World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i26.8004

World J Gastroenterol 2015 July 14; 21(26): 8004-8013
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Perioperative thrombotic complications in liver transplantation

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Author contributions: Feltracco P designed the study, collected and analyzed the data, wrote the manuscript, and gave final approval of the manuscript; Barbieri S, Cillo U, Zanus G, Senzolo M and Ori C contributed to acquisition of data, drafting, revising, and editing the manuscript; all authors gave their full approval to publication of this manuscript.

Conflict-of-interest statement: The Authors declare that they have no conflicts of interest.

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Received: January 20, 2015
Peer-review started: January 20, 2015
First decision: April 13, 2015
Revised: April 30, 2015
Accepted: June 9, 2015

Article in press: June 10, 2015
Published online: July 14, 2015

Abstract

Although the perioperative bleeding complications and the major side effects of blood transfusion have always been the primary concern in liver transplantation (OLT), the possible cohesion of an underestimated intrinsic hypercoagulative state during and after the transplant procedure may pose a major threat to both patient and graft survival. Thromboembolism during OLT is characterized not only by a complex aetiology, but also by unpredictable onset and evolution of the disease. The initiation of a procoagulant process may be triggered by various factors, such as inflammation, venous stasis, ischemia-reperfusion injury, vascular clamping, anatomical and technical abnormalities, genetic factors, deficiency of profibrinolytic activity, and platelet activation. The involvement of the arterial system, intracardiac thrombosis, pulmonary emboli, portal vein thrombosis, and deep vein thrombosis, are among the most serious thrombotic events in the perioperative period. The rapid detection of occlusive vascular events is of paramount importance as it heavily influences the prognosis, particularly when these events occur intraoperatively or early after OLT. Regardless of the lack of studies and guidelines on anticoagulant prophylaxis in this setting, many institutions recommend such an approach especially in the subset of patients at high risk. However, the decision of when, how and in what doses to use the various chemical anticoagulants is still a difficult task, since there is no common consensus, even for high-risk cases. The risk of postoperative thromboembolism causing severe hemodynamic events, or even loss of graft function, must be weighed and compared with the risk of an important bleeding. In this article we briefly review the risk factors and the possible predictors of major thrombotic complications occurring

in the perioperative period, as well as their incidence and clinical features. Moreover, the indications to pharmacological prophylaxis and the current treatment strategies are also summarized.

Key words: Vascular complications; Thromboembolic phenomena; Liver transplantation; Hepatic artery occlusion; Postoperative complications; Pulmonary emboli

Core tip: Data from many transplant centers demonstrate an underlying hypercoagulative state during liver transplantation. A dysfunctional hypercoagulable condition may persist for a variable time period after the transplant procedure. Occlusive vascular events deserve special attention because they pose a major threat to both patient and graft survival. Regardless of the lack of definitive guidelines on postoperative preventive antithrombotic treatment, many institutions recommend prophylactic anticoagulation in liver recipients at high risk of vascular thrombotic events. The present paper reviews the characteristics and risk factors of thrombotic complications after liver transplantation; in addition it presents valuable information on the relevance of pharmacologic thromboprophylaxis.

Feltracco P, Barbieri S, Cillo U, Zanus G, Senzolo M, Ori C. Perioperative thrombotic complications in liver transplantation. *World J Gastroenterol* 2015; 21(26): 8004-8013 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i26/8004.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i26.8004

INTRODUCTION

Liver transplantation (OLT) has become a particularly successful therapy for patients with end stage liver disease. Innovations in surgical techniques, anaesthesiological approaches and post-operative care, along with improvements in immunosuppressive regimens, have led to 80%-90% one-year survival rates for transplant recipients and satisfactory long-term overall outcomes[1].

Perioperative bleeding complications in liver transplantation and the major side effects of blood transfusion have always been the primary concern accompanying this procedure, as surgery includes native liver dissection and removal under conditions of deranged coagulation, portal hypertension, and diffuse collateral venous flow. However, improved surgical skill during hepatic dissection, the introduction of modern devices for the prompt haemostasis of the small vascular structures, a dedicated, protocol-guided, anaesthesia care team, and intraoperative continuous monitoring and treatment of coagulative abnormalities have contributed to an important decline in blood losses. Currently, not only is the number of liver recipients who undergo massive transfusions steadily decreasing but clinical evidence has also emerged to support the opposite trend, attesting to a possible cohesion of an underestimated intrinsic hypercoagulative state during and after the transplant procedure. The better definition and understanding of the so called re-balanced haemostatic system in end-stage liver disease has in fact underlined the substantial risk of developing perioperative thrombotic complications that is present in certain liver recipients[2].

Thrombotic events, although much more less frequently encountered than bleeding complications, deserve special attention because they pose a major threat to both patient and graft survival.

Fortunately, in the majority of institutions, the strict and continuous point-of-care, perioperative monitoring of haemostasis has led to the abandonment of traditional attempts to prophylactically reverse perioperative abnormal coagulation tests. An on-demand strategy of coagulation factor transfusion is, in fact, safe and allows for a restrictive transfusion policy.

It has to be underlined that surgical factors and abilities make critical contributions to the minimisation of blood loss. Operative approaches aiming at preventing splanchnic organ stasis, careful handling of perihepatic inflammatory adhesions, and the maintenance of meticulous haemostasis of damaged collateral vessels originating from portal and splanchnic hypertension may result in a substantial proportion of patients who receive transplants without any need for coagulative blood products. Furthermore, surgical technique and skill are among the central determinants of the intraoperative release of tissue factor, which, in association with possible related technical defects, undoubtedly contributes to OLT-related vascular thrombosis[3].

RISK OF THROMBOEMBOLISM IN OLT

Thromboembolism during OLT is complex in aetiology and unpredictable in onset and evolution. The initiation of a procoagulative process may be triggered by abnormal thrombin generation and platelet function, along with a lack of efficacy of the profibrinolytic system. Secondary to cirrhosis, pro- and anti-coagulants make up an unstable balance, and several factors inherent to the procedure of transplantation can promote a hypercoagulable state[2].

Liver-related vascular thrombosis, such as portal vein thrombosis and hepatic artery thrombosis, systemic thromboembolic processes, and the formation of thrombi in the central venous and pulmonary circulation, are among the reported causes of either graft failure or life-threatening adverse events (Table 1).

Various transplantation-related triggers, such as surgical damage, the release of activators from the donor liver, blood stasis, and systemic inflammatory responses, can activate coagulation or induce platelet

Table 1 Perioperative thromboembolic events in liver transplantation

Arterial complications
Intraoperative hepatic artery thrombosis
Early postoperative hepatic artery thrombosis
Coronary artery thrombosis
Peripheral arterial occlusion
Intracardiac thrombosis
Pulmonary emboli
Paradoxical air/thromboembolism
Early portal vein thrombosis/re-thrombosis
Post-orthotopic liver transplantion deep vein thrombosis and inferior vena cava thrombosis

Table 2 Major risk factors for perioperative thromboembolic events in liver transplant

Abnormal thrombin generation
Defective profibrinolitic system due to elevated plasminogen activator inhibitor 1 endothelial type levels
Platelet activation from venous stasis or inflammation
Intestinal ischaemia and liberation of infectious mediators
Tissue thromboplastin release
Vascular clamping/unclamping
Platelet aggregates and microthrombosis around catheters
Severe ischaemia-reperfusion phenomena
Veno-venous by-pass
High pulmonary artery pressure
Anatomical and/or technical causes

activation. Other factors capable of increasing the thrombotic risk include clamping (total or partial) of the vena cava or portal vein, ischemic insults to the intestine, liberation of splanchnic infectious mediators, injury to a large capillary bed, release of tissue thromboplastin and use of venovenous bypass (Table 2).

A causative role of venovenous bypass in the development of thrombosis has been suggested, as the exposure of blood to the foreign surface of the tubing system is a well-known trigger activating coagulation, despite any heparin coating. However, some authors have suggested that, by reducing the stasis of blood in the inferior vena cava and splanchnic region during the anhepatic phase, venovenous bypass can reduce the risk of thrombus formation[3].

Perioperative thromboembolic complications can also occur after the migration of thrombi produced around pulmonary artery catheter or venous catheters or originating from a transjugular intrahepatic portosystemic shunt (TIPS)[3,4]. Additional factors include the excessive use of haemostatic agents (*i.e.*, fresh-frozen plasma, anti-Vitamin K agents, platelets, recombinant factor Ⅶa and antifibrinolytic drugs). Microthrombosis of the pulmonary circulation has also been attributed to platelet aggregates that are activated in the liver graft during reperfusion[4,5].

The impaired clearance of activated coagulation factors with gradual increases in the thrombin-antithrombin-Ⅲ complex, excessive activation of coagulation and consumptive coagulopathy may also be caused by a decreased hepatic blood flow or the poor recovery of a new graft. High pulmonary artery pressures, haemodynamic instability, and increased levels of serum lactate have also been recognised as intraoperative factors predisposing to thrombotic complications[6].

An enhanced haemostatic capacity not only related to an altered local flow dynamics but also to various acquired and genetic thrombotic risk factors may be observed in patients with Budd-Chiari-syndrome, pre-existing portal vein thrombosis, pelvic and deep leg vein thrombosis, Factor V-Leiden (APC resistance), protein C deficiency, primary biliary cirrhosis, primary sclerosing cholangitis, and malignant liver tumors[7].

The incidence, distribution, and severity of hypercoagulative state with associated complications in liver transplant recipients are still unknown. Krzanicki *et al*[8] by retrospectively reviewing the database of intraoperative thromboelastography (TEG) of 124 liver transplant recipients, observed a high rate of hypercoagulation in patients with cholestatic pathologies (42.9%) and with primary biliary cirrhosis (85.7%), in those with primary sclerosing cholangitis, and in those fulminant hepatic failure (50%) and non-alcoholic steatohepatitis (37.5%).

INTRACARDIAC THROMBOSIS AND PULMONARY EMBOLI DURING OLT

Although the estimated incidence of intracardiac thrombosis (ICT) and/or pulmonary emboli (PE) is low (reported ranges from 1.2% to 6.2%)[6], these serious complications are an often-overlooked cause of mortality during adult liver transplantation that can occur in any phase of the transplant. As reported by Lerner *et al*[9], approximately 30% of the cases were noted during the preanhepatic phase versus over 30% during the anhepatic and the reperfusion phase of the procedure.

In a review by Warnaar *et al*[10], the number of intraoperative reported episodes up to 2006 was 74, with PE alone in 32 patients (43%) and a combination of PE and ICT in 42 patients (57%). In the retrospective, single-centre review by Cherian *et al*[11], out of approximately 3000 OLTx performed from 1982 until 2007, only 36 patients were suspected of developing a PE (incidence rate of 0.37%).

A more recent series by Sakai *et al*[6] showed that the incidence of PE was 4.0% (20 cases).

Many case reports have been published with different onsets, treatment and outcomes. Most of the ITC and PE during OLT occurred within a few minutes after graft reperfusion[12].

The lower rate of ITC and PE observed in previous studies may be due to the absence or very infrequent use of intraoperative transoesophageal echocardiography (TEE), which could have helped to identify ITC and/or PE as a possible cause of sudden serious

haemodynamic derangement.

The suggested association between intraoperative PE and ICT and the use of antifibrinolytic drugs remain controversial and have not been completely demonstrated[11,13].

In the review by Cherian *et al*[11] of 74 patients with PE and/or ICT, 34 (46%) did not receive any antifibrinolytic drugs; in various other cases, antifibrinolytics were not implicated[9]. The case reports of patients who developed an intraoperative PE and/or ITC when aprotinin was given[14] have led to criticisms of the clinical safety of aprotinin. However, Warnaar *et al*[15] in a retrospective analysis of 1492 patients, demonstrated that intraoperative treatment with aprotinin was not associated with a significantly increased risk of postoperative thromboembolic events in comparison with controls.

Very rarely in liver recipients with porto-pulmonary syndrome or as a consequence of severe post-reperfusion pulmonary arteriolar severe vasoconstriction or pulmonary emboli, an abrupt increase in pulmonary artery pressure and right ventricular pressure can develop. In the presence of a significant increase in the right atrial pressure, an intra-atrial patent septum or foramen ovale may facilitate the passage of air bubbles from the right heart into the systemic circulation. Paradoxical air emboli and thromboemboli may thus be distributed to the terminal arteriolar bed of the brain and heart[16].

Serious ITC and PE manifest intraoperatively with systemic hypotension associated with increased pulmonary artery pressure or persistent haemodynamic instability not responding to supportive therapy. The combination of haemodynamic compromise and TEE imaging allows for a correct diagnosis. The identification of ITC with TEE is quite easy, but the identification of clots in the peripheral pulmonary arterial tree is almost impossible.

The overall mortality in the reported cases is high (from 45% to 68%), and better survival rates have been observed when aggressive cardioactive therapies and thrombolysis are immediately initiated. Thrombolytic therapy with recombinant tissue plasminogen activator (rTPA), despite the increased risk of significant haemorrhage, may reduce the mortality of patients with massive pulmonary embolism, generating superior survival (77%) over embolectomy (53%) or heparin[17]. Surgical pulmonary embolectomy, despite the potential serious risks facing a recipient with end-stage cirrhosis, has also been performed in such cases, generating more favourable results and complications than aggressive haemodynamic support alone[10].

INTRAOPERATIVE HEPATIC ARTERY THROMBOSIS

Acute thrombosis of the hepatic artery is a complication that develops more frequently in the paediatric population due to their smaller vessel diameters[18]. In adults, anatomic abnormalities of either native or graft hepatic arteries, multiple donor arteries requiring reconstruction, and thrombophilia have been implicated.

Mechanical factors, including internal flaps, prolonged clamping of the hepatic artery during the performance of the anastomosis, the kinking of a long artery, and intra-arterial haematoma predispose for the unexpected abrupt development of hepatic artery thrombosis[18]. Other attributable factors include poor arterial flow, increased sinusoidal resistance, preservation injury and an imbalance in the coagulation factors, predisposing to hypercoagulability[18,19]. The diagnosis is confirmed by hepatic artery palpation or intraoperative Doppler ultrasonography. Immediate surgical arterial thrombectomy and/reconstruction are fundamental to restoring graft function.

EARLY POSTOPERATIVE HEPATIC ARTERY THROMBOSIS

Thrombosis of the hepatic artery (HAT) can occur both early and/or months after the transplantation. The reported incidence of HAT ranges between 2.5% and 6% in adults and 15%-20% in children[18]. Early HAT may frequently occur when laboratory values indicate an incomplete recovery of graft function, suggesting the presence of a hypocoagulable state. Children are more susceptible to the development of HAT due to the small arterial vessels, split procedures, and involuntary development of a high haematocrit[19].

Although, in many cases of HAT, no anatomical or technical causes can be identified, the following conditions are among the prominent predisposing factors: graft oedema due to poor initial graft function, multiple recipient arteries, coeliac trunk stenosis, lienalis steal syndrome, injury of the intima of the donor hepatic artery, previous transarterial chemoembolisation, split and living related liver transplantation, aneurysm of the donor hepatic artery, aberrant arteries with fragile intima and long backtable arterial reconstruction before implantation[20,21]. Additional risk factors include increased blood product transfusion during transplant procedure, aortohepatic grafting, the need for infrarenal aorta vascular extension with respect to the use of supracoeliac aorta, and the presence of portal vein thrombosis before transplant[20-22].

A reduction in postanastomotic hepatic artery flow after revascularisation has been considered one of the most important predictors of early HAT after OLT[23].

A transient state of hypercoagulability, mainly postoperative hypercoagulability (*e.g.*, due to unnecessary excessive fresh frozen plasma or platelet administration), especially when associated with anatomical or technical abnormalities, can particularly act to precipitate HAT[24].

Postoperative cytomegalovirus infection, which leads to endothelial cell activation and increased platelet reactivity, has been associated with an increased risk of HAT[25].

Early HAT typically leads to the ischaemia/necrosis of the graft. Unexpected dramatic increases in transaminases associated with a decrease in the bile flow and lightening of the bile colour, fever and haemodynamic impairment (septic-like syndrome) are typical signs of diffuse hepatic cell necrosis from early HAT[21].

Biliary complications (intrahepatic biliomas and biliary stenosis) with the preservation of graft function, represent signs of late HAT. Ischemic insults can, in fact, induce direct injury to the cholangiocytes and/or damage to the arterioles of the peribiliary vascular plexus. These microcirculatory disturbances lead to the apoptosis and necrosis of the cholangiocytes, resulting in the formation of strictures, biliary apoptosis, necrosis, and cholangitis[20,21].

In liver recipients at risk for HAT, thromboprophylactic strategies with heparin followed by aspirin are beneficial, particularly in children. Sufficient anticoagulation is most significantly mandatory during the early postoperative period, despite its increased risk of postoperative haemorrhage. The risk of late HAT seems to be substantially decreased in patients receiving aspirin (3.6% *vs* 0.6%), suggesting a potential role of excessive platelet activation in the aetiology of this complication[26].

The early detection and prevention of HAT is of utmost importance, as these factors can heavily influence the prognosis of patients, particularly when found early after OLT. When not associated with "evident" graft failure, these features invariably involve the biliary strictures due to bile duct ischaemia.

Doppler ultrasounds of the hepatic artery and MRI angiography are effective for the diagnosis of early postoperative arterial stenosis and thrombosis.

Treatment of early HAT relies rarely on interventional radiological thrombolysis, on surgical thrombectomy, and sometimes on reconstruction as the definitive therapy. A late diagnosis of HAT or a failed surgical approach may require urgent re-transplantation[27].

Treatment of early HAT relies rarely on interventional radiological thrombolysis; surgical thrombectomy and sometimes anastomotic arterial reconstruction are the definitive therapy.

Portal vein thrombosis

Portal vein thrombosis (PVT) has been reported to occur in 4.9% to 10.6% of liver recipients, with the highest incidence occurring in the paediatric living donor population receiving left-side grafts[28,29].

Postoperative PVT may be partial, if there is some preservation of portal flow, or complete, if the occlusion involves the entire lumen. PVTs can emerge in the transplanted patients early after OLT, with marked clinical and biochemical signs, or at a variable time in the long-term course, with more subtle manifestations.

One important risk factor for the development of postoperative PVT is the presence of preoperative PVT, which is frequently associated with cirrhosis and liver cancer. However, this association is still controversial and has not consistently been demonstrated. In a report by Enestvedt *et al*[30], patients with preoperative PVT who did not have a higher rate of postoperative thrombotic events showed no adversely impacted patient survival after OLT.

Previous studies have shown that the incidence of early post-OLT rethrombosis in liver recipients with native PVT ranged from 5% to 21%[31]. In more recent data, the incidence of post-OLT portal vein rethrombosis after previous portal vein thrombectomy was found to be highly variable (6% to 40%)[32,33].

The preoperative extent of a thrombus within the portal venous bed is the main determinant of post-reperfusion portal flow, guiding both the risk and the speed of portal vein re-thrombosis. Patients with complete PVT with extension throughout the portal venous bed were once excluded from receiving an OLT[31]. Currently the decision to include among OLT candidates those with a diffuse preoperative PVT is based on both the centre's expertise and the surgeon's skill and decision.

Optimal perfusion of the portal vein is very important during the early postoperative period, and factors causing a steal phenomenon (*e.g.*, previous splenectomy, or large collaterals) may decrease the portal vein blood flow.

Other risk factors for post-transplant PVT include severe pre-transplant portal hypertension, other treatments for portal hypertension (*e.g.*, TIPS, portocaval shunt, splenectomy, and splenic vein embolisation), hypoplastic portal veins, mismatches in the size of the donor and the recipient portal vein, severe graft oedema, and large portosystemic collaterals[22]. Any injury to the portal vein wall (intimal injury) caused by a previous thrombectomy may also predispose to PVT, as well as any technical factors leading to redundancy, kinking, torsion, and stenosis at the site of the anastomosis[34].

Liver transplant recipients with significant preoperative portal vein occlusion, apart from their increased risk of rethrombosis, seem to be affected by a higher rate of serious postoperative complications and have a higher mortality[34]. Sharma *et al*[35] compared the incidence of postoperative complications in 78 recipients with PVT (study group) with a random sample of 78 contemporaneous recipients without PVT (control group). In the study group, the rate of primary non-functioning was significantly higher than in control group (9.0% and 1.3%, $P = 0.063$), with retransplantation rates of 17.9% and 7.7%, respectively ($P = 0.055$).

Early PVT causes severe graft ischaemia, ascites and increased portal vein pressure. Hepatic infarction

may develop, even in the absence of arterial compromise[36]. Irreversible graft loss mandates the need for emergency retransplantation (when possible). The clinical signs of early PVT parallel those of ingravescent allograft dysfunction, which can lead to haemorrhage, haemodynamic instability, intestinal ischaemia, and higher associated mortality[20]. A delayed onset of PVT is often not associated with severe graft failure but instead determines unavoidable portal hypertension. Frequent Doppler ultrasonography in the immediate postoperative period is essential to the early detection of PVT, especially in patients who have had a previous PVT. MRI-angiography and CT scans can confirm the diagnosis.

Percutaneous treatment of post-OLT PVT, with mechanical and/or pharmacologic thrombolysis, has been attempted, but the favourable results are mostly described in case reports.

Cherukuri *et al*[37] reported a successful transjugular approach on postoperative day 10 following OLT with an overnight infusion of urokinase, followed by a pushing of the residual clot into a competitive splenorenal shunt. Mechanical fragmentation of a portal vein thrombus with contemporaneous use of urokinase and subsequent stent positioning has also been described[38].

However, percutaneous interventions, thrombolysis, and systemic heparinisation are not always effective alternatives to surgery. Immediate reoperation with acute thrombectomy or surgical resection followed by direct anastomosis with/without a venous graft, is frequently the most successful option.

Early post-operative anticoagulation with a short course of heparin should be recommended in high risk liver recipients with an underlying prothrombotic state, and especially in those undergoing caval transposition and "non-anatomical" procedures[39]. Patients with the persistence of a prothrombotic state not reversed by transplantation should receive long term anticoagulation (*e.g.*, with antiVit K agents). The effect of low dose aspirin on the prevention of PVT or re-thrombosis is still not defined[40].

POST-OLT DEEP VEIN THROMBOSIS AND INFERIOR VENA CAVA THROMBOSIS

Deep vein thrombosis (DVT) is a rare post-transplant complication, with a reported incidence of < 3% in previous studies and between 3.5% and 8.6% in more recent series[41-43].

Major risk factors for post-OLT deep-vein thrombosis include venous stasis due to prolonged immobilisation, the development of a hypercoagulable state as a result of an aggressive surgery, the administration of excessive procoagulant factors, lupus anticoagulant, and the prolonged maintenance of indwelling femoral vein catheters[43].

An apparently well-functioning graft may also synthesise abnormal proteins that could increase the risk for thrombosis.

It is worth noting that some defects in the proteins involved in the regulation of anticoagulation (inherited antithrombin, protein C or protein S deficiency, the factor Ⅱ G20210A mutation) can also be transmitted through liver grafts from donors to recipients[44,45].

Recurrent deep-vein thromboses have been described in patients with "acquired" activated protein C resistance caused by a homozygous factor V Leiden gene mutation in a donor liver and in a liver recipient with a heterozygous protein C deficiency associated with dysfibrinogenaemia[45].

Liver-transplanted patients who receive a graft from a donor who was not screened for thrombophilic abnormalities are most likely not diagnosed as having a prothrombotic tendency until the first thrombotic episode occurs. In fact, screening for prothrombotic abnormalities is very rarely performed emergently before cadaveric transplantation. On the contrary, living-donor liver transplantation, which is a scheduled procedure, generally includes donor screening for genetic thrombophilic abnormalities.

In a retrospective review of 917 patients over 15 years, Salami *et al*[42] reported a 4.58% incidence of venous thromboembolism occurring up to 1 year after OLT. Twelve (1.31%) patients had pulmonary emboli and DVT originating from both the upper and lower extremities. Upper extremity DVT is infrequently or not reported in this setting, even though liver recipients who need large bore catheters into the subclavian or internal jugular veins for a long time could easily develop this complication. Upper extremity DVT seems to be a risk factor for PE comparable with that of the lower extremities DVT, and with a similar, or even higher, mortality[46,47].

Doppler ultrasound is the preferred method for detecting a venous thrombosis.

In the presence of either upper or lower extremity DVT, therapeutic doses of LMWH should be administered, followed by oral anticoagulant therapy. Liver recipients with major risk factors for bleeding are candidates for to inferior vena cava filter insertion. This device is also essential in those who require urgent surgery that precludes anticoagulation and in cases of combined DVT and PE.

RELEVANCE OF PHARMACOLOGIC THROMBOPROPHYLAXIS AFTER OLT

Owing to the risks of bleeding and coagulopathy, antithrombotic prophylaxis to prevent DVT, HAT, PVT or PE is not routinely used in the immediate postoperative period. Clinical practice and laboratory data demonstrate that the normalisation of a stable haemostatic system by a new liver may take some time; furthermore, thrombocytopenia may persist for weeks. However, it has been shown that end-stage

Table 3 Major indications for post-orthotopic liver transplantion thromboprophylaxis

Thrombophylic states
Excessive intraoperative administration of procoagulant factors
Split and living donor transplant
Small arteries or reconstructed arteries
Pre-transplant portal vein thrombosis
Complicated vascular anastomosis
Decreased portal vein blood flow
Hypoplastic portal vein
Caval transposition and "non-anatomical" procedures
Poor arterial flow
Multiple recipient arteries
Infrarenal aortohepatic grafting

cirrhotic patients may be at risk of DVT and PE, and some subset of liver recipients are at a very high risk of vascular thrombotic complications. For this reason, regardless of the lack of studies and guidelines on prophylactic anticoagulation in this setting, many institutions recommend such an approach in very particular circumstances[34]. The most difficult task is the decision of when, how and at which dose to use chemical anticoagulants, as no consensus exists, even in special high-risk situations. The risk of postoperative thromboembolism causing either serious haemodynamic events or loss of graft function needs to be weighed against the risk of bleeding. Bleeding complications may lead to intra-abdominal hematomas, graft dysfunction, infections, haemodynamic instability, renal dysfunction, or the need for the transfusion of blood products. Postoperative anticoagulation may preclude or delay urgent re-operations or other procedures, such as biopsy, endoscopy, and drainage insertion[48].

Patients who mostly benefit from routine thromboprophylaxis are those with recognised thrombophilia (as in Budd-Chiari syndrome) or those receiving massive amounts of fresh frozen plasma, platelet transfusions, or fibrinogen intraoperatively, especially if the recovery of graft function is rapid (Table 3).

Another group who should be considered for routine thromboprophylaxis consists of living donor transplants, paediatric transplants, pretransplant PVTs, recipients of grafts with reconstructed donor arteries, or those with complicated anastomosis at the portal site or difficult portal vein thrombectomy[49].

The value of a decreased PT, prolonged aPTT or increased INR as a predictor of hypocoagulability remains unclear after OLT, and some patients go on to develop a hypercoagulable state as a result of diminished anticoagulant and fibrinolytic activity. In addition to laboratory tests, the point-of-care monitoring of coagulation by ROTEM/TEG or other devices may help physicians to better identify "real-time" coagulation profiles.

In general, whether to administer prophylaxis depends on the clinical status of the patient, whereas the clinical presentation of any specific thrombotic event dictates the degree of anticoagulation required. A recent paper by Mukerji *et al*[48] advises not to begin anticoagulation until the post-transplant INR is above 1.5 to 2 and the platelet count is below 50000.

Paediatric patients or those with preoperative PVT, diabetes, obesity, hepatic cancer and a high cardiovascular risk may benefit from more intensive thromboprophylactic treatments.

These pharmacological strategies mainly rely on IV LMWH heparin and the combination of heparin plus aspirin. The risk/benefit of each approach must also be evaluated in relation to the distance from surgery, the protein synthetic function of the graft, and the possibility of strictly monitoring the pharmacologic effects of the drug. Assessing the efficacy of thromboprophylaxis is, in fact, difficult because the monitoring of antiXa activity may be unpractical; that of protein C, S, and antithrombin post-operatively produced, defective; and that of platelet function, unknown.

The administration of antithrombotic drugs in high-risk OLT recipients requires careful watching, as the anticoagulation efficacy in the presence of both graft and distant organ dysfunction may be unpredictable.

For example, a reduction in the dosage of LMWH is recommended because LMWH has demonstrated an increased anticoagulant potency in patients with cirrhosis[50]. Heparin, which enacts its anticoagulant activity by virtue of the enhancing effect provided by antithrombin, may display wide variations in activity depending on the graft synthesis of antithrombin. In addition, in the presence of renal dysfunction, heparin may accumulate, leading to the need for frequent dose adjustments.

In the study by Shay *et al*[51] post-transplant prophylaxis with 325 mg daily of aspirin was associated with a significantly lower incidence of early HAT and a non-significant lower incidence of PVT. As previously mentioned, the effectiveness of antiplatelet prophylaxis in reducing the incidence of Hat was also demonstrated by Vivarelli *et al*[26].

Combination therapy with i.v. heparin or LMWH plus aspirin has also been proposed to prevent early events in individuals at a high risk of PVT or HAT. The use of bivalirudin in a patient with Budd-Chiari syndrome who required post-OLT anticoagulation and with a history of heparin-induced thrombocytopenia was reported by Anderegg *et al*[52].

P2Y12 blockers (such as clopidogrel) and/or aIIbb3 blockers (such as abciximab), as well as thrombin inhibitors and inhibitors of activated factor X, such as dabigatran and rivaroxaban, have been proposed to prevent post-transplant arterial thrombosis. However, the lack of established reversal agents, their mechanism of clearance *via* the kidneys or liver, the risk of excessive anticoagulation in the immediate postoperative period, and unknown dose regimens have led to their very scarce consideration for the

purpose of thromboprophylaxis.

The use of an implantable pump into the portal vein with the purpose of preventing and treating any rethrombosis of the portal vein after OLT has been reported by Shi *et al*[53] Using a minitype implantable pump that was implanted through the right gastro-epiploic vein and had an extracorporeal tip on the skin surface slightly below the right costal arch, the authors delivered 250 U/kg of heparin every 24 h. The rate of rethrombosis in the portal vein was significantly lower than the rate of PVT among patients without an implantable pump. The implantable pump in their series significantly reduced the rate of relaparotomy or retransplantation and the in-hospital mortality rates.

CONCLUSION

Despite the traditional belief that a prolonged PT and APTT suggest a hypocoagulable state and a bleeding tendency, some liver recipients in the early postoperative period are prone to developing micro- and macro-thrombi within the splanchnic, systemic and pulmonary circulation. A dysfunctional coagulation system associated with hypercoagulability may persist for a variable time period, and some individuals may display a normal or even higher thrombin generation capacity[1].

It is worth noting that patients who are examined with conventional coagulation tests may not have their potentially reduced level of anticoagulant proteins be detected; more sophisticated investigations are often necessary. The delayed recovery of the anticoagulant proteins along with the normal activity of almost all of the procoagulant factors achieved from day 1 to 3 postoperatively was established several years ago[54].

Because conventional coagulation tests do not provide information about the quality or the dynamics of clot formation, the correction of postoperative coagulation parameters is unjustified unless clinical bleeding manifests.

An increasing awareness that hypercoagulability may potentially be exacerbated during transplant procedures should put physicians on alert for the rapid identification of possible predictors of vascular thrombosis. This awareness may help with the selection of those liver recipients most suitable for prophylaxis, a practice that continues to vary widely among centres.

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P- Reviewer: Berg T, Viegas C **S- Editor**: Ma YJ **L- Editor**: A
E- Editor: Ma S

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ISSN 1007-9327