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ORIGINAL ARTICLE

Preoperative proximal splenic artery embolization: a safe and efficacious portal decompression technique that improves the outcome of live donor liver transplantation

Yuzo Umeda, Takahito Yagi, Hiroshi Sadamori, Hiroyoshi Matsukawa, Hiroaki Matsuda, Susumu Shinoura, Takayuki Iwamoto, Daisuke Satoh, Hiromi Iwagaki and Noriaki Tanaka

Gastroenterological surgery, Transplant and Surgical oncology, Okayama University Graduate School of Medicine, Okayama, Japan

Keywords
embolization, ligation, liver transplantation, portal hypertension, splenic artery.

Correspondence
Yuzo Umeda, MD, Gastroenterological surgery, Transplant and Surgical oncology, Okayama University Graduate School of Medicine, 2-5-1 Shikata-cho, Okayama-shi, Okayama 700-8558, Japan.
Tel.: 81 86 223 7151;
e-mail: y.umeda@d9.dion.ne.jp

Abbreviations:
LDLT, living donor liver transplantation; ASS, arterial steal syndromes; MELD, Mayo End-Stage Liver Disease; CT, computed tomography; PT, prothrombin time; IL-6, interleukin-6; ANOVA, analysis or variance.

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Summary

Terminal liver cirrhosis is associated with marked severe portal hypertension, which increases the risk of intraoperative hemorrhage and graft hyper-perfusion, especially, in small-for-size graft. In cases with developed collateral vessels, we often face difficulties in perihepatic dissection with blood stanching against bleeding during recipient hepatectomy. For aseptic preoperative portal decompression, we established the proximal splenic artery embolization (PSAE) technique. Sixty adult living donor liver transplantation recipients with viral/alcoholic hepatic failure were divided into two groups; PSAE group ($n = 30$) and non-PSAE ($n = 30$). In the PSAE group, the splenic artery was embolized proximal to the splenic hilum 12–18 h before surgery. PSAE enabled shortening of operating time, reduced blood loss, led to less need for transfusion, and significantly reduced the post-transplant portal venous velocity and ascites. PSAE was not associated with complications, e.g., splenic infarction, abscess, or portal thrombosis. Six of the non-PSAE patients required additional surgical intervention to resolve postoperative hemorrhage and three patients required secondary PSAE for arterial-steal-syndrome. The hospital mortality rate of PSAE patients (3.3%) was significantly better than that of the PSAE group (13.3%, $P < 0.05$). Preoperative noninvasive PSAE makes more efficient use of portal decompression; thus, it can potentially contribute to improvement of outcome.

Introduction

Many patients with terminal liver cirrhosis, especially, those with viral/alcoholic liver cirrhosis, are suitable candidates for liver transplantation but have marked portal hypertension. With respect to liver transplantation, portal hypertension poses various difficulties that could hinder the success of surgery and postoperative prognosis. Among the surgery-associated problems is potential massive hemorrhage. Furthermore, portal overperfusion-related small-for-size syndrome and arterial steal syndromes (ASS, both of which are caused by liver cirrhosis-related changes in portal hemodynamics), have negative effects on the post-transplantation prognosis. The impact of previously reported portal flow modification techniques, such as splenectomy, ligation of the splenic artery, and porto-caval shunt, on outcome remains controversial; there is no consensus regarding treatment at present. However, even ligation and splenectomy can sometimes lead to complications because of peri-celiac trunk collaterals and visceral hyperdynamism. We devised a preemptive splenic approach; proximal splenic artery embolization (PSAE), against the risk of intraoperative bleeding and postoperative graft portal hyperperfusion. We describe here our strategy of PSAE to reduce portal pressure prior to surgery in liver transplant recipients with severe portal hypertension.

Materials and methods

Patient population

Between August 1998 and December 2005, 137 living donor liver transplantations (LDLTs) were performed in our institution. These cases consisted of 114 adult patients (age ≥18 years) and 23 children (<18 years). Of the 114 adults, 54 patients with liver cirrhosis had mild portal hypertension and included 12 with acute liver failure, 15 with metabolic disorders, and 27 patients with cholestatic disease. The remaining 60 patients had terminal liver cirrhosis caused by viral hepatitis or alcohol liver cirrhosis, and all were considered to have severe portal hypertension [1–3] based on the clinical features of splenomegaly, history of variceal bleeding, intractable ascites and thrombocytopenia. These 60 patients, who were considered candidates for LDLT since January 2003, were selected for the present study to assess the influence of severe portal hypertension in the perioperative phase. They were divided at random to undergo either PSAE prior to LDLT ($n = 30$) or LDLT without PSAE ($n = 30$). We analyzed the two groups retrospectively with regard to surgical complexity and various clinicopathological factors during the perioperative period to investigate the effects of preoperative PSAE in patients scheduled for liver transplantation. The study protocol was approved by the Human Ethics Review Committee of Okayama University School of Medicine and a signed consent form was obtained from each subject.

Proximal splenic artery embolization

Abdominal angiography and embolization were performed 12–18 h before transplantation. As a rule, a metallic coil was placed in the area adjacent to the root of the splenic artery and proximal to the bifurcation of the major pancreatic artery, to produce total embolization of the splenic artery trunk.

In a representative patient, a 36-year-old male, transplantation was indicated for hepatitis B liver cirrhosis [Child-Pugh score: 11 points, Grade C, Mayo End-Stage Liver Disease (MELD) score: 19 points]. Computed tomography (CT) showed splenomegaly, dilatation of the left gastric vein, para-umbilical vein, and perihepatic retroperitoneal blood vessel. Portal flow velocity measured by Doppler ultrasonography was 12 cm/s, suggesting hepatopetal flow. However, PSAE was performed the day before transplantation, which resulted in reduction of portal flow velocity to 8 cm/s and immediate increase of hepatic arterial flow volume after PSAE. Splenomegaly was markedly reduced on the seventh postoperative day (POD) (Fig. 1).

Surgical technique

Donor hepatectomy and recipient transplantation procedures were performed as described previously with minor modifications [4,5]. The volume of the resected liver segment was calculated before surgery by CT volumetry. The choice of resected segments for donation was dictated by the need to obtain a graft volume of more than approximately 30% of the recipient's standard liver volume or more than 0.8% of the graft-to-recipient body ratio. The resected segments included the left lobe, extended left lobe with left caudate lobe, and the right lobe. As for the donor procedure, parenchymal dissection was performed without inflow occlusion of Glissonian pedicle of the liver graft. The liver graft was flushed and preserved in cold UW (University of Wisconsin) solution. As for the recipient procedure, the native liver was resected, preserving the inferior vena cava. In the anhepatic phase, massive hemorrhage from the perihepatic area was almost completely stanched. After reconstructing the hepatic and portal veins, the hepatic artery was anastomosed under microscopy. The biliary tract was reconstructed by Roux-en-Y hepatico-jejunostomy or duct-to-duct hepatico-choledochostomy. As a rule, in cases with massive porto-systemic shunts, the main shunt system was treated with ligation or cutting-off to avoid the escape of portal inflow through collaterals.

Postoperative care

The initial immunosuppressive regimen consisted of tacrolimus and steroids. Coagulation was controlled intensively in the first postoperative week. Fresh-frozen plasma was administered, and prothrombin time (PT) was monitored. Fresh-frozen plasma was given during and after LDLT in patients with prothrombin-international normalized ratio (PT-INR) of ≥1.5. Platelet count was evaluated before surgery and on days 1, 3, 5, 7, 14, 21, and 28 (POD1, 3, 5, 7, 14, 21, 28) post-transplantation. Plasma concentrations of interleukin-6 (IL-6; Fujirebio Inc., Tokyo, Japan) and soluble IL-6 receptor (sIL-6R; R & D Systems, Minneapolis, MN, USA) were measured using an enzyme-linked immunosorbent assay (ELISA) kit. To evaluate the preoperative liver and postoperative graft hemodynamics, we measured the maximum velocity of portal vein flow (Vp max) and hepatic artery flow (Va max) on preoperative phase and POD1, 3, 5, 7, by Doppler ultrasonography imaging with a 5–0 MHz transducer, the Aloka Prosound 5500 (Aloka Co., Tokyo). The volume of ascites, estimated by abdominal drain discharge, was also determined on POD1, 3, 5, 7, 14. Post-transplant mortality and morbidity were evaluated.

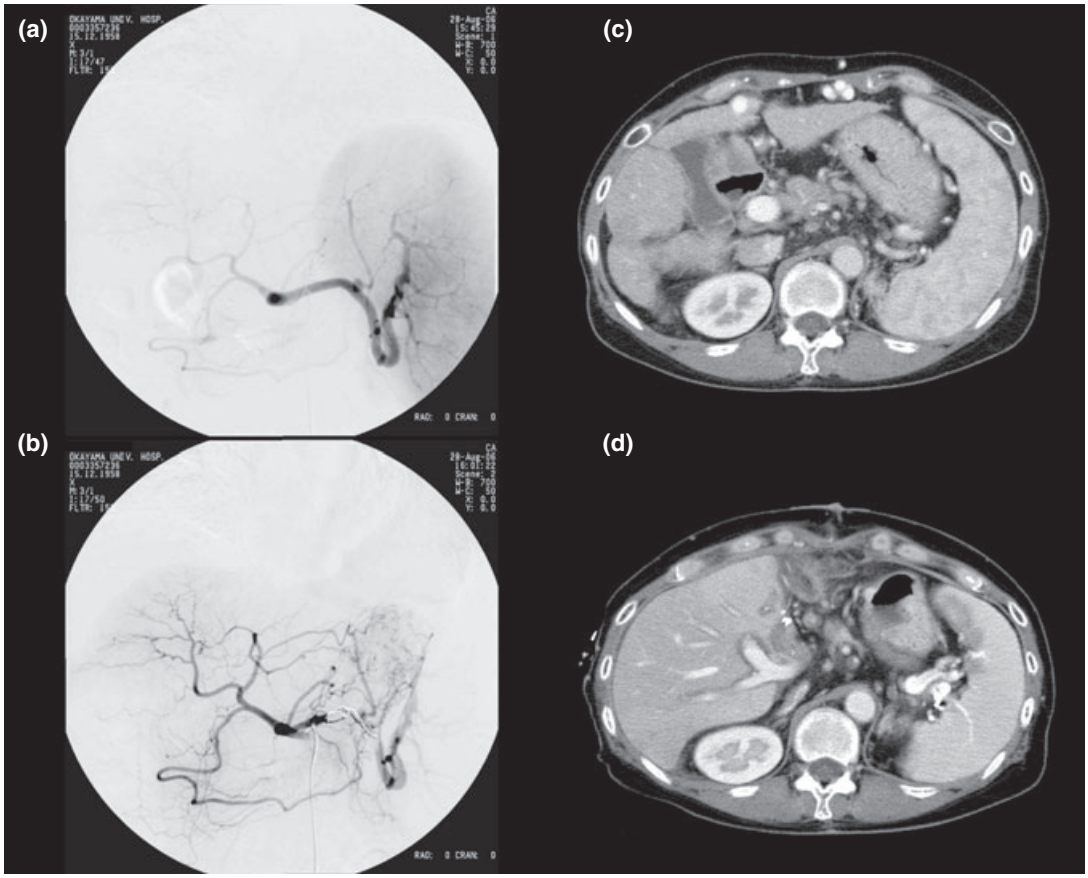

Figure 1 (a) Preoperative abdominal angiography shows hyperdynamism of splenic artery. (b) Splenic artery was embolized with a metallic coil placed in the root of the splenic artery trunk to produce total occlusion. This resulted in marked increase in flow volume of hepatic artery, reflecting a shift from the spleen. (c) Pretransplant recipient's abdominal CT revealed splenomegaly and collateral vessel formation. (d) Splenomegaly was markedly improved on the seventh post-transplant day.

Statistical analysis

Differences between PSAE and non-PSAE recipients were analyzed with the Mann–Whitney *U*-test, chi-squared test, and analysis of variance. Differences in mortality ratios were calculated by the nonparametric Kaplan–Meier method and compared by the Wilcoxon test. All statistical analyses were performed with SPSS software (Release 9.0.1; Microsoft Corp., Redmond, WA, USA), and *P*-values of <0.05 were regarded as significant.

Results

Clinical background factors

There were no significant differences between the PSAE and non-PSAE recipients with respect to age, gender, underlying disease, hepatic reserve and preoperative severity, as evaluated by the Child-Pugh scores and MELD scores. A positive history of gastrointestinal bleeding, as a clinical feature of portal hypertension, was recognized in 26 cases of the PSAE group and in 24 cases of the non-PSAE group. All other features showed a similar pattern. Donor age and graft volume were not significantly different between the two groups (Table 1).

Preoperative liver hemodynamism before and after splenic embolization

A low hepatopetal portal flow and a high hepatic arterial flow were noted in almost all patients during the preoperative phase. In the PSAE group, PSAE resulted in further reduction of portal flow and increase of hepatic arterial flow (Fig. 2).

Results of surgery

Systemic hemodynamics, measured by Swan Ganz catheter just before surgery, revealed low-grade hyperdynamism in the PSAE group compared with the non-PSAE, though the difference was not significant. The volume of

Table 1. Patients characterstics.

	non-PSAE group (n = 30)	PSAE group (n = 30)	*P*-value
Age (years)	51.1 ± 1.6	52.7 ± 1.2	0.417
sex (male/female)	23/7	22/8	0.765
Viral hepatitis (B/C)/ alcoholic LC	13/12/5	10/18/2	0.237
Preoperative status			
Child-Pugh score	10.1 ± 0.46	10.3 ± 0.34	0.682
Child-Pugh Grade (B/C)	10/20	11/19	0.787
MELD score	17.4 ± 1.5	17.3 ± 0.9	0.970
Platelet count (10^4/mm^3)	5.6 ± 0.6	5.8 ± 0.2	0.279
Gastrointestinal bleeding	24	26	0.488
Intractable ascites	22	25	0.347
Donor and graft characteristics			
Donor age (years)	37.1 ± 2.3	38.9 ± 2.4	0.577
Blood type combination (Identical/compatible pair)	22/8	20/10	0.573
Graft (right/left lobe)	21/9	20/10	0.781
Graft.weight (g)	566.4 ± 26.0	589.0 ± 21.6	0.507
GWRBW	0.919 ± 0.050	0.918 ± 0.041	0.991

MELD, model for end-stage liver disease; GW RBW, Graft Recipient body weight ratio. Values represent mean ± SD.

blood loss in the PSAE group was significantly lower than that of the non-PSAE group. The amount of intraoperative blood transfusion, reflecting the volume of blood loss, was lower in the PSAE group than in non-PSAE group. The operation time was significantly shorter in the PSAE group than in the non-PSAE group (Table 2). In the non-PSAE group, the serum levels of IL-6 and sIL-6R, a proinflammatory cytokine representing parameters of surgical invasiveness, were significantly higher immediately after surgery compared with before surgery (Fig. 3).

Postoperative course

In both groups, the hyperdynamic state improved early after surgery, together with reduction in portal flow velocity. Especially in the PSAE group, the flow velocity was significantly lower immediately after surgery compared with the non-PSAE group. The value was constant during the course of the study period (1 month). Furthermore, hepatic artery flow velocity was significantly higher during the postoperative phase, reflecting arterial flow shift from the spleen to the hepatic artery (Fig. 4). The volume of ascites postoperatively, as estimated by drainage, was significantly higher in non-PSAE group than in the PSAE group (Fig. 5). Before surgery, hypersplenism caused thrombocytopenia in the two groups. The platelet count was significantly higher in the post-transplantation period compared with prior to transplantation, accompanied by improvement of hypersplenism (Fig. 6).

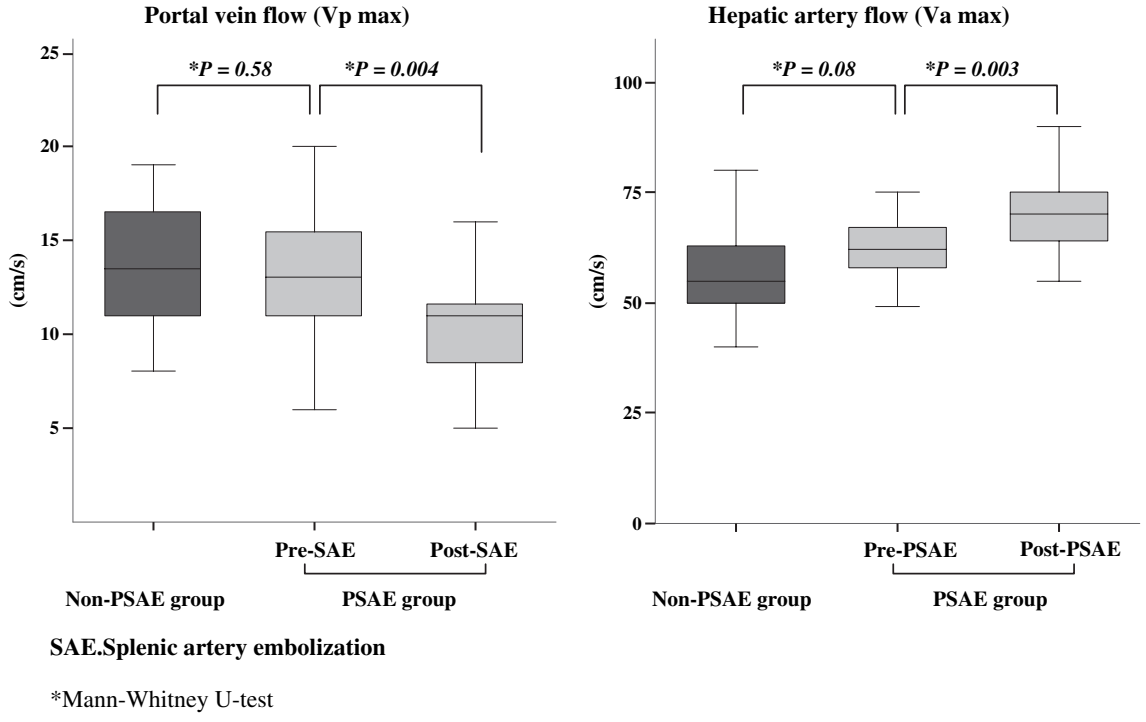

Figure 2 Preoperative portal vein and hepatic arterial peak velocity before and after splenic embolization.

Table 2. Comparison of surgical variables.

	non-PSAE group ($n = 30$)	non-PSAE group ($n = 30$)	*P*-value
Operative data			
Cardiac index (l/min/m2)	5.2 ± 0.31	4.9 ± 0.19	0.118
Cardiac output (l/min)	8.60.58	8.1 ± 0.37	0.434
CVP (cmH2O)	7.3 ± 0.65	7.2 ± 0.52	0.829
Blood loss (ml)	15,338 ± 3,050	6,726 ± 1,048	0.010
Blood loss/body weight (ml/kg)	236.3 ± 43.6	104.8 ± 17.0	0.007
Operating time (min)	680.9 ± 27.2	599.0 ± 17.4	0.013
Requiring transfusion			
MAP (unit)	47.5 ± 8.7	23.7 ± 3.3	0.014
FFP (unit)	117.1 ± 18.6	65.1 ± 5.7	0.010
CIT (min)	70.1 ± 6.5	68.1 ± 7.4	0.542
WIT (min)	44.8 ± 3.9	42.1 ± 2.9	0.443
Complications			
Postoperative hemorrhage	6	2	0.254
Biloma	3	2	0.640
Arterial steal syndrome	2	0	0.157
Acute rejection	5	9	0.222
PV thrombosis/ splenic infarction	0	0	–

CVP, central venous pressure; MAP, mannitol-adenine-phosphate; FFP, fresh frozen plasma; CIT, cold ischemic time; WIT, warm ischemic time. Values represent mean ± SD.

Complications and prognosis

There were no PSAE-related complications such as hemorrhage or vascular injury, as confirmed by angiography. Angiographic imaging demonstrated reduced splenic blood flow; however, none of the patients developed fusion necrosis or infection. Among the non-PSAE group, two patients developed splenic ASS-associated graft liver dysfunction after transplantation. In these two patients, secondary PSAE increased arterial perfusion in the graft. Furthermore, among the non-PSAE group, six patients required additional surgical intervention to resolve postoperative hemorrhage; compared with two patients only of the PSAE group. In all cases, the cause of postoperative hemorrhage was oozing from collateral pathways, such as the perihepatic or retrohepatic blood vessels.

The hospital mortality rate was significantly higher in the non-PSAE group (13.3%) than in the PSAE group (3.3%, $P = 0.0364$). The main causes of death in the immediate period after surgery were additional hemorrhage and infection related to poor general condition associated with postoperative hemorrhage in the non-PSAE group. Graft failure developed in one patient of the PSAE group due to small-for-size syndrome with aged-graft (graft-to-recipient body ratio, 0.55; donor age, 56 years) (Table 2).

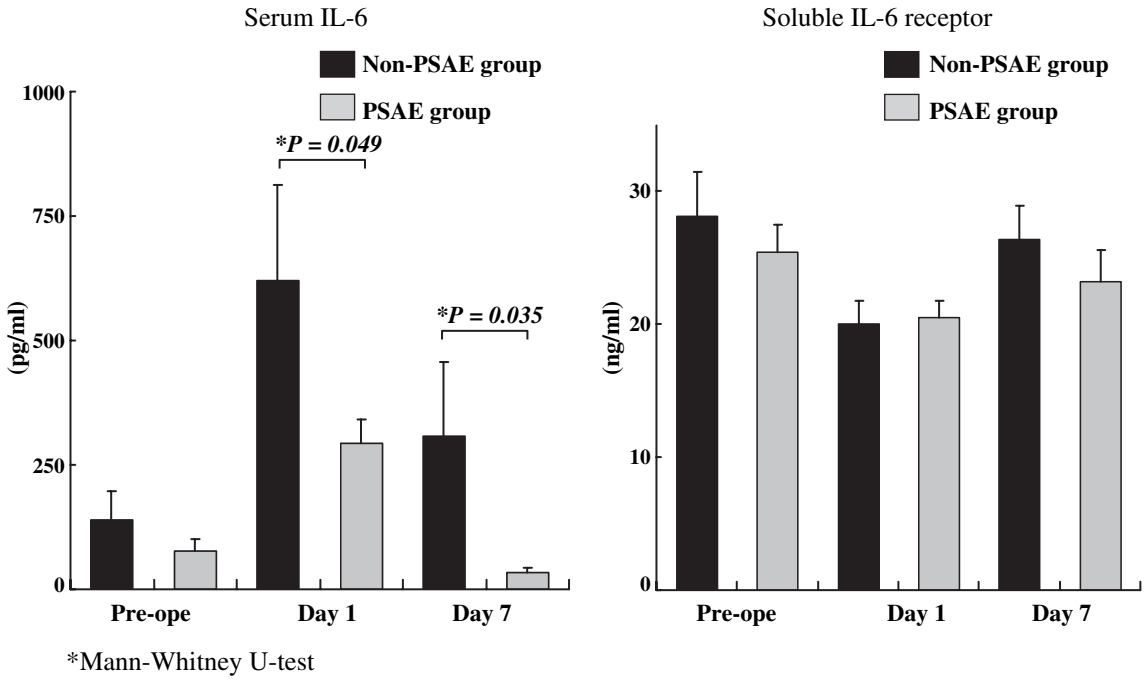

Figure 3 Cytokine release in perioperative phase: the serum level of IL-6 was significantly higher immediately after surgery in the non-PSAE group.

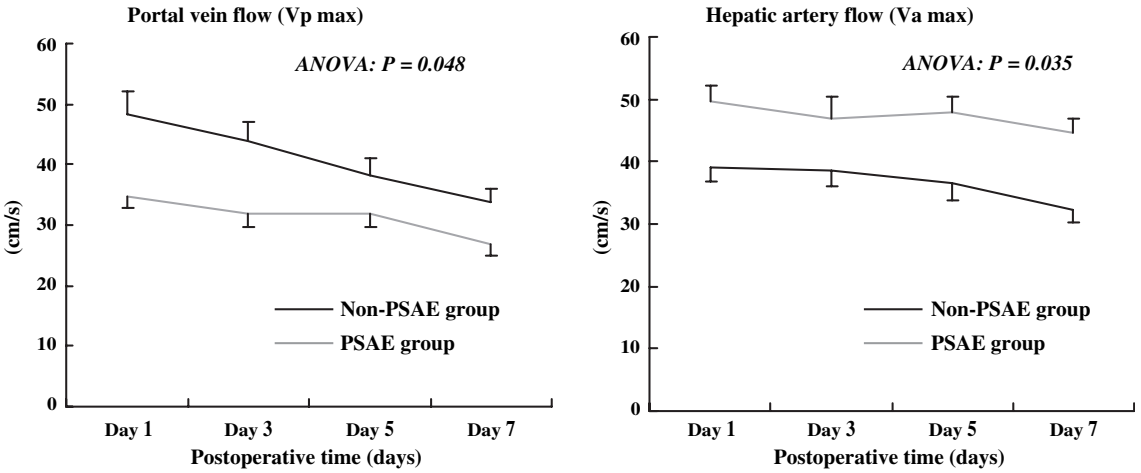

Figure 4 Serial changes in constructed portal vein and hepatic artery peak velocity.

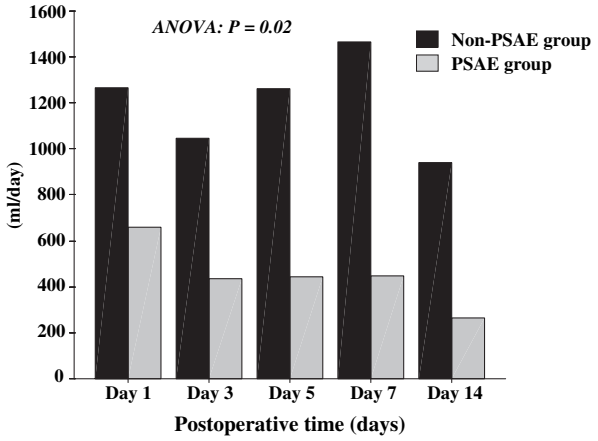

Figure 5 Serial changes in the volume of postoperative ascites.

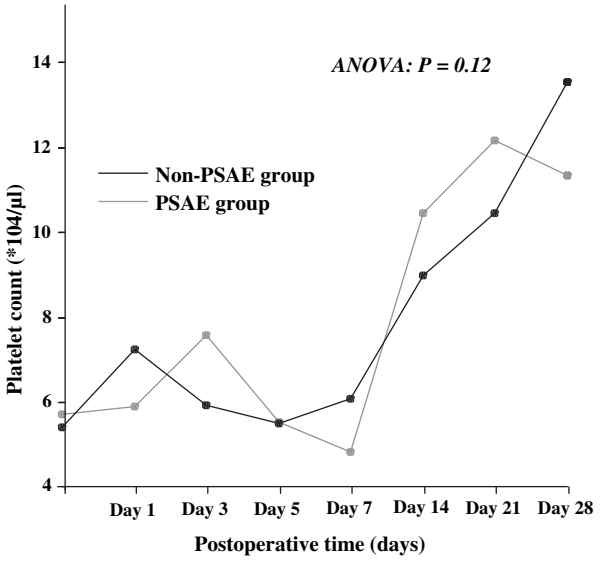

Figure 6 Course of thrombocytopenia after proximal splenic artery embolization.

Discussion

Liver transplantation raises several issues that could influence the outcome of surgery with respect to portal hypertension. Such surgery-related problems, such as hemorrhage, surgical invasiveness, including hemorrhage-associated direct stress, blood transfusion loading for hemorrhage, reduced immunity in the late phase, and infection-enhancing conditions, could markedly influence the outcome of surgery. For the recipient surgery, the volume of blood loss from laparotomy until hepatectomy accounts for the majority of the volume of intraoperative blood loss. Compared with healthy individuals, patients with liver cirrhosis show hyperdynamic visceral organ blood flow [6]. In most patients, collateral pathways are advanced, e.g., the development of a portal hypertension-related paraumbilical vein, swelling of blood vessels on the lesser curvature of the stomach, development of a circulatory route from the perihepatic retroperitoneal blood vessel to the inferior vena cava/azygos venous system, and splenorenal venous shunting. Circulatory treatment involving collateral pathways before hepatectomy should directly influence the volume of intraoperative blood loss.

Portal overperfusion-related small-for-size syndrome and ASS, representing liver cirrhosis-associated changes in hemodynamics, influence graft function after transplantation. The small-for-size syndrome is defined as postoperative liver hypofunction related to lack of absolute graft liver capacity with respect to the recipient's physical status. Recent studies have reported that after reperfusion, the graft is exposed to excessive portal perfusion related to the hyperdynamic splanchnic state before transplantation [7–9], which leads to protracted hyperbilirubinemia/

ascites and the development of serious conditions in some patients. Partial liver transplantation, in which the graft liver capacity is insufficient, frequently causes small-for-size syndrome.

With regard to ASS, one group has reported that the hemodynamic impedance in the splenic artery reflects portal blood flow resistance in patients with liver cirrhosis [10]. The reported incidence of ASS is 5.9% [11]. ASS after liver transplantation is characterized by low arterial perfusion in a graft, due to a shift in blood flow to the splenic and gastroduodenal arteries. In ≥30% of the patients, the syndrome may cause ischemic necrosis of the bile duct and functional failure of the graft, leading to serious complications [11,12]. In our study, two patients of the non-PSAE group developed ASS after transplantation with reduced graft liver function. However, in these patients, PSAE reversed the reduced arterial perfusion.

To overcome the above limitations, we designed the preoperative PSAE technique. This procedure allows direct approach to the splenic artery, thus influencing portal pressure and reducing the portal perfusion volume and perfusion pressure. With regard to portal hemodynamics, PSAE on the proximal side appears to be as effective as ligation of the splenic artery during surgery. In patients undergoing liver transplantation, ligation of the splenic artery reduces portal pressure and portal perfusion [13]. In cirrhotic patients with portal hypertension, especially, those with a spleen/liver volume ratio of >0.5, splenic artery occlusion causes a significant reduction in portal pressure [1].

In the assessment of PSAE, it is difficult to measure portal pressure directly before and after PSAE; however, hemodynamic evaluation by Doppler ultrasonography in the same patient reflects the state of portal perfusion. In clinical practice, portal flow velocity diminishes after PSAE in liver cirrhosis patients with hepatopetal flow. Furthermore, in the present study, the reconstructive portal flow velocity after transplantation in PSAE patients was significantly lower than in non-PSAE group; thus, PSAE could reduce both the portal perfusion volume and perfusion pressure. This may in turn have resulted in a reduction of blood influx into collateral pathways via the portal system, thereby decreasing the volume of intraoperative blood loss and shortening the duration of surgery. IL-6 is considered a representative marker of surgical invasiveness [14], and serum IL-6 level is increased in the presence of excessive invasion such as massive intraoperative hemorrhage [15]. The results of this study support the hypothesis that IL-6 serves as a marker of the invasiveness of surgery [16].

Portal decompression [e.g., porto-systemic shunt (porto-caval shunt)] [17], splenectomy [18], and ligation of the splenic artery [19,20] are frequently indicated in patients with small-for-size syndrome, in order to reduce portal perfusion. However, with regard to portal shunt, previous studies reported that a shift in portal flow into an extrahepatic route may occur with subsequent increase in portal resistance of the graft involving rejection, resulting in a fatal outcome in some cases [21,22]. In cases with massive shunt, such as splenorenal shunt and left gastric vein, it is our policy to ligate or cut off the shunt. Especially, in patients who underwent PSAE, this procedure is indispensable because PSAE may lead to marked decrease in splanchnic blood stream through the portal vein. None of the patients of the PSAE group showed signs of graft portal hypoperfusion. In comparison to splenectomy and ligation of the splenic artery, extension of the dissection area would increase intraoperative bleeding under visceral hyperdynamic conditions and could lead to an increase in postoperative ascites. The purpose of preoperative PSAE is preoperative; not intraoperative, preparation to reduce the absolute volume of potential blood loss, and to reduce the duration of surgery, including that related to laparotomy or portal attenuation, such as splenectomy and ligation of splenic artery. Thus, it is thought that preoperative PSAE may be more advantageous than splenectomy or ligation of the splenic artery.

Furthermore, it should be noted that sepsis-related complications such as portal thrombosis and infection-related features may even lead to more serious conditions, although the incidence of such complications is low [11,23]. In the case of PSAE, portal perfusion can be reduced safely in comparison to the above procedures, which are associated with unpredictable effects; therefore, this procedure may be useful for reducing the incidence of small-for-size syndrome. In our hands, PSAE resolved hyperbilirubinemia and reduced the volume of ascites. In addition, therapeutic strategies for latent ASS include splenectomy, ligation of the splenic artery, and PSAE.

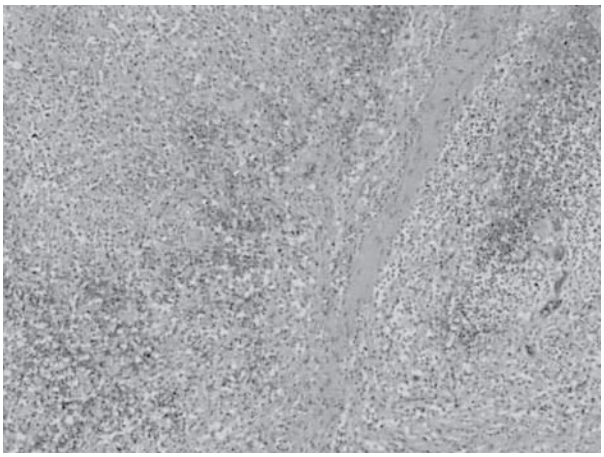

Figure 7 Microscopic findings of autopsied spleen, after proximal splenic embolization.

However, preoperative PSAE may safely and accurately achieve prophylactic effects in this regard [11].

Several groups have reported the complications generally observed after PSAE including a high incidence of splenic infarction, abscess formation, reduced immunity-related septic complications, and portal thrombosis [24,25]. In our hands, there were no PSAE-related complications, including no sepsis or portal thrombosis, probably due to the performance of PSAE proximal to the spleen. A distal PSAE at an area adjacent to the spleen may completely block blood influx to the spleen, causing fusion necrosis related to blood flow blockage. However, proximal embolization is known to lead slowly to low perfusion-associated coagulation necrosis, despite a decrease in blood influx. Histological investigation in autopsied cases revealed that fibrous tissue replaces the splenic tissue, with slight coagulation necrosis (Fig. 7). Therefore, PSAE with a coil at an area adjacent to the splenic artery root and proximal to the bifurcation of the major pancreatic artery may achieve the goal of treatment without causing the above complications. It has been reported that partial PSAE on the distal side is useful for treatment of thrombocytopenia related to enhancement of splenic function [26], however, proximal PSAE may not be useful in such cases.

Taking into consideration the above findings, we recommend preoperative PSAE in patients with clinical features of severe portal hypertension, such as splenomegaly (especially with a spleen/liver volume ratio of >0.5) [11], evidence of collaterals and massive ascites, and those with planned small-size graft (GW/RBW < 1.0%), to secure portal decompression and improve the outcome of LDLT. With respect to medical cost–benefit analysis, improvement in the intraoperative/perioperative condition may shorten the duration of surgery, reduce the required dose of frozen plasma or blood protein preparations, and minimize the duration of postoperative hospitalization, thus achieving good cost–benefits [27].

Conclusions

Preoperative proximal PSAE allows less complicated liver transplantation by safely reducing portal pressure, decreasing the volume of blood loss, and shortening the duration of surgery. This procedure may be also useful for ameliorating small-for-size syndrome and ASS.

Authorship

YU: designed research/study, performed research/study, collected data, analyzed data, wrote the paper; TY and NT: designed research/study; HS, HM, HM, SS, TI, DS, and HI: collected data.

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