Deep Vein Thrombosis and Pulmonary Embolism in Liver Transplant Patients: Risks and Prevention

James Yip, MSc, David A. Bruno, MD, Charlotte Burmeister, MS, Marwan Kazimi, MD, Atsushi Yoshida, MD, Marwan S. Abouljoud, MD, Gabriel T. Schnickel, MD

Introduction. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are surgical complications estimated to occur in 5% to 10% of patients. There are limited data regarding DVT/PE in the early postoperative period in liver transplant patients. The aim of this study was to determine risk factors that influence the incidence of DVT/PE and the effectiveness of prophylaxis. Methods. We reviewed the records of 999 patients who underwent initial liver transplant between January 2000 and June 2012 at Henry Ford Hospital. In 2011, a standardized prophylactic regimen using subcutaneous (SQ) heparin was initiated. All patients that developed either upper/lower extremity DVT or PE within the first 30 days of transplant formed the cohort of this study. Results. On multivariate analysis, only peripherally inserted central catheter (PICC) placement and SQ heparin were associated with DVT/PE. In patients receiving heparin, 3 (1.0%) had DVT/PE versus 25 (3.5%) who did not receive heparin (P < 0.03). Sixteen (6.9%) patients that had a PICC developed DVT/PE compared with 12 (1.6%) patients without a PICC (P < 0.001). In the heparin group, DVT/PE with PICC was reduced to 3 (3.0%) versus 13 (9.9%) in those with a PICC and did not receive heparin (P = 0.03). Mean time from transplant to DVT/PE diagnosis was 12.3 days. Length of hospitalization was significantly longer in patients who developed DVT/PE (18.5 vs 10.0 days, P < 0.001). Conclusions. In this study, we demonstrated that PICC placement significantly increases the likelihood of DVT/PE in liver transplant recipients. Prophylactic SQ heparin effectively reduced DVT/PE events in this patient population.

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patients with liver disease have a higher bleeding tendency, which was supported by abnormal coagulation tests including prolonged prothrombin time, activated partial thromboplastin time (aPTT), and low platelet count. These patients typically have significantly lower levels of factors responsible for coagulation, fibrinolysis, and platelet function. Interestingly, levels of von Willebrand factor (vWF) and factor VIII are elevated in these patients.12,13 It has been postulated that vWF elevation may be due to enhanced production by the endothelium or reduced clearance by the liver.14 The increased plasma levels of factor VIII may be secondary to the elevation of its carrier protein vWF. Because the platelet count does not take the elevated vWF levels into account, and because the prothrombin time and aPTT are insensitive to the plasma levels of anticoagulants, such as protein C, antithrombin, and tissue factor pathway inhibitor, they fail to reflect the true hemostatic profile and cannot predict the risk of bleeding in patients with liver disease.15-19 Studies have described the concept of rebalanced hemostasis due to reduction in both procoagulants and anticoagulants, and a marked resistance to the inhibitory action of thrombomodulin.20,21

Currently, the difficulty that physicians encounter is to determine when postreperfusion changes and coagulopathy revert in the postoperative phase to a normal or procoagulant state. Patients may be hypercoagulable early after OLT because of an imbalance between coagulation and fibrinolytic mechanisms, favoring a sustained prothrombotic state in the early postoperative phase.22 Furthermore, immunosuppressive drugs, such as cyclosporine, tacrolimus, and dexamethasone, may play a role in increasing platelet aggregation and thrombogenicity.23-25 It is well established that even as the graft regains normal function, there are transient defects in coagulation and fibrinolysis leading to altered clot formation and breakdown.22 There is currently limited data regarding VTE in the early postoperative period in liver transplant patients. The aim of this study is to identify risk factors associated with either DVT or PE and establish the effectiveness of thrombo-prophylaxis, specifically subcutaneous (SQ) heparin, in reducing the risk of DVT or PE in the OLT patient population.

MATERIALS AND METHODS

This was a retrospective review of all 1001 patients who underwent 1107 OLTs in the period of January 2000 to June 2012 at Henry Ford Hospital. One hundred and one patients had more than 1 transplant. Only the first transplant was included in this study. Two patients with missing VTE information were excluded. All patients older than 18 years with symptomatic VTE within 30 days after OLT were included in the study. Data were gathered from patient medical records which reflects inpatient hospitalization or outpatient visits. A 30-day cutoff was established to decrease the chance of including transplant-unrelated VTE events. Techniques of OLT included the traditional caval interposition technique with or without venovenous bypass and caval sparing, or piggyback technique, without venovenous bypass. In 2011, a standardized prophylactic regimen using SQ heparin (5000 U) every 8 hours was initiated. All patients with symptomatic upper extremity DVT, lower extremity DVT, and/or PE formed the cohort of this study. Diagnosis of DVT was confirmed radiologically using Doppler ultrasound; diagnosis of PE was confirmed using computed tomography pulmonary angiography. Peripherally inserted central catheter (PICC) lines were placed postransplant after the removal of the perioperatively placed cords and Swan-Ganz catheter in patients requiring central venous access for induction immunosuppression and/or total parental nutrition. Rabbit antithymocyte globulin was given as an induction agent centrally per institutional protocol. Patients diagnosed with DVT or PE were treated by PICC line removal and anticoagulation.

Results

Baseline characteristics of the patient cohorts are provided in Table 1. Of the 999 patients included in the analysis, 28 (2.8%) developed postransplant DVT or PE either during their initial hospitalization or within the first 30 days posttransplant. Eight patients with VTE events were women (28.6%) and 20 patients were men (71.4%), which were not statistically significant. The mean patient age was 54.8 years. The mean donor age in the VTE cohort was

### TABLE 1

| Patient demographics | Overall | No VTE (N = 971) | VTE (N = 28) | P |
|----------------------|---------|----------------|-------------|---|
| **Sex**              |         |                |             |   |
| Female               | 348 (34.8%) | 340 (35.0%) | 8 (28.6%) | 0.4804 |
| Male                 | 651 (65.2%) | 631 (65.0%) | 20 (71.4%) |        |
| **Age, y**           | 53.3 (9.8), 54.0 | 53.3 (9.8), 54.0 | 54.8 (10.3), 56.0 | 0.3362 |
| **MELD at TX (N = 887)** | 19.9 (8.8), 19.0 | 19.8 (8.7), 19.0 | 22.2 (10.7), 20.0 | 0.3694 |
| **Donor age (N = 642)** | 43.1 (17.0), 44.5 | 43.3 (17.0), 45.0 | 36.3 (14.9), 39.0 | 0.0615 |
| **Cold ischemia time (N = 957)** | 332.8 (116.9), 330.0 | 332.8 (116.9), 330.0 | 318.3 (119.5), 349.0 | 0.9513 |
| **Warm ischemia time (N = 965)** | 45.8 (24.0), 43.0 | 45.9 (24.3), 43.0 | 43.0 (10.4), 42.0 | 0.5213 |

Numbers in table reported as frequency (%) or mean (STD), median. Data were analyzed by Wilcoxon rank sum test for numeric variables and χ² test of independence for categorical variables.
slightly lower at 36.3 years, although it was not statistically significant. The average MELD score at transplantation was 22.2. Mean cold and warm ischemia times were 318.3 and 43.0 minutes, respectively.

In the VTE group, the etiology of cirrhosis are as follows: 3 patients due to alcohol, 3 patients due to hepatitis C, 1 patient due to nonalcoholic steatohepatitis, 2 patients due to hepatocellular carcinoma, and 2 patients due to autosomal-dominant polycystic kidney disease. In the VTE + PICC group: 5 patients were due to alcohol, 1 patient due to hepatitis C, 1 patient was cryptogenic, 1 patient due to hereditary hemochromatosis, 1 patient due to primary sclerosing cholangitis-uloerative colitis, 1 patient due to nonalcoholic steatohepatitis, 2 patients due to lupus, 1 patient drug-related, 2 patients due to hepatocellular carcinoma, 1 patient was benign, and 1 patient due to autosomal-dominant polycystic kidney disease.

Orthotopic liver transplantation patients that developed VTE stayed in the hospital for an average of 24.8 days compared with 14.2 days by patients without VTE ($P < 0.0001$, Wilcoxon rank sum test). Peripherally inserted central catheter line placement was not associated with an increased length of stay in VTE patients ($P > 0.05$, Wilcoxon rank sum test). The minimum time to develop VTE after transplant was 2 days. The mean time to VTE within 30 days of transplant was 12.3 days.

Peripherally inserted central catheter line placement in OLT patients was assessed to determine whether it affects the risk of VTE. From the 766 patients who did not have a PICC line placed during their initial hospitalization, 12 (1.6%) patients developed VTE within the first 30 days postransplant (Figure 1). Seven (58.3%) of the DVTs were located in the upper extremity, 3 (25.0%) in the lower extremity, and 2 (16.7%) were PEs. From the 233 patients who had a PICC line placed, 16 (6.9%) patients developed VTE (Figure 1). Seven (41.2%) of the DVTs were located in the upper extremity, 6 (35.3%) in the lower extremity, and 4 (23.5%) were PEs ($P > 0.05$, $\chi^2$ test of independence). One patient developed simultaneous lower-extremity DVT and PE.

Prophylactic SQ heparin was given to patients as a preventative strategy for VTE. From the 288 patients who took SQ heparin, only 3 (1.0%) patients developed VTE within 30 days posttransplant. Twenty-five of 711 (3.5%) OLT patients that did not take SQ heparin developed posttransplant VTE within the 30-day period (Figure 2).

Of the 233 OLT patients with PICC line placement, 132 patients did not take SQ heparin. Thirteen (9.9%) patients that had a PICC line and did not take SQ heparin developed VTE within 30 days postransplant. Of the 101 patients who had a PICC line and took SQ heparin, only 3 (3.0%) patients developed postransplant VTE (Figure 2).

On multivariate analysis, PICC line placement in OLT patients resulted in a 6.3 times greater odds (95% CI, 2.9-13.8) of developing postransplant VTE within the 30-day postransplant period ($P < 0.0001$). Prophylactic SQ heparin was associated with a decrease in transplant-associated VTE, as patients without SQ heparin prophylaxis had a 5 times greater odds (95% CI, 0.1-0.7) of developing VTE ($P < 0.01$).

White blood cell count, platelet count, INR, age, and MELD score were collected as possible factors associated with postransplant VTE. Values for WBC count, platelet count, and INR were collected preoperative, day 1, day 5, and day 7 posttransplant. Using the Wilcoxon rank sum test, however, there was no difference between these factors and VTE in this study (Table 2).

**DISCUSSION**

A general population study that monitored 21 680 persons for VTE events over 7.6 years demonstrated that about half of all thrombotic events were considered secondary to triggering factors, with multiple risk factors present in 65% of cases. We previously found that diabetes, previous history of VTE, and the diagnosis of end-stage renal disease all increase the risk of VTE in OLT patients. Another retrospective study associated an increased risk of DVT after transplantation with patients who were discharged to rehabilitation centers, received factor VII during surgery, or had postoperative pneumonia. In our present study, we discovered that PICC line placement also significantly increases the risk of VTE. A meta-analysis review of 29 503 hospital patients demonstrated a risk of DVT at 2.7% with PICC line placement, compared with 6.9% in our transplant-specific population. In the meta-analysis review, PICC line was associated with a higher risk of DVT than central venous catheters, with...
Possible predictive and risk factors for posttransplant VTE

|          | No VTE, N: mean (STD), median | VTE, N: mean (STD), median | P     |
|----------|------------------------------|---------------------------|-------|
| WBC      |                              |                           |       |
| Preoperative | 970: 6.7 (10.2), 5.5       | 27: 7.1 (3.8), 6.0         | 0.2720|
| Day 1     | 961: 11.5 (12.9), 10.3      | 28: 10.8 (6.3), 8.2       | 0.4339|
| Day 5     | 932: 8.6 (9.7), 7.1         | 27: 10.2 (8.9), 7.8       | 0.2665|
| Day 7     | 825: 9.2 (5.7), 8.0         | 26: 9.5 (5.5), 7.5        | 0.9137|
| Platelet  |                              |                           |       |
| Preoperative | 971: 102.8 (70.9), 88.0    | 28: 111.3 (79.2), 89.5    | 0.5521|
| Day 1     | 961: 71.3 (44.2), 62.0      | 28: 71.1 (52.5), 60.5     | 0.5014|
| Day 5     | 933: 71.1 (43.5), 61.0      | 27: 73.6 (43.5), 54.0     | 0.7211|
| Day 7     | 826: 93.2 (52.1), 81.0      | 28: 93.0 (51.5), 81.0     | 0.8946|
| INR       |                              |                           |       |
| Preoperative | 969: 1.8 (4.3), 1.5         | 28: 1.9 (1.0), 1.5        | 0.3884|
| Day 1     | 947: 1.7 (3.0), 1.5         | 28: 1.8 (0.6), 1.7        | 0.0214|
| Day 5     | 565: 1.3 (1.8), 1.2         | 20: 1.3 (0.2), 1.2        | 0.1500|
| Day 7     | 477: 1.3 (2.8), 1.1         | 25: 1.3 (0.1), 1.2        | 0.0212|
| Age       | 971: 53.3 (9.8), 54.0       | 28: 54.8 (10.3), 56.0     | 0.3662|
| MELD      | 859: 19.8 (8.7), 19.0       | 28: 22.2 (10.7), 20.0     | 0.3694|

TABLE 2. Possible predictive and risk factors for posttransplant VTE

WBC count, platelet count, INR, age, and MELD score were collected. Data were analyzed by Wilcoxon rank sum test.

The highest proportion in patients who were critically ill (13.91%) or with cancer (6.67%). As we demonstrate a baseline VTE incidence of 1.6% in OLT patients without PICC in our study, it is possible that both OLT and PICC line placement act synergistically as risk factors for VTE. We initially began using PICC lines to limit the risk of infection associated with central lines based on earlier data. However, based on our study, it is clear that the decision to insert PICC lines in liver transplant recipients should be guided by evaluating its benefits versus the risk for VTE.

Multiple studies have demonstrated that many procoagulants are altered in liver transplant recipients. One study showed that factors V and VII did not return to normal activity until 3 days after transplant, whereas another study found elevated levels of factor VIII. Von Willebrand factor was demonstrated to be substantially elevated in patients for up to 10 days post-OLT. Another study found that platelet count, INR, and MELD score were ineffective predictors of VTE. However, the authors in that study found low serum albumin to be an independent predictor for VTE. Multiple studies have also linked low serum albumin as an independent risk factor for VTE in cirrhotic patients, specifically with albumin lower than 1.9 g/dL.

Another study found an increased risk of VTE in cirrhotic patients younger than 45 years, beyond which the risk was modestly lower in compensated cirrhotic patients. In our study, we did not find an association between age and VTE events in the OLT patient population. An understanding of the risk factors for VTE is necessary to minimize the incidence of this disease in the transplant patient population, and further studies are needed to discover which markers can effectively predict a patient’s risk for VTE.

Vascular diseases account for 21% to 50% of deaths in transplant patients after 5 years. In a large population-based study, patients with liver disease were shown to have an increased risk for VTE events compared to the general population. A hypercoagulative state has been demonstrated to worsen cirrhosis, possibly through Ito cell activation or as a consequence of hepatic microthrombi. A recent study has shown that prophylactic enoxaparin therapy decreases the risk of decompensation in cirrhosis. The overall DVT incidence after liver transplantation has ranged between 2.7% and 8.6% in studies. Despite these findings, there is currently limited data regarding VTE prophylaxis in liver transplant recipients in the immediate postoperative phase. There is tremendous potential for the use of thromboprophylaxis in patients at risk for VTE, and it is estimated that up to 25% of all VTE events may be avoided. In our study, we demonstrated that prophylactic SQ heparin significantly reduces VTE events. Although antithrombin deficiency in the early postoperative phase is of concern for the effectiveness of heparin as a prophylaxis, our study identifies SQ heparin as a viable prophylactic tool to prevent VTE in OLT patients. In support of thromboprophylaxis, studies have found that heparin did not increase the risk of bleeding in patients with cirrhosis. Other therapies include enoxaparin, which has been shown to prevent portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Aspirin use has been demonstrated to have an 80% relative risk...
reduction in hepatic artery thrombosis. As a retrospective clinical study, we were limited to symptomatic patients captured in medical records and did not evaluate patients with asymptomatic VTE. We also did not adjust for other risk factors that are both associated with PICC line requirement and VTE, thus it is possible that PICC lines are merely a marker of greater underlying severity of illness or an unmeasured confounder. Similarly, SQ heparin prophylaxis may have been avoided in patients with greater bleeding risk, such as difficult operations or multiple comorbidities, which could potentially skew the data. Despite these limitations, however, we believe that SQ heparin should be used as a prophylaxis in OLT patients suspected to be at high risk for VTE. We did not pursue details specific to PICC device or site, because our focus was simply on the presence of the PICC rather than a study focusing on PICC-related factors. We decided to use unfractionated heparin as opposed to enoxaparin due to its shorter half-life, lack of contraindication with renal insufficiency, and low cost. Although newer anticoagulants, such as dabigatran, rivaroxaban, and apixaban, have the advantages of oral intake and lack of requirement for laboratory monitoring, there is currently no reversible agent for these drugs in case of active bleeding, and the limited data regarding their use in cirrhotic patients restrict their clinical applicability. Because of the lack of a clinically applicable coagulation test that reliably predicts the risk of bleeding or thrombosis, further studies are needed to identify patients who are most susceptible for VTE and would benefit most from SQ heparin prophylaxis. In liver transplant recipients who require a PICC line for central venous access, we recommend SQ heparin prophylaxis to minimize the risk of postoperative VTE and its associated complications.

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