Utility of Oral Anticoagulants as Prophylaxis of Recurrent Portal Thrombosis after Liver Transplantation

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ABSTRACT

Introduction. Portal vein thrombosis (PVT) is a relatively common finding in patients undergoing liver transplantation. Although the recommendation to prevent its recurrence is anticoagulation for a duration of 3 to 6 months, this is controversial.

Aim. The aim of our study was to determine the efficacy of oral anticoagulants (OAC) as prophylaxis for recurrent PVT after liver transplantation.

Materials and Methods. Our study included 215 liver transplant patients who underwent surgery in our center from January 2012 to August 2017. We selected all patients diagnosed with PVT either pre-transplantation (using Doppler echography or Angio-CT) or during transplant surgery. All patients with PVT were initially anticoagulated with low-molecular-weight heparin in the postoperative period; at discharge they received OAC for a duration of six months. Control Doppler ultrasound was performed at 3, 6, and 12 months post-transplantation.

Results. PVT was identified in 37 out of 215 patients (17.2%). PVT was diagnosed with a pre-transplant vascular study in 17 out of 37 cases (45.9%). All patients were anticoagulated with OAC (warfarin) for at least 6 months. There were no cases of recurrent thrombosis and no complications associated with anticoagulant treatment throughout the follow-up period.

Conclusions. The prevalence of portal thrombosis in liver transplant patients in our study was fairly high, at 17.2%. PVT was identified in nearly 50% of patients using high-quality vascular studies prior to transplant surgery. Anticoagulation with OAC for 6 months was effective in preventing a recurrence of thrombosis and there were no associated complications.

PORTAL vein thrombosis (PVT) is a well-recognized complication in patients affected by cirrhosis with or without hepatocellular carcinoma and is frequently observed in candidates awaiting liver transplantation (LT). The incidence of PVT in patients on the waiting list is described, ranging between 6.5% to 7.5% [1,2]. On the other hand, the prevalence of PVT varies between 5% and 26%, taking into account the oldest and newest series [3]. For the diagnosis of PVT, computed tomography (CT) with contrast, portal venography, or Doppler ultrasonography can be used to evaluate venous patency and thrombosis in most cases. CT offers better-defined images of the mesenteric veins, renal veins, and inferior vena cava, and allows for the identification of spontaneous portosystemic shunts. Ultrasound provides quantification and qualification of the flow direction in the portal vein (PV) trunk and intrahepatic

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branches [4]. PVT was sometimes identified during the surgical procedure.

For patients with PVT awaiting LT, anticoagulation is not universally adopted, although high rates (up to 42%) of successful complete recanalization have been observed in patients receiving anticoagulants. The use of anticoagulants in candidates for LT is still debated due to the risk of gastrointestinal bleeding and intra-abdominal hemorrhage before and after surgery [3]. The post-transplant PVT recurrence varies according to the series reviewed, ranging from 36% of pioneering experiences to 2-3% of some recent series [4]. Re-thrombosis occurs, especially in the early post-operative period. With regard to the survival of patients with or without post-transplant PVT, the most current series show no significant differences between the groups [5].

No fixed protocol is established for patients with PVT undergoing LT. Among post-transplant patients with portal vein anastomoses (anastomosis or thrombosis) and adequate portal flow, some transplant groups recommend a short course of heparin or fractionated heparin within the first post-operative days to minimize the risk of early re-thrombosis. Others recommend a course of low-molecular-weight heparin or warfarin lasting several months [4]. Anticoagulation has been recommended for 3 to 6 months in patients with portal vein thrombosis, although the usefulness of this intervention is controversial [6]. Patients with a documented pro-thrombotic state should receive long-term anticoagulation if the prothrombotic state has not been reversed by transplantation [7].

Although PVT is not a contraindication to LT, it may cause technical difficulties during surgery and have a negative impact on the outcome. Occasionally, it may represent a definitive contraindication for transplantation [7,8] and it is associated with increased intraoperative and postoperative morbidity and mortality. PVT imparts a risk of recurrent thrombosis [9]. Early re-thrombosis generally results in graft loss with the need for emergency re-transplantation [10].

AIM

The aim of our study was to study the efficacy of an oral anticoagulant (OAC) protocol to prevent the recurrence of PVT after LT.

MATERIALS AND METHODS

We performed a retrospective study from January 2012 until the end of August 2017 including 235 LT in 215 patients. We selected all the patients with PVT diagnosed before LT or during surgery. All the patients with a PVT were included in the prevention protocol with OAC for a duration of 6 months.

When evaluating PVT, we must distinguish between a bland thrombus and tumor thrombus. Imaging characteristics of tumor thrombus include a nearby mass with characteristics of hepatocellular carcinoma or other malignancy, enlargement of the vessel by endoluminal material which might have contrast enhancement on the arterial phase, and thrombosis in the setting of an elevated alpha-fetoprotein [1]. All patients in the pre-transplant study underwent an imaging study with Doppler ultrasound and angio-CT scan. If thrombosis was identified and the presence of esophageal varices was ruled out, anticoagulation was initiated with low-molecular-weight heparin until the moment of transplantation. When PVT was identified during the surgical procedure the anticoagulation was begun post-LT.

In both cases, an anticoagulant regimen with low-molecular-weight heparin was started on day 4 or 5 post-transplant for 4 weeks and subsequently changed to a daily oral anticoagulation regimen with warfarin. During the follow-up, Doppler ultrasound was performed on days 0, 1, 3, and 7 post-transplant and at the first, third, sixth, and twelfth month after procedure. At the sixth month, the need to continue with the oral anticoagulation regimen was evaluated. The anticoagulant was withdrawn if there were no signs of re-thrombosis of the portal vein in the sixth month, but if there were genetic predisposing states to thrombosis OR pro-thrombotic states (such as atrial fibrillation or antiphospholipid syndrome) anticoagulant treatment was continued for these patients.

RESULTS

We included 215 patients in the study. The etiology of liver cirrhosis (Table 1) included alcohol (54%), HCV (18%), HBV (8%), cholestatic liver disease (8%), cryptogenic (8%), and AIH (2%).

Portal vein thrombosis was identified in 37 out of 215 patients (17.2%) (Figure 1). PVT was diagnosed with a pre-transplant vascular study in 17/37 (45.9%) of cases and 20/37 (54.1%) during LT surgery. In patients with PVT, the

Table 1. Clinical and Demographic Characteristics of the Sample Population

Variables	Statistics (N = 215)
Female	76 (35.35%)
Male	139 (64.65%)
Age at Tx, mean ± SD	60.3 ± 9.03
Original Diagnosis:	
Alcohol	117 (54%)
HCV	40 (18%)
HBV	18 (8%)
Cholestatic	18 (8%)
Cryptogenic	18 (8%)
AIH	4 (2%)
Body Mass Index, mean ± SD	27.6 ± 4.9
Protrombine Activity	60.82%
INR, mean	1.7
Donor Source:	
Cadaveric	100%
Follow-up time post-Tx (months)	37.59
Pre-Disposing Conditions:	
AF (Pre-Tx)	16 (7.44%)
AF and PVT (n = 37)	2/37
Anti-P Syndrome	2 (0.92%)
Smoking:	
Never	45.36%
Ex-smoker	34.02%
Current	20.62%
Cholesterol (mg/dl), mean ± SD	161 ± 65
Triglycerides (mg/dl), mean ± SD	104 ± 49

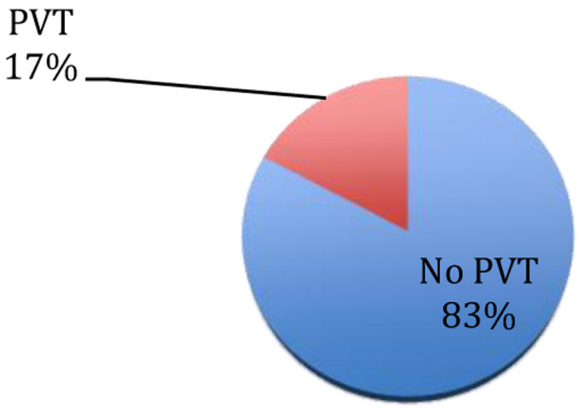

Fig 1. Rate of portal vein thrombosis (PVT).

extension of the thrombosis was short in 26 of the 37 (70%) and long in 11 (30%) (Table 2), according to Yerdel's classification [11], considering short grades I and II and long grades III and IV. Incidentally, we found cavernous transformation in 5 of the 37 patients (13.5%). Hypercoagulability syndrome was identified in only 2 patients. None of these findings prevented LT.

According to the protocol, all patients received low-molecular-weight heparin (1 mg/kg twice a day) in the immediate postoperative period and were discharged with OAC (warfarin) for at least 6 months. Most of the patients (33 of the 37, or 89.19%) were on OAC for 6 months. There were 4 patients (10.81%) for whom anticoagulation was not withdrawn after 6 months due to atrial fibrillation (2 patients, 5.4%) or the detection of hypercoagulability syndrome (2 patients, or 5.4%).

There were no cases of recurrent thrombosis and no complications associated with anticoagulant treatment throughout the follow-up period. Anticoagulation was withdrawn in the rest of the patients (89.19%) in the sixth month after LT.

DISCUSSION

In this retrospective, descriptive study, we can see that the main indication for LT in our Center is alcoholic cirrhosis, followed by HCV cirrhosis. Despite conducting an exhaustive evaluation of patients before LT, the detection of PVT is similar during the surgery itself than before transplantation (45.9% and 54.1%, respectively). This has been reported in previous studies in which preoperative imaging detected the presence of PVT in 53% of cases [12]. The reported rate of preoperative detection of PVT ranged from 21% to 87%, which may depend primarily on two factors: the grade of thrombosis and the follow-up protocol for each center, which determines the time interval between imaging and transplant [3]. It is possible that performing 2 image tests to assess vascular permeability can increase the pre-transplant diagnostic rate.

Table 2. Prevalence and Types of PVT in LT Patients

Prevalence of PVT	31/215 (17.2%)	
Portal Vein Thrombosis	Short (Grades I-II)	26/37 (70%)
	Long (Grades III-IV)	11/37 (30%)
	Cavernous Transformation	5/37 (13.5%)

We did not identify any adverse events related to anticoagulation and there was no recurrence of PVT in our study cohort. This result coincides with the results published in the most recent series [3]. Re-thrombosis was been reported in 10.3% of cases in the absence of a preventive strategy and decreased to 6.1% with the utilization of anticoagulation to prevent re-thrombosis [13]. Male sex, prior PVT therapy, Child C class, and alcoholic liver disease are the risk factors for recurrence [2].

Currently there is no consensus on the indication of anticoagulation in PVT in LT, but in our series it seems that anticoagulation is a safe and effective prophylaxis for re-thrombosis, as there were no hemorrhagic complications.

CONCLUSIONS

The incidence of portal thrombosis in patients undergoing LT in our study was fairly high at 17.2%. Portal vein thrombosis was identified in nearly 50% of patients despite the use of high-quality vascular studies prior to transplant surgery. Anticoagulation with OAC for 6 months was effective in preventing recurrence of thrombosis and there were no associated complications. Ongoing anticoagulation is needed for those in whom a prothrombotic state was reversed by transplantation. In our study, 10% of the patients needed chronic OAC because they presented with associated risk factors for thrombosis, such as atrial fibrillation or hypercoagulability syndromes.

We postulate that 6 months of OAC is a useful standard in cases of patients with PVT after LT. However, this was an observational, retrospective study in a single center, which limits our ability to make definitive conclusions. Prospective and randomized studies are needed in the future.

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