. Heparin increases the binding rate and amount of AT3 to thrombin. In fulminant hepatic failure and chronic liver diseases, the AT3 level decreases. This may be related to decreased synthesis, increased destruction or both. AT3 may be found to be high in biliary obstructions, hepatitis with chronic cholestasis and vitamin K deficiency.

Antiplasmin inactivates plasminogen. Its level is decreased in severe liver diseases. In addition, it is thought that it is released from the lymphocytes in the blood.

Protein C inhibits factor V and VIII. Protein S is the cofactor of protein C. In addition to both these proteins, thrombomodulin and t-PA also decrease in liver diseases. Thrombin which is involved in coagulation activates protein C. Thus, coagulation activates the system which will restrain itself while starting and inhibits excessive formation of clot. Decrease in protein C and S is not reflected to PT or aPTT. Therefore, thrombosis which is the other wing of hemostasis is not evaluated, when the risk of bleeding is examined in the tests. Generally, portal vein thrombosis (PVT) may be observed with a rate of 2-54% and deep vein thrombosis may be observed with a rate of 1.2% in patients

with liver disease. In patients with cirrhosis, PVT may be observed with a rate of 3-13,8%. This rate increases to 35% in patients who have hepatocellular carcinoma or who have undergone surgical portosystemic shunt surgery (19,20). In patients with cirrhosis, development of ascites or bleedings should suggest PVT. It is not always easy to make the diagnosis. Therefore, clinical thinking is very important for the diagnosis. Portal vein thrombosis:

Slowed flow : a. Portal vein obstruction

b. Malign cell extention

c. Develops as a result of systemic excessive coagulation (most commonly prothrombin 20120 mutation).

Most of the time, microthrombi develop rather than macrothrombi and clinical findings may be absent without organ failure. However, presence of microthrombus is found with a high rate on autopsies. In 3-8% of the patients, the portal vein pressure is >35 mmHg. Although there is a risk for thrombosis in most patients with liver disease, anticoagulant and antiagregant treatment is avoided, since use of these types of drugs may increase the present risk of bleeding.

Plasminogen which is involved in the fibrinolytis system is present in the tissue as zymogen and is activated as a result of interaction with tissue plasminogen activator (t-PA) which is also present in the tissue. The liver also participates in elimination of t-PA. Plasminogen breaks down fibrinogen by adhering to it in the lysine or arginine regions. Its level is decreased in liver diseases.

In patients with liver disease, the clinic status is mostly silent, since there is a decrease in both the coagulant and anticoagulant mechanism. This is caricaturised in figure 1. Disruption of this sensitive balance with a triggering factor may result in hemorrhage or thrombosis clinically (Figure 2).

Plateletes and liver diseases

Platalets are decreased in liver diseases and this decrease is by >65% in severe liver diseases (17). Portal hypertension and related splenomegaly and reserving of the platalets in the spleen is the most important reason for

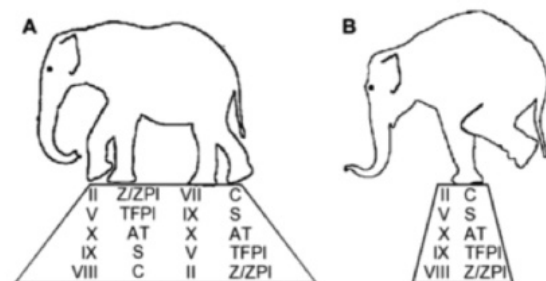| Table 2. Tests to be used in evaluation of coagulation in patients with liver disease |
|---|
| • PT and aPTT |
| • Fibrinogen level |
| • Thrombin-thrombomodulin |
| • Fibrinolysis |
| • Clot lysis time |
| • Alpha-2 plasmin inhibitor |
| • Platalet number and function tests |
| • PFA (Platelet Function Analyzer) |
| • Bleeding time |

Figure 1. The state of balances as a result of change in blood components in normal individuals (A) and in patients with liver disease (B) (2)

thrombocytopenia (21). In addition, DIC and decreased production also contribute to thrombocytopenia. The number of megacariocytes in the bone marrow is normal or even high (22,23). However, production is also decreased in alcoholism, folic acid deficiency and viral hepatitis. Although thrombocytopenia is found very frequently in patients with liver disease, it is very rarely a cause of clinical hemorrhage. The lower limit of platelet number which will lead to hemorrhage clinically in patients with liver disease is not known. As far as clinical thrombocytopenia and leukopenia do not lead to life-threatening outcomes,
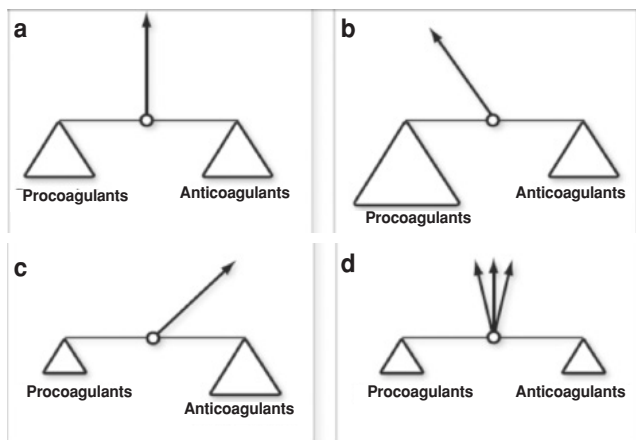

Figure 2. Blood levels of coagulants and anticoagulants in different diseases a: normal individual, b: thrombosis, c: hemophilia, d: liver diseases (3)

splenectomy is not recommended. Both the number and function of platalets are decreased (Table 2) (24). Especially, aggregation disorder and prolongation in the bleeding time are found frequently. Platalet dysfunctions are generally related with the severity of liver disease. When platalet-poor plasmas of these patients are incubated with normal platalets, normal platalet functions can not be observed and this is thought to be related with presence of fibrin destruction products in the plasma of the patients with liver disease (21).

In addition, large platalets which are active and known to be more efficient in hemostasis are found with a low number in patients with liver disease (21). The altered cholesterol/phospholipid ratio in patients with liver disease also disrupts platalet functions by inhibiting sufficient "prostoglandin" production in the arachidonic acid (AA) pathway (25,26). As a result of insufficient AA production in this platalet membrane, secondary activation of platalets occurs insufficiently. Insufficient interaction in the platalets may lead to insufficient trombomodulin production. This means activation disorder in the coagulant and anticoagulant systems.

Platalet number and function disorders in patients with liver disease (Table 1) is compensated with the increase in the FVIIIa/ vWF ratio. Thus, adhesion and regional control in the platalets are provided favourably. The causes of increased blood vWF include endothelial activation, decreased elimination from the liver and infection.

In patients with cirrhosis, platalet transfusion is performed before interventions including liver biopsy and

Table 3. Causes of platalet number and function disorders	
Insufficient production in the bone marrow	• Hepatitis C
	• Folic acid deficiency
	• Ethanol toxicity
Increased destruction	• Presence of autoantibody
	• DIC
Dysfunction	• Adhesion disorder
	• Aggregation disorder
	• Acquired storage pool disease
	• Decreased thromboxane A2 synthesis
	• Transmembrane conduction disorder
	• Decreased number of GP1b, GP2b3a deficiency (due to active fibrinolysis)
	• Increased HDL
	• Decreased hct
	• Increased endothelium-derived NO and prostocycline (the strongest platalet inhibitors)

tooth extraction (21). However, volume load, infection and transfusion complications may be observed frequently. Again, it was shown that requirement for platalet transfusion and number of platalets were independent variables for one-year survival rates after transplantation (27). In recent years, the approaches of performing platalet transfusion and bringing the number of platalets to normal have been questioned. In these patients, presence of active infection, accompanying renal failure or presence of altered lipid profile have been found to be more significant compared to the number of platalets (1,2,3,4,12,13,14).

Hyperfibrinolysis and liver disease

In patients with liver disease, hyperfibrinolysis is found with a rate of 30-46% (28,29). However, the diagnosis of fibrinolysis is difficult because of difficulties of laboratory evidence. Fibrinolytic proteins are also synthesized in the liver like coagulation factors. The production of plasminogen, alpha-2 antiplasmin, histidine-rich glycoprotein and FXIII is decreased in liver diseases. Blood t-PA level is increased, since elimination in the liver is decreased. The level of plasminogen activator inhibitor (PAI) may be increased, decreased or normal depending on the underlying disease (for example: PAI-1 is increased in chronic liver disease and decreased in severe hepatic failure). In acute hepatic diseases, the level of PAI-1 in increased as acute phase response and leads to hypofibrinolysis. Thrombin activatable fibrinolysis inhibitor (TAFI) is decreased in patients with cirrhosis, but hyperfibrinolysis is not observed clinically in these patients because fibrinolytic factors are also decreased (30). Thus, these patients are in a very sensitive balance (Figure 1). Therefore, preventive approach in these patients is definitely not recommended in these patients, if there is no clinical finding, since it will disrupt the balance.

Hyperfibrinolysis occurs in patients with liver disease who have ascites (31,32). Systemic fibrinolysis may be observed during absorption of ascites. Hyperfibrinolysis leads to thrombolysis and inhibits platelet aggregation and formation of hemostatic plaque.

It is found in 30% of the patients with liver disease. Endotoxins which enter the systemic circulation increase monocyte expression in patients with acute or chronic liver diseases or by portosystemic shunt interaction. Increase in monocytes leads to tissue factor release from the tissue. The tissue factor interacts with FVIII in the circulation, activates coagulation and protein factor 1+2 and d-dimer are increased. These affect the endothelium and cause coagulation to increase further.

In patients with chronic cirrhosis, bleeding from the varices occur with a rate of 5-15% yearly. The mortality rate related with hemorrhage in the first 6 weeks after the first

bleeding from esophageal varices is 20% (33). The chance of recurrence of hemorrhage in the 1-2 years in these patients is 60%.

In patients with liver disease, the reason for onset of hemorrhage is generally not coagulopathy, but the severity and persistence of hemorrhage is related with coagulopathy. It may sometimes be very difficult especially to control variceal bleedings. Fibrinolysis which is added to the picture makes it more difficult to control bleeding by causing to presence of increased fibrin destruction products in the tissue and blood (31,32,33). Presence of portal hypertension is one of the factors which complicates bleeding control.

In 50-70% of the patients with acute hepatic failure, spontaneous hemorrhage develops. 30% of these cases are severe and 27% of these are lost because of hemorrhage (34). A low FVIII level in acute hepatic failure indicates presence of DIC. In acute hepatic failure, administration of 10 mg/kg vitamin K for 3 days is recommended because control of bleeding will be difficult, if vitamin K deficiency is added to the picture.

In children with liver disease, renal problems are also found frequently. In these patients, platalet functions including especially platelet adhesion function are disrupted in presence of uremia (24). The risk of hemorrhage increases. In uremic patients, formation of ADP-serotonine and AA in the palatalet membrane is also decreased. Thus platalet-entothelium interaction is disrupted. Increased NO in uremia leads to endothelial damage and platalet adhesion and agregation disorder. In addition, anemia is also added to the picture in uremic patients by way of insufficient synthesis in the bone marrow and increased loss. When Hct is <25-30 in these patients, the risk increases exponentially. When hematoctrit decreases, blood viscosity increases, turbulent flow occurs, adherence of platalets with decreased number and function to the endothelium becomes more difficult and the possibility of haemostasis decreases. Therefore, Hct should be kept at a high level in patients with both hepatic and renal function with an increased risk of hemorrhage. In patients with liver disease in whom renal disease is also present, EPO (erythropoietin), DDAVP and estrogen may be tried instead of platelet suspension.

Treatment of hemorrhage in patients with liver disease

In this group of patients, decision for treatment of hemorrhage and being successful may be difficult for the physician. Since the cause of hemorrhage is generally insufficient synthesis in most patients, fresh frozen plasma (FFP) may be used in treatment (35). Fresh frozen plasma is sufficient for all factors except for fibrinogen. When fibrinogen is needed, cryoprecipitate is more efficient, since it contains 200-300 mg fibrinogen in each bag and does not lead to volume load.

If vitamin K deficiency is considered in the patient, administration of vitamin K may be beneficial. Platalet suspension is used in platalet number and function disorders.

In more severe liver diseases, the prognosis of the patient may be improved with supportive treatment and prevention of hemorrhage and complications of hemorrhage. Some physicians think that the liver reserve will be kept active with rapid and sufficient replacement treatment and thus dysfunction will not be reflected in the clinical status. In this group of patients, another unclear issue is use of heparin. Although some articles stated that DIC could be controlled with use of heparin, there are no evidence-based studies about the dose, time and benefit/harm of heparin. AT3, DDAVP can be used to control bleeding. It was shown that FV, VIII, XIII levels increased especially with use of DDAVP (1,2,3,4,14).

If the patient has hyperfibrinolysis, EACA (epsilon amino caproic acid), tranexamic acid and aprotinine may be used in treatment (33,36). Tranexamic acid inhibits breakdown of plasminogen by binding to fibrin and is used at a dose of 25-40 mg/kg. It should be kept in mind that it may lead to thrombosis at high doses. Aprotinine is a serine protease inhibitor. It inhibits plasmin and kallicrein. It is generally used in patients who have received a liver transplant. It was shown to decrease the need for blood transfusion by 30% (33). The dose is initiated with 2x106 and continued with 0.5x106/h. Although no risk for thromboembolism has been observed with the use of the drug, it may lead to transient renal failure.

Liver disease-infection-hemorrhage

Infection is found with a rate of 47% in patients with cirrhosis and 66% in patients with liver disease who have gastrointestinal hemorrhage. In patients who present with hemorrhage, the most important risk factor for recurrence of hemorrhage in the first five days has been stated to be infection (37,38). The pathophysiological causes which are thought to lead to hemorrhage in presence of infection include:

- Infection => endotoxin => increased tension in the portal area => endothelial contraction in the hepatic cells => hemorrhage
- Infection => NO release => prostacycline release => inhibition of platelet aggregation => hemorrhage
- Infection => formation of endogeneous-exogeneous heparinoid in the endothelium => should be eliminated in the liver => if it is not eliminated, it increases in the tissue => hemorrhage
- Infection => tissue ischemia => reperfusion => macrophage activation => formation of heparinoid => hemorrhage

Liver Transplantation

When irreversible damage occurs in the liver, transplantation is a treatment option (39,40,41,42). The decision of transplantation should be given by a committee and should be tried in patients who have a chance of survival for at least three months.

Generally, PT and aPTT are prolonged and platalets are decreased during the time between removal of the liver of the patient and transplantation of the new liver and the tests persist to be abnormal when perfusion starts on reengraftment. Thromboelastography also shows abnormal findings and fibrinolytic activity and the effect of heparin are reflected in the clinical status. In children, all these effects are observed less often compared to adults. After transplantation coagulation proteins are synthesized rapidly (41). The most common complications include intensive hemorrhage during and after operation, infection, rejection and the side effects of immunosuprresive drugs used for a long-term. The risk of hemorrhage in the operation area in the early postoperative period is high and leads to disruption of graft. However, the most common causes of mortality in patients who have undergone transplantation have been reported to be trauma and intracranial hemorrhage. Again, the risk of hepatic or portal vein thrombosis is high in the early postoperative period. If the patient is an adolescent or child, the risk of thrombosis has been reported to be higher. The mortality rate increases to 40% in hepatic artery thrombosis. The effect of heparin in this issue is controversial.

Coagulation tests have been examined to predict the amount of hemorrhage during transplantation. Altough hemorrhage with a two-fold intensity compared to the total blood volume is observed in 50% of the patients, it has been reported that this finding can not be predicted with the bleeding tests (3). Blood transfusion is not necessarily recommended before transplantation. Transplantation has been reported to increase the risk of hemorrhage by leading to fullness in the vessels. Prophylactic rFVIIa–PCC (prothrombin-complex concentrate) is not recommended either (45). However, it is recommended to be used, when hemorrhage can not be stopped and in presence of fibrinolysis and ascites (46,47,48,49,50). Portal hypertension and thrombocytopenias related with hypersplenism gradually improve in the first year.

In Cerrahpaşa Medical Faculty, we always order hemogram, peripheral blood smear, bleeding time, PT anda PTT and ALT and AST values for diagnostic purpose in patients who present with hemorrhage. We watch out in terms of underlying liver diseases in multiple factor deficiency. We generaly do not administer prophylaxis before hemorrhage occurs in our patients with liver disease. We are watchful that the platalet number

is>50 000/mm^3, fibrinogen is>100 mg/d L and INR is <1.2 before minor surgical procedures and liver biopsy. However, we use TDP, PCC, aPCC or rFakVIIa in patients in whom this clinical state can not be provided, who have a history of hemorrhage and who need interventions for diagnostic and therapeutical purposes. In some patients who have thrombocytopenia (<20 000/mm^3) and who have a history of hemorrhage, we administered platalet transfusion rarely before biopsy. As an antifibrinolytic agent tranexamic acid which is especially inexpensive and efficient is very useful in stopping short-term hemorrhages in the form of leakage. However, it should be kept in mind that one of the side effects of tranexamic acid is hepatic toxicity and long-term use should be avoided. We have not lost any patient with liver disease because of purely hemorrhage. In this group of patients, thrombosis creates difficulty in treatment rather than hemorrhage. In some patients with thrombosis and with a predisposition to thrombophilia in terms of etiology, we used heparin, LMWH (low molecular weight heparin), vitamin K antagonist and t-PA, when necessary. Our clinical experience indicates that especially t-PA is useful in the early period of thrombosis and if a response is to be obtained, the first two doses are responsed. We most frequently prefer LMWH in treatment. Our reasons for preferring LMWH are the facts that hemostasis returns in 12 hours when it is discontinued and very frequent tests are not needed for monitoring. Warfarin monitorization is more difficult in these patients, since they are used in combination with many other drugs. Even if the drug is discontinued, its effects last long because the half-life is 5 days.

Conclusively, we think close hematological monitoring and avoiding drugs and blood products constitute the best approach, if marked clinical findings are absent in patients with liver disease.

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