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Risk Factors and Outcomes of Intracardiac Thrombosis During Orthotopic Liver Transplantation

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ABSTRACT

Background. Intracardiac thrombosis incidence during orthotopic liver transplantation is estimated at 0.36% to 6.2% with mortality up to 68%. We aimed to evaluate risk factors and outcomes related to intracardiac thrombosis during orthotopic liver transplantation.

Materials and Methods. A comprehensive retrospective data review of 388 patients who underwent orthotopic liver transplantation at an urban transplant center from January 2013 to October 2016 was obtained.

Results. Six patients were found to have documented intracardiac thrombosis; 4 cases were recognized during the reperfusion stage and 1 during pre-anhepatic stage. All allografts were procured from decreased donors with a median donor age of 44 years (interquartile range, 35.25-49.75) and the cause of death was listed as cerebrovascular accident in 5 donors. Preoperative demographic, clinical, laboratory, and historical risk factors did not differ in patients with thrombosis. None had a prior history of transjugular intrahepatic portosystemic shunt or gastrointestinal bleeding. Three patients had renal injury, but no intraoperative hemodialysis was performed. Transesophageal echocardiographic findings included elevated pulmonary artery pressure (1/6), right ventricular strain (1/6), and pulmonary artery thrombus (1/6). Three patients died intraoperatively. Tissue plasminogen activator alone was given to 1 patient who did not survive, intravenous heparin only to 1 patient with resolution, and a combination of both was used in 2 patients with clot resolution achieved.

Conclusion. Cardiac thrombosis should be considered in patients having hemodynamic compromise during liver transplantation. Transesophageal echocardiography is a useful diagnostic tool. Intracardiac thrombosis treatment remains challenging; however, using both thrombolytics and heparin could achieve better results.

INTRACARDIAC thrombosis (ICT) is a rare complication that can occur during orthotopic liver transplantation (OLT). The incidence of the event varies among the studies in the literature ranging between 0.36% and 6.2% depending on the study examined [1,2]. Most recently, a study that included one of the largest cohorts of adult liver transplant recipients (n = 65,308) found that devastating intracardiac and pulmonary thromboembolisms occurred at a rate of 0.13% within 24 hours of liver

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transplants [3]. Moreover, the mortality and morbidity rate of the complication is exceedingly high despite interventions [2,4,5] with most of the deaths, up to 82%, occurring intraoperatively [6].

The clinical presentation for ICT during OLT includes a sudden increase in the pulmonary artery pressure, systemic hypotension. and cardiac arrest [5]. The complication can occur during any stage of OLT but has been shown to occur most frequently during the pre-anhepatic and post-reperfusion stages [2,5].

The pathophysiology of ICT during OLT is poorly understood. It is suggested that multiple factors such as inflammation, stasis, ischemia, vascular clamping, deficiency of profibrinolytic activity, and platelet activation could initiate the procoagulant state [7]. Multiple risk factors have been linked with the development of ICTs including symptomatic or surgically treated portal hypertension (gastrointestinal bleeding, trans-jugular intrahepatic portosystemic shunt [TIPS] procedure, or portocaval shunt surgery), intraoperative hemodialysis, and atrial fibrillation [5]. Other risk factors include a prior history of pulmonary embolism, portal vein thrombosis, functional status (Karnofsky score) <20, preoperative ventilator support, diabetes mellitus, and Asian ethnicity [3]. Lastly, aminocaproic acid and other antifibrinolytic therapies have not been shown to contribute to thromboembolic complications following liver transplants [8].

Currently, transesophageal echocardiogram (TEE) is the only confirmatory tool for ICT, but it is not a routine procedure in many transplant centers [2]. Most common indications for use of intraoperative TEE during OLT are hemodynamic monitoring and hemodynamic instability [9].

Due to the scarcity of cases reported of ICT during OLT, further research is needed to better define the complication and clinical signs. Our study aims to contribute to the relatively small pool of available cases by examining its rate of occurrence, risk factors, and patients' outcomes.

MATERIALS AND METHODS

A retrospective data review of patients who underwent liver transplantation at a single transplant center from January 2013 to October 2016 was completed using data from an urban center with high referral rates from the surrounding areas. Patients with a documented history of ICT during OLT in the Henry Ford Health System database were identified. Preoperative and intraoperative data were reviewed in liver transplant patients who developed intraoperative ICT. Clinical demographics data were obtained for each patient including socioeconomic information, end-stage liver disease etiology, and other comorbidities including but not limited to hypertension, diabetes status, history of atrial fibrillation, thrombo-embolism history, acute and chronic renal dysfunction, and prior transplant history. Model for End-Stage Liver Disease (MELD) score at the time of liver transplantation was obtained. Comprehensive review of preoperative laboratory, imaging and clinical parameters, intraoperative laboratory and hemodynamic data, and clinical diagnosis was completed. Intraoperative TEE findings, location of thrombus, and management were also gathered. Complications and outcomes of each patient were reviewed. Descriptive data analysis was performed.

Protocol number 10803 was reviewed and approved by the Henry Ford Health System Institutional Review Board. Formal consent was not required owing to the nature of the study. Retrospective electronic data review met human subjects and Health Insurance Portability and Accountability Act privacy requirements. This study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. A documentation of compliance with the ethical standards set forth in the Helsinki Congress was included with the submission.

RESULTS

Six (1.5%) patients with ICT from a total of 388 liver transplants during the study period were identified. Patient characteristics and specifics are detailed in Tables 1 and 2. Of the patients identified, 2 were female and 4 were male. Median patients' age was 53 years (interquartile range [IQR], 48.75-57). Etiologies of liver failure included alcoholism, autoimmune hepatitis, primary sclerosing cholangitis, and hepatitis B and C. MELD scores ranged from 13

Table 1. Characteristics of Patients Who Developed Intracardiac Thrombosis During Orthotopic Liver Transplantation

Patient	Age	Sex	Etiology	Other Comorbidities	MELD	Intraoperative Stage
1	52	Female	Alcoholism	HRS status postconcomitant renal transplant	39	Pre-anhepatic
2	60	Male	Hepatitis B	HTN, DM, pulmonary HTN, and CKD	18	Reperfusion
3	56	Female	Hepatitis B	AKI, prior DVT, HTN, DM, and mesenteric thrombosis	24	N/A
4	54	Male	Primary sclerosing cholangitis	AKI and bile duct resection	31	Reperfusion
5	51	Male	Hepatitis C	HTN, pulmonary HTN, and prior liver transplantation	18	Reperfusion
6	42	Male	Autoimmune	None	13	Reperfusion

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; DM, diabetes mellitus; DVT, deep vein thrombosis; HRS, hepatorenal syndrome; HTN, hypertension.

Table 2. Medications Administered, Coagulation Studies, and Mortality for Patients Diagnosed With Intracardiac Thrombosis During Orthotopic Liver Transplantation

					INR/PT (s)			
Patient	Aminocaproic Acid	Protamine	tPA	Heparin	Preclot	Postclot	Site of ICT	Death
1	Yes	Yes	Yes	Yes	3.1/32	2.1/23.4	RA	No
2	Yes	No	Yes	Yes	1.1/14.7	2.2/24.1	RA	No
3	Yes	No	No	No	5.8/48.5	N/A	All chambers	Yes
4	Yes	Yes	No	Yes	1.3/15.9	3.3/33.4	RA and RV	No
5	Yes	Yes	No	No	1.6/18.9	4.3/40.8	Unknown	Yes
6	No	No	Yes	No	1.4/16.7	N/A	LA	Yes

Abbreviations: INR, international normalized ratio; LA, left atrium; PT, prothrombin time; RA, right atrium; RV, right ventricle; tPA, tissue plasminogen activator.

to 39. Three patients had MELD scores less than 20. Hypertension was the most common comorbidity found in 3 patients followed by diabetes mellitus and renal disease. All allografts were procured from decreased donors with a median donor age of 44 years (IQR, 35.25-49.75), and the cause of death was listed as cerebrovascular accident in 5 donors. Cause of death data was not available for 1 of the donors.

Four cases were recognized during the reperfusion stage, and 1 occurred during the pre-anhepatic stage. Preoperative thrombocytopenia (platelets count $<150 \times 10^9$/L) was present in 4 patients. Two patients had portal vein thrombosis. One patient had hepatorenal syndrome requiring concomitant renal transplant, and 2 patients had acute kidney injury prior to transplant, but no intraoperative hemodialysis was needed. Patient #3 was actually listed for multivisceral transplantation (liver, pancreas, and small bowel). Aminocaproic acid was used in 5 patients, and 3 patients were given protamine. All patients received blood products during surgery. None had a prior history of atrial fibrillation, TIPS, or gastrointestinal bleeding.

Systemic hypotension (n = 5), elevated pulmonary arterial pressure (n = 1), or loss of pulses (n = 2) were the clinical manifestations observed in patients with ICT. TEE findings included elevated pulmonary artery pressure (1/6), right ventricular strain (1/6), pulmonary artery thrombus (1/6), and ICT (Fig 1) in all 6 patients with 4/6 of them having right-sided thrombi.

Five patients had cardiac arrest; of those, 3 patients died intraoperatively. One patient was re-transplanted owing to hepatic artery thrombosis with extensive hepatic necrosis. Treatment modalities used included the following: tissue plasminogen activator (tPA) therapy alone was given to 1 patient who did not survive, heparin only to 1 patient with resolution, and a combination of both was used in 2 patients with clot resolution achieved. Two patients did not receive either therapy and died.

DISCUSSION

Incidence and Diagnosis

The incidence of ICT in the study was 1.5%, which is consistent with the incidence rate that has been reported in the literature [1,2]. There is no uniform practice for diagnosis of ICT during liver transplantation. Although some centers use routine intraoperative TEE, similar to our institution, others use TEE selectively as dictated by clinical suspicion. Peiris et al diagnosed their patients based on clinical suspicion and TEE was done selectively; however, it was not detailed what led to the suspicion of ICT and subsequent use of TEE. [2]. Selective TEE may lead to underdiagnoses and potential delays in treatment, which is mostly time-dependent. On the contrary, the routine use of intraoperative TEE could lead to a more accurate incidence rate than on a selective basis [2]. The cases presented by Xia et al support the proactive routine use of TEE, considering that some ICTs in patients could present silently without hemodynamic compromise intraoperatively [5]. In the Xia et al study, 4 out of 8 cases diagnosed with ICT had no clinical signs.

Systemic hypotension was the most common sign found in our patients (5/6), which was higher than a comparable study that reported that 2 out of 8 patients presented with systemic hypotension [5]. In a systematic review, 10% of ICT/pulmonary embolism cases were diagnosed based on clinical signs [6]. This raises a question of whether

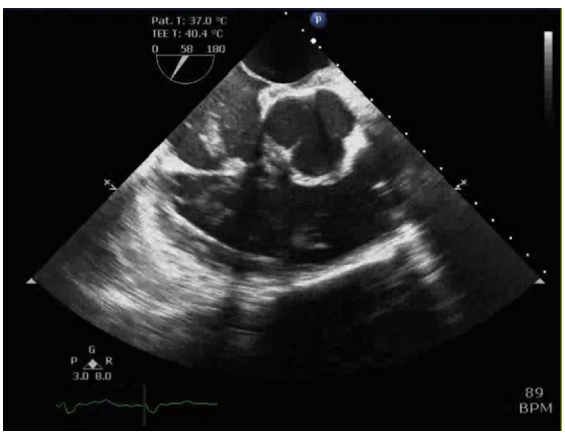

Fig 1. Intraoperative diagnosis of cardiac thrombi by echocardiography during orthotopic liver transplantation. This is an image from intra-operative transesophageal echocardiogram at the midesophageal aortic valve short-axis view with thrombi visualized in the right atrium and right ventricle.

hemodynamic changes should be considered to aid in the diagnosis of ICT. Further research is needed to determine whether clinical signs are reliable.

Risk Factors

The reported risk factors for development of ICT during OLT reported in the literature were the use of antifibrolytics, portal hypertension (including history of gastrointestinal bleeding or TIPS), intraoperative dialysis, and veno-venous bypass [6]. In our study, antifibrolytics were administered to 5 out of 6 patients. None of our patients had prior gastrointestinal bleeding or TIPS procedure. There appears to be a controversy regarding the risk factors in the literature due to the low number of cases. The most common risk factor in this study was antifibrolytic use, which has been previously reported [10,11]. A recent systematic review could not establish or refuse a cause-effect relationship between antifibrolytic medications and ICT [6]. Another systemic review that included 1407 patients showed no difference in the incidence of thrombotic complications between those who received antifibrolytic drugs compared with placebo [10]. In regard to portal hypertension, Peiris et al reported prior TIPS procedure in 40% of patients, and Xia et al showed that TIPS procedure history was present in 75% of their patients, which was interestingly of statistical significance [2,5]. However, in the current study, none of our patients had prior TIPS or gastrointestinal bleeding. The majority of ICTs has occurred during the reperfusion phase in the current review. Nonetheless, ICT has also been reported in both the pre-reperfusion [2] and post-reperfusion phases [1].

Management and Outcome

In this study, the most effective modality of treatment was the combined use of tissue plasminogen activator and heparin. Again, there is no uniform practice in the management of ICT during OLT. There is no clear evidence to support one treatment strategy over the other. Both Xia et al and Gologorsky et al reported that the majority of their patients survived without the use of thrombolysis [1,5]. Furthermore, Peiris et al demonstrated that the survived patient, who was managed conservatively, had a similar course of thrombus dissolution to those who received heparin and tissue plasminogen activator [2]. Further research is necessary to learn more about what is the best treatment strategy. However, this could be challenging owing to the scarcity of cases and an individualized approach is usually sought owing to a heterogeneous patient cohort developing this fatal condition.

The mortality rate was high, 50% (3/6), similar to the high mortality rates reported in the literature reaching up to 68% in some studies [6]. The majority of patients had a MELD score less than 30. There does not appear to be a clear correlation between high MELD score and ICT. ICT has been identified in patients with MELD scores as low as 13, and 1 study reported ICT in a patient with a MELD score of 10 [2]. In this study, the 3 patients who died had lower MELD scores compared with those who survived.

Limitations

As in any retrospective observational study, the data presented cannot be generalized. Additionally, the number of diagnosed cases with ICT limited our ability to perform inferential statistical analysis. However, it is a scarce condition overall and we believe any additional information added to the literature could be of benefit. This is a single-center study at an urban center; however, our institution receives high referral rates from the surrounding institutions that could help diversify the population.

CONCLUSIONS

Cardiac thrombosis should always be considered in any patient having hemodynamic compromise during liver transplant surgery. Preoperative demographic, clinical, laboratory, and historical risk factors did not differ in the patients with thrombosis. TEE is a useful diagnostic tool in identifying ICT. Treatment of ICT is challenging; however, using both tPA and intravenous heparin could achieve better outcomes.

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