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Analysis of Portal Vein Embolization Using Absolute Ethanol Before Major Hepatectomy

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Portal vein embolization (PVE) is widely considered to improve the safety and extend the indication of major hepatectomy. There are various embolization materials and techniques in each facility. The safety and efficacy of absolute ethanol (EOH) in PVE were analyzed. Fifty-one patients who underwent PVE prior to major hepatectomy were enrolled in this study. Two types of embolization techniques were performed: transileocolic portal vein embolization (TIPE) and percutaneous transhepatic portal vein embolization (PTPE). The embolization material consisted of 20 mL of EOH and 2 mL of iodized oil. Multislice computed tomography (CT) scans were performed before and after PVE. The mean time interval between PVE and the follow-up CT scan was 16.3 ± 5.0 days. The mean future liver remnant ratio to total liver (FLR%) significantly increased from 32.1% ± 7.6% to 43.5% ± 9.5% after PVE ($P < 0.001$). The mean hypertrophy ratio was 41.1% ± 34.5%. There were 3 major complications, subcutaneous hematoma in the TIPE group, hemobilia, and bile leakage in the PTPE group. Although the levels of aspartate transaminase and alanine transaminase increased dramatically after PVE, they subsequently returned to pre-PVE levels. There were no patients whose liver dysfunction was prolonged until hepatectomy. In conclusion, PVE using EOH is a safe and effective method to induce hypertrophy in the future remnant liver before major hepatectomy.

Key words: Portal vein embolization – Absolute ethanol – Hepatectomy

Liver resection is usually the only option for long-term survival for patients with primary and secondary liver malignancies, apart from liver transplantation. Portal vein embolization (PVE) has been widely accepted as an effective method to increase the future liver remnant (FLR) volume in patients requiring major hepatectomy. Future liver remnant ratio to total liver (FLR%) >25% to 30% has

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been recommended in patients with normal liver in most studies. In patients with a compromised liver function such as liver cirrhosis, a threshold of 35% to 40% is preferred as the minimum FLR%.[1] Patients with an insufficient FLR volume will generally undergo PVE to induce compensatory hypertrophy of the remnant liver and improve the recovery from major hepatectomy.[2] The safety and efficacy of PVE have previously been confirmed by several studies, including a recent meta-analysis and in a systematic review.[1,3–6] Previous PVE studies demonstrated that FLR% increased by 20% to 50% within a 3- to 7-week interval between PVE and hepatectomy.[7–11] Several techniques for portal vein occlusion have been reported, including intraoperative portal branch ligation, transileocolic PVE, and the percutaneous transhepatic ipsilateral or contralateral PVE technique. In addition to these different techniques, different embolization materials are used clinically, such as lipiodol, polyvinyl alcohol particles (PVA), coils, fibrin glue, gelatin sponge, and n-butyl cyanoacrylate. Absolute ethanol (EOH) was selected as the embolic materials for PVE due to its manageability and low cost. In the present study, we analyzed the procedure, safety, and efficacy of PVE using EOH.

Materials and Methods

Patients

Fifty-four patients underwent PVE prior to major hepatectomy between August 2002 and March 2015 in our hospital. Fifty-one of these patients (33 men and 18 women), with available computed tomography (CT) images, were enrolled in this study. The mean age was 70.9 ± 8.9 years. The underlying pathology is summarized in Table 1. All patients did not undergo any chemotherapy before PVE.

Procedure

PVE was performed by 2 kinds of techniques: via the transileocolic approach known as transileocolic portal vein embolization (TIPE; n = 42), which required minilaparotomy and the percutaneous transhepatic ipsilateral approach known as percutaneous transhepatic portal vein embolization (PTPE; n = 9). Since April 2012, PTPE was performed when the target vessels could be punctured percutaneously with the guide of ultrasonography. The embolization material consisted of 20 mL of EOH (dehydrated ethanol; Mylan, Tokyo, Japan) and 2 mL of iodized oil (Lipiodol Ultra-Fluide; Mitsui, Tokyo, Japan). It has not been changed for 13 years due to its favorable outcome. The catheter specific for vascular enhancement: 6 Fr balloon catheter (Selecon MP, balloon diameter 20 mm, Terumo, Tokyo, Japan) was used.

CT volumetry

Liver volumes were measured using CT. Multislice CT scans were performed before and after PVE. Liver volume was measured on a Ziostation workstation (Amin, Tokyo, Japan). The future liver remnant (FLR) percentage and hypertrophy ratio were calculated using the following formulas:

$$\text{FLR\%} = \frac{\text{FLR}}{\text{total liver volume}} \times 100$$

and

$$\text{Hypertrophy ratio}(\%) = \frac{\text{FLR after PVE} - \text{FLR before PVE}}{\text{FLR before PVE}} \times 100$$

Blood levels of liver enzymes

Blood chemistry studies were performed before and after PVE following standard protocols.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS; Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD). The levels of liver enzymes and volumetric differences before and after PVE were compared using paired *t* test, whereas other continuous variables were compared using unpaired *t* test. Comparisons between qualitative variables were performed using the Chi square test. Correlations between variables were tested using the Pearson correlation coefficient r. All tests were two-tailed and differences were evaluated at the 5% level of significance.

Results

The mean time interval between PVE and the follow-up CT scan was 16.3 ± 5.0 days. The FLR% (FLR volume) significantly increased from 32.1% ± 7.6 % (372.9 ± 111.7 mL) to 43.5% ± 9.5% (503.4 ±

Table 1 Underlying pathologic characteristics

	No. of patients (%)
Hilar cholangiocarcinoma	23 (45.1)
Hepatocellular carcinoma	14 (27.5)
Metastatic colorectal carcinoma	8 (15.7)
Gallbladder carcinoma	2 (3.9)
Upper cholangiocarcinoma	2 (3.9)
Metastatic gastric carcinoma	1 (2.0)
Intrahepatic cholangiocarcinoma	1 (2.0)

118.9 mL) after PVE ($P < 0.001$). The mean hypertrophy ratio was 41.1% ± 34.5% (range: –6.2 to 34.2). The mean increase in the portal venous pressure due to PVE was 4.9 ± 2.3 cm H_2O (range: 1.0 to 11.0) and had no correlation with hypertrophy ratio (r = 0.981). The mean levels of aspartate transaminase (AST) and alanine transaminase (ALT) significantly increased from 49.8 ± 39.8 (IU/L) to 1231.0 ± 924.9 (IU/L) and from 71.1 ± 84.4 (IU/L) to 797.9 ± 556.1 (IU/L) after PVE. These increased levels were the highest between the first and third postembolization day. They returned to nearly initial conditions about 1 and 2 weeks after PVE (median: 8 and 17 days). There was no significant difference between the levels of AST and ALT before PVE and approximately 2 weeks after PVE (49.8 ± 39.8 IU/L versus 42.8 ± 16.6 IU/L; $P = 0.155$, 71.1 ± 84.4 IU/L versus 55.0 ± 27.1 IU/L; $P = 0.099$). There was also no significant difference in the levels of alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and total bilirubin (T.Bil) between before PVE and approximately 2 weeks after PVE. After PVE, 26 patients (50.1%) underwent extended right lobectomy, 12 patients (23.5%) underwent right lobectomy, 3 patients (5.9%) underwent right hepatic trisectionectomy and 1 patient (2.0%) underwent extended left lobectomy. Five patients (9.8%) underwent laparotomy without resection due to intraoperative finding of peritoneal dissemination. Four patients (7.8%) did not undergo laparotomy due to inadequate hypertrophy of remnant liver (n = 1, 2.0%), severe progression of liver metastasis (n = 1, 2.0%), poor general condition (n = 1, 2.0%), and accidental out-of-hospital death (n = 1, 2.0%; Fig.1).

There were no significant differences in age, gender, and duration of operation between PTPE group and TIPE group. Postoperative complications were subdivided into "minor" (grades I and II) or "major" (grades III, IV, V) according to the revised 2004 Clavien classification.[12] There were 3 major complications after PVE. One patient in the TIPE group experienced subcutaneous hematoma, which was managed with percutaneous drainage. Two cases were in the PTPE group, where 1 case was complicated by hemobilia and the other by bile leakage. Both cases were also managed with percutaneous drainage (Table 2). Between normal liver parenchyma and chronic liver disease group, there was no significant difference in the FLR% before and after PVE (32.0% ± 6.4% versus 31.5% ± 10.0%; $P = 0.811$, 45.0% ± 8.6% versus 39.5% ± 10.3%; $P = 0.063$) and in the HR (44.7% ± 35.1% versus 34.4% ± 32.9%; $P = 0.390$; Table 3). All patients with chronic liver disease underwent major hepatectomy after PVE.

Discussion

Since the initial description of preoperative PVE by Kinoshita in 1986,[13] many authors have studied the

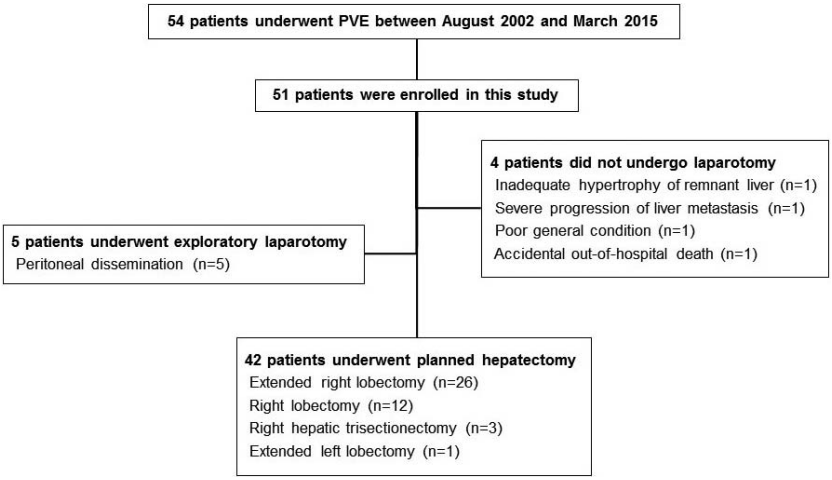

Fig. 1 Study population, surgical procedures, and reasons for unresectability after PVE.

Table 2 Comparison of clinical data between TIPE and PTPE

	TIPE (n = 42)	PTPE (n = 9)	*P* value
Age (years)	72.1 ± 8.2	65.8 ± 11.3	0.055
Gender (male, %)	26 (62)	7 (78)	0.355
Operation duration (minutes)	94.9 ± 26.3	82.9 ± 37.5	0.259
Major complications after PVE (n)			
Subcutaneous hematoma	1		
Hemobilia		1	
Bile leakage		1	

safety and efficacy of this procedure. FLR% >25% to 30% in patients with normal liver and >35% to 40% in patients with chronic hepatitis or cirrhosis have been recommended. In the present study, 35 out of 37 patients (94.6%) with normal liver parenchyma and 10 out of 14 patients (71.4%) with chronic liver disease achieved FLR% >30 and >40, respectively after PVE.

In a recent systematic review, the mean hypertrophy ratio was reported to be 37.9% ± 0.1%, which was measured 25.9 ± 10.1 days after PVE.[1] In the present study, the mean hypertrophy ratio was 41.1% ± 34.5% in 16.3 ± 5.0 days. There are some reports about PVE with EOH that showed microscopic findings including periportal inflammatory reaction and fibrosis, portal vein endothelial injury, portal obstruction with leukocyte infiltration and scattered foci of hepatocyte necrosis.[13–15] This may be the reason why EOH could induce liver damage and subsequent atrophy of the embolized lobe, and hypertrophy of the nonembolized lobe in a short time.

We achieved good outcome within a relatively shorter period, thus suggesting the possibility of preventing PVE patients from dropping out due to rapid disease progression of existing liver tumors.

Some complications of PVE have been reported, such as portal thrombosis, liver hematoma, and embolization of nontarget vessels.[16] In the present study, there were 2 complications of hemobilia and bile leakage in the PTPE group. With regards to the former, the right lobe of the liver was located on the posterior side of the patient, whereas in the latter, the patient with hilar cholangiocarcinoma had hyperbilirubinemia and dilated biliary tract. Therefore, it is important to choose suitable cases for PTPE.

Although many authors have reported on the clinical efficacies of various embolic materials for PVE, there has been no randomized controlled study to compare the efficiencies of these embolic materials. We selected EOH plus iodized oil as the embolic materials for PVE due to their combined efficacy, manageability, and low costs. According to 2 reports, the mean volumes of EOH used for PVE were 20.7 mL (n = 7) and 32 mL (n = 14), respectively,[13,14] more than that in the present study (20 mL). It was reported that the volume of EOH positively correlated with the maximum levels of AST and ALT, but was not related to changes in liver volume after PVE.[17] The present study showed that levels of AST and ALT were elevated after PVE, and were usually the highest on the following day and returned to initial conditions about 2 weeks after PVE. These recoveries required little longer period than those in patients in other reports, 7 to 14 days[13] and within 7 days.[17] The levels of a group of biliary tract enzymes (ALP, GGT, T-Bil) after PVE were almost equal to those before PVE, as compared with AST and ALT.

In the present study, complications were infrequent and there was no mortality directly related to

Table 3 Comparison of clinical data of patients with normal liver parenchyma and chronic liver disease

	Normal liver parenchyma (n = 37)	Chronic liver disease (n = 14)	*P* value
Age (years)	71.8 ± 7.7	68.8 ± 11.8	0.097
Gender (male, %)	20 (54)	13 (93)	<0.001
TIPE/PTPE (TIPE, %)	28 (76)	0 (0)	0.049
FLR% before PVE (%)	32.0 ± 6.4	31.5 ± 10.0	0.811
FLR% after PVE (%)	45.0 ± 8.6	39.5 ± 10.3	0.063
Hypertrophy ratio (%)	44.7 ± 35.1	34.4 ± 32.9	0.390

the procedure. It is also important to highlight that there were no patients whose liver dysfunctions were prolonged until liver resection. All these significantly demonstrated that we can safely and effectively perform PVE using EOH.

In conclusion, PVE using EOH is a safe and effective method of inducing hypertrophy in the FLR before major hepatectomy. This procedure can be considered for any patient with an insufficient FLR volume.

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