Management of Portal Hypertension After Liver Transplantation

D. Korda*, P.Á. Deák, G. Kiss, Z. Gerlei, L. Kóbori, D. Görög, I. Fehérvári, L. Piros, Z. Máthé, and A. Doros

Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary

ABSTRACT

Introduction. Post-transplantation portal hypertension has severe complications, such as esophageal varix bleeding, therapy refractory ascites, extreme splenomegaly, and graft dysfunction. The aim of our study was to analyze the effectiveness of the therapeutic strategies and how to visualize the procedure.

Methods. A retrospective study involving liver transplantation patients from the Semmelweis University Department of Transplantation and Surgery was performed between 2005 and 2015. The prevalence, etiology, and leading complications of the condition were determined. The applied interventions' effects on the patients' ascites volume, splenic volume, and the occurrence of variceal bleeding were determined. Mean portal blood flow velocity and congestion index values were calculated using Doppler ultrasonography.

Results. The prevalence of post-transplantation portal hypertension requiring intervention was 2.8%. The most common etiology of the disease was portal anastomotic stenosis. The most common complications were esophageal varix bleeding and therapy refractory ascites. The patients' ascites volume decreased significantly (2923.3 $\pm$ 1893.2 mL vs. 423.3 $\pm$ 634.3 mL; $P < .05$), their splenic volume decreased markedly. After the interventions, only one case of recurrent variceal bleeding was reported. The calculated Doppler parameters were altered in the opposite direction in cases of pre-hepatic versus intra- or post-hepatic portal hypertension. After the interventions, these parameters shifted towards the physiologic ranges.

Conclusion. The interventions performed in our clinic were effective in most cases. The patients' ascites volume, splenic volume, and the prevalence of variceal bleeding decreased after the treatment. Doppler ultrasonography has proved to be a valuable imaging modality in the diagnosis and the follow-up of post-transplantation portal hypertension.

POST-TRANSPLANTATION portal hypertension (HTN) is a rare but challenging disorder. The main cause of its significance is the severity of the complications. The most frequent complications are variceal bleeding, therapy refractory ascites, hydrothorax, splenomegaly, and graft dysfunction [1]. Portal HTN can be divided into three groups on the basis of the pathogenesis: pre-hepatic, intrahepatic, and post-hepatic origins can be differentiated. After liver transplantation, the most common pre-hepatic etiologies are portal vein thrombosis and portal vein anastomotic stenosis [2]. Intrahepatic causes include chronic cholangitis, hepatitis C virus recurrence, and graft rejection. A rare post-hepatic cause is the stenosis of the caval anastomosis [3]. The diagnosis of the condition is mainly radiological. The first-choice diagnostic modality is color Doppler ultrasound. According to literature, mean portal flow velocity is decreased, whereas the congestion index is increased in case of portal HTN [4]. Computed tomographic (CT) angiography is useful in the detection of vascular anastomotic stenosis. A definitive diagnosis can be established by direct portal pressure measurement [5], which is a diagnostic procedure that is often left out due to its invasiveness. Treatment options include various interventional radiology procedures. Portal anastomotic stenosis can be

*Address correspondence to Dávid Korda, MD, Department of Transplantation and Surgery, Semmelweis University, Ürmény Street 3, Budapest 1141, Hungary. E-mail: kordadavid91@gmail.com

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treated effectively with portal venous stent placement [6], whereas caval vein stent placement can be applied in cases of caval venous anastomotic stenosis [7]. With transjugular intrahepatic portosystemic shunt (TIPS) placement portal pressure and portal-systemic pressure gradient can be reduced; therefore, it is a therapeutic option in cases of portal HTN with intrahepatic etiologies [8]. Another interventional radiology procedure is portosystemic collateral embolization, which can prevent variceal bleeding [9]. Finally, partial splenic artery embolization has two main therapeutic effects. It improves liver perfusion and decreases the splenic volume [10]. The main surgical treatment options are Denver shunt implantation [11] and retransplantation [12]. In cases of esophageal varices, endoscopic sclerotherapy or ligation is also performed [13].

PATIENTS AND METHODS

In Semmelweis University Department of Transplantation and Surgery, 540 orthotopic liver transplantations have taken place during the time period from January 2005 to December 2015. These patients' medical histories were analyzed retrospectively. The prevalence of post-transplantation portal HTN requiring surgical, radiological, or endoscopic intervention was determined. The condition's etiology and leading complication was registered in all cases. The applied treatments were reviewed; their effects on the patients' ascites volume, splenic volume, the occurrence of variceal bleeding, and on the calculated Doppler parameters were examined. The ascites volume was measured using axial abdominopelvic CT sequences performed before and after treatment. The thickness of ascites in centimeters was measured in three planes (the bilateral sub-phrenic space, the bilateral paracolic space, and the pre-bladder space). The average thickness was then multiplied by the area of standard abdominal cavity in the anterior projection, which was assumed to be 1000 cm^2 [14]. The splenic volume was measured before and after treatment using CT volumetry. The pre- and post-treatment prevalence of variceal bleeding was also registered. In our radiology department, the maximum flow velocity of the portal vein is measured using the color Doppler ultrasound technique once a year after liver transplantation as a regular follow-up and in case of complaints. Mean portal blood flow velocity was evaluated as the time-averaged maximum velocity multiplied by the coefficient 0.57 [15]. Congestion index was calculated as the ratio between the cross-sectional area and the mean blood flow velocity of the portal vein [4]. These two parameters were determined before and after the treatment of post-transplantation portal HTN. The calculated Doppler parameters and ascites volumes were statistically analyzed with the paired Student *t* test.

Table 1. The Etiology of Post-transplantation Portal Hypertension

Mechanism	Etiology	Number of Cases
Pre-hepatic	Portal anastomotic stenosis	5
	Partial portal vein thrombosis	1
Intrahepatic	Chronic cholangitis	4
	HCV recurrence	2
	Liver graft rejection	1
	Idiopathic	1
Post-hepatic	Caval anastomotic stenosis	1

Abbreviation: HCV, hepatitis C virus.

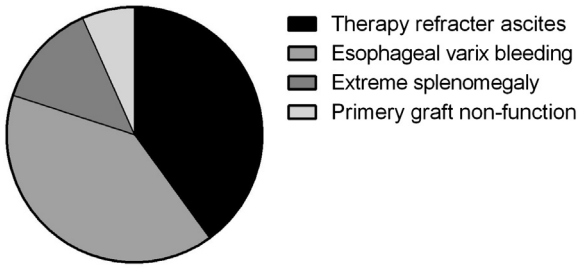

Fig 1. The main complications of post-transplantation portal hypertension.

RESULTS

Prevalence

The prevalence of post-transplantation portal HTN that required surgical, radiological, or endoscopic intervention was 2.8% in the observed period.

Etiology

The most common cause of post-transplantation portal HTN among patients of Semmelweis University Department of Transplantation and Surgery was portal anastomotic stenosis (five cases). The most frequent intrahepatic cause was chronic cholangitis (four cases). Finally, one patient had post-hepatic portal HTN caused by the stenosis of the caval anastomosis (Table 1).

Complications

The most frequent complications were therapy refractory ascites (six cases) and esophageal varix bleeding (six cases). Further complications included extreme splenomegaly (two cases) and primary nonfunction of the liver graft (one case) (Fig 1).

Therapeutic Strategies

Portal anastomotic stenosis was treated with portal venous stent placement after percutaneous portal vein puncture and portography in three cases. Portal HTN with intrahepatic etiology was treated with TIPS placement in three cases. The only case of post-hepatic portal HTN was treated with caval venous stent placement. One patient had portovenous collateral embolization and three patients had endoscopic sclerotherapy to prevent variceal bleeding. Partial splenic artery embolization was combined with other

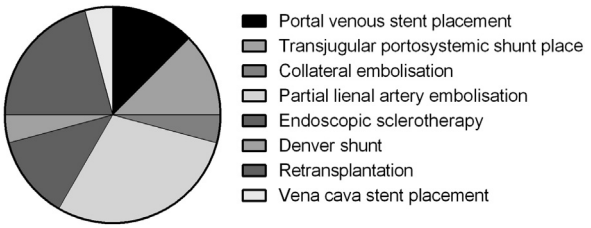

Fig 2. The therapeutic strategies in post-transplantation portal hypertension.

Table 2. Summary of Patients' Data

No.	Etiology	Leading Complication	Interventions	Results of the Interventions	Patient Survival
1	Portal anastomotic stenosis	Therapy refractory ascites	PV stent	Ascites vol. ↓ with 66.25%	Alive and well
2	Portal anastomotic stenosis	Therapy refractory ascites	PV stent PSE ESC	Ascites vol. ↓ with 61.54%	Alive and well
3	Portal anastomotic stenosis	Therapy refractory ascites	PV stent	Ascites disappeared	Alive and well
4	Idiopathic	Therapy refractory ascites	TIPS Denver shunt	Ascites disappeared	Alive and well
5	HCV recurrence	Esophageal varix bleeding	TIPS ESC	Variceal bleeding did not recur	Alive and well
6	Acute graft rejection	Therapy refractory ascites	TIPS	Ascites vol. ↓ with 87.10%	Alive and well
7	Chronic cholangitis	Esophageal varix bleeding	PSCVE	Variceal bleeding did not recur	Alive and well
8	Partial hepatic artery thrombosis	Esophageal varix bleeding	PSE	Recurrent variceal bleeding	Alive and well
9	Chronic cholangitis	Extreme splenomegaly	PSE	Splenic vol. ↓ with 22.73%	Alive and well
10	HCV recurrence	Therapy refractory ascites	PSE	Ascites disappeared	Died in variceal bleeding
11	Chronic cholangitis	Esophageal varix bleeding	Re-TX	Variceal bleeding did not recur	Alive and well
12	Chronic cholangitis	Esophageal varix bleeding	Re-TX ESC Re-re-TX PSE	Variceal bleeding did not recur	Died in multi-organ failure
13	Portal anastomotic stenosis	Primary graft nonfunction	PSE Re-TX	Functioning liver graft	Alive and well
14	Chronic cholangitis	Extreme splenomegaly	PSE Re-TX	Splenic vol. ↓ with 53.31%	Alive and well
15	Caval anastomotic stenosis	Esophageal varix bleeding	IVC stent	Variceal bleeding did not recur	Died in multi-organ failure

Abbreviations: PV, portal venous; PSE, partial splenic artery embolization; ESC, endoscopic sclerotherapy; TIPS, transjugular intrahepatic portosystemic shunt; vol. ↓, volume decreased; PSCVE, portosystemic collateral vein embolization; Re-TX, retransplantation; IVC, inferior vena cava.

interventions in four cases and performed alone in three cases. Surgical interventions included retransplantation (five cases) and Denver shunt placement (one case) (Fig 2).

Patient Survival

The median follow-up time after the patients' first therapeutic intervention was 45 months. Of 15 patients who had post-transplantation portal HTN requiring intervention, 12 are alive and have stable liver graft function. Two patients died due to multi-organ failure and 1 patient died from variceal bleeding (Table 2).

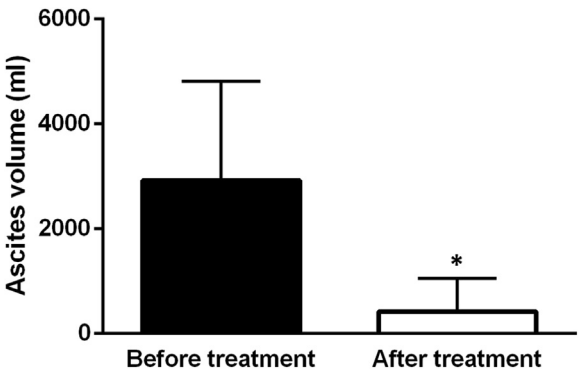

Fig 3. The decrease of the patients' ascites volume was significant ($^{*}P < .05$; paired Student t test; n = 6).

Change of Ascites Volume

The calculated volume of the patients' ascites decreased significantly after the interventions (2923.3 ± 1893.2 mL vs. 423.3 ± 634.3 mL; $P < .05$; paired Student t test; n = 6) (Fig 3).

Change of Splenic Volume

Two patients had extreme splenomegaly as a complication of portal HTN. Their splenic volume decreased markedly after treatment (Fig 4). In the first case, the decrease was 22.7%; in the other case it was 53.3%.

Change in the Prevalence of Variceal Bleeding

There were seven reported cases of variceal bleeding before treatment, and only one case of recurrent variceal bleeding was reported after the interventions.

Change of Doppler Parameters

The normal value of mean portal blood flow velocity is 15 cm/s to 35 cm/s, the congestion index of normal subjects was reported to be 0.07 ± 0.029 cm/s. Patients with pre-hepatic post-transplantation portal HTN had elevated portal blood flow velocity values and decreased congestion index values. In cases of intra- and post-hepatic post-transplantation portal HTN, these parameters were altered in the opposite direction: the portal blood flow velocity was lower and the congestion index values were higher than in normal subjects. After the interventions, the calculated Doppler parameters

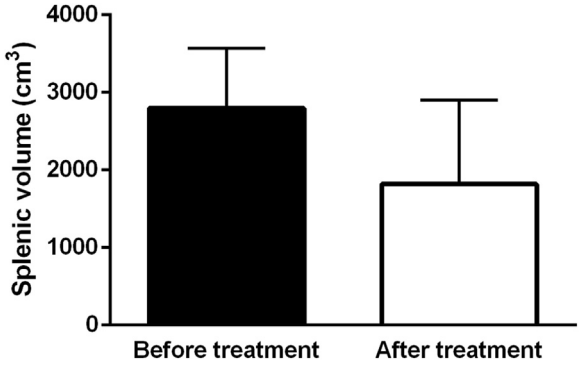

Fig 4. The patients' splenic volume decreased after the interventions.

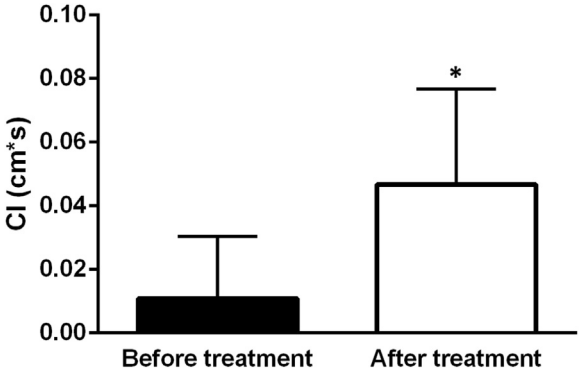

Fig 6. The change of congestion index values was significant in pre-hepatic portal hypertension ($^{*}P < .05$; paired Student t test; n = 6).

shifted toward the physiologic ranges. In the pre-hepatic group, the decrease of mean portal blood flow velocity was not significant (45.08 ± 42.36 cm/s vs. 25.84 ± 15.63 cm/s; P = NS; paired Student t test; n = 6) (Fig 5) and congestion index values increased significantly (0.011 ± 0.019 cm*s vs. 0.047 ± 0.030 cm*s; $P < .05$; paired Student t test; n = 6) (Fig 6). Among patients with intra- and post-hepatic portal HTN, the mean portal blood flow velocity increased significantly (12.75 ± 3.5 cm/s vs. 20.55 ± 7.93 cm/s; $P < .05$; paired Student t test; n = 7) (Fig 7) and the decrease of congestion index values was also significant (0.167 ± 0.082 cm/s vs. 0.119 ± 0.097 cm/s; $P < .05$; paired Student t test; n = 7) (Fig 8).

DISCUSSION

The prevalence of post-transplantation portal HTN that required intervention was 2.8% in our clinic in the observed period. The most common cause of the condition was portal anastomotic stenosis, whereas the most common complications were esophageal varix bleeding and therapy refractory ascites. There is a broad spectrum of therapeutic possibilities in portal HTN which include surgical, radiological, and endoscopic interventions. The therapeutic strategy was determined by an interdisciplinary team in each case, and the main influence factors were the etiology and the leading complication of the disease. Portal venous stent placement can be performed in cases of portal anastomotic stenosis, and caval venous stent placement can be performed in cases of caval anastomotic stenosis, whereas TIPS placement is a therapeutic option in portal HTN with intrahepatic origin. Denver shunt implantation can be performed in cases of ascites refractory to conservative therapy. Esophageal varices can be treated with endoscopic sclerotherapy or ligation, whereas partial splenic artery embolization is most effective in the treatment of splenomegaly. Finally, retransplantation is the last alternative in therapy refractory portal HTN and in cases of liver graft failure. The above-mentioned interventions can be combined to increase their effectivity.

The performed interventions were effective in most cases. After treatment, the patients' ascites volume decreased significantly, their splenic volume also decreased, and there was only one case of recurrent variceal bleeding. The calculated Doppler parameters were different in cases of pre-hepatic and in intra- or post-hepatic portal HTN. The explanation of this finding is that in pre-hepatic HTN the

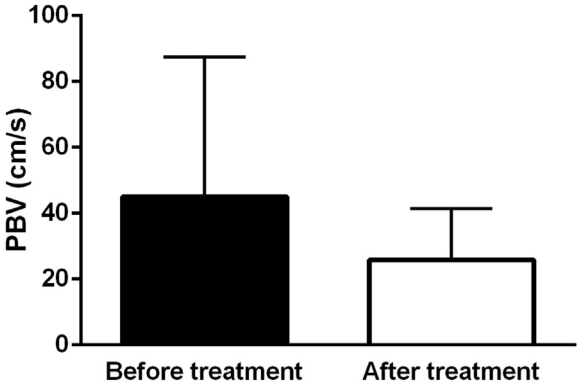

Fig 5. In pre-hepatic portal hypertension, mean portal blood flow velocity values did not change significantly (paired Student t test; n = 6). PBV, portal blood flow velocity.

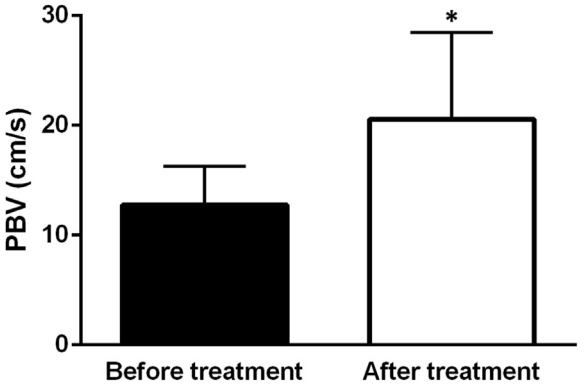

Fig 7. Mean portal blood flow velocity values changed significantly in intra- or post-hepatic portal hypertension ($^{*}P < .05$; paired Student t test; n = 7). PBV, portal blood flow velocity.

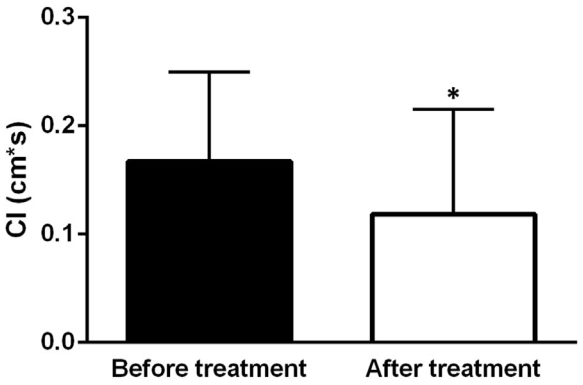

Fig 8. Congestion index values changed significantly in intra- or post-hepatic portal hypertension ($^{*}P < .05$; paired Student *t* test; n = 7).

measuring point is distal to the stenotic section of the vein, whereas in intra- or post-hepatic HTN it is proximal to the high-resistance section. After the interventions, the calculated Doppler parameters shifted towards the physiologic ranges. In conclusion, the complications of post-transplantation portal HTN can be effectively treated with the above-mentioned interventions. We suggest performing Doppler ultrasonography as a first-choice imaging modality in suspicion of portal HTN. Via portal flow measurements, pre-hepatic portal HTN can be differentiated from the intra- or post-hepatic form and the efficacy of the therapy can also be assessed with the Doppler technique.

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