Portal Vein Embolization: History and Current Indications

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Summary

Portal vein embolization (PVE) was first adapted for patients undergoing major hepatectomy for hepatocellular carcinoma (HCC). In these patients, PVE caused hypertrophy of the unaffected liver and increased the volumetric ratio of future liver remnant (FLR) to total liver volume. ^{99m}Techetium-galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy revealed that PVE also induced a shift in hepatic function from the embolized part to the nonembolized part of the liver. Various hepatobiliary malignancies can be treated using PVE, and PVE is increasingly being used to expand the indication for major hepatectomy in patients with initially insufficient FLR volume or function. The indication for PVE is determined by the underlying liver function and standardized FLR volume. In patients with chronic hepatitis, the histologic inflammatory activity was negatively correlated with the increase in FLR volume, and PVE is not suitable for patients with high serum 7s collagen concentrations (>8 ng/ml). This finding may predict the efficacy of PVE. PVE before major hepatectomy can act as a tolerance test to avoid postoperative hepatic failure. PVE also improved long-term survival after liver resection in patients with HCC. Presently, PVE is a safe and useful treatment for patients undergoing major hepatectomy.

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Introduction

In 1975, Honjo et al. [1] reported portal vein ligation (PVL) as a treatment for unresectable liver cancer. However, in their series, the effect of PVL was unclear because histologic examination of the affected cancer was not done. PVL requires laparotomy. Therefore,

we developed the percutaneous transhepatic portal vein embolization (PVE) technique that does not require laparotomy, and investigated the anticancer effects of PVE on hepatocellular carcinoma (HCC). These results were first reported by Kinoshita et al. [2] of our group. PVE was first performed to strengthen the anticancer effects of transcatheter arterial embolization (TAE) in patients with HCC, followed by liver resection. We found that PVE was safer than TAE, and while strengthening the anticancer effects of TAE it also caused hypertrophy of the unaffected liver. We also performed experiments using rats to clarify that PVE caused hypertrophy of the unaffected liver and atrophy of the affected liver.

Since our first report [2], PVE has been increasingly used at various institutes to expand the indication for major hepatectomy in patients with initially insufficient future liver remnant (FLR) volume or function [3, 4]. The indication for PVE was also extended to various hepatobiliary malignancies, including HCC with portal thrombi, hilar carcinoma, and metastatic liver tumors [3, 4].

Here we introduce the clinical and experimental studies conducted by our group and the current indications for PVE.

Development of Portal Vein Embolization

Several years before our first report [2], we performed percutaneous transhepatic portography to investigate the portal invasion of hepatobiliary malignancies and branching patterns of the portal vein in such patients. Conversely, TAE had been developed as a treatment for HCC. However, it was not effective for extracapsular invasion and portal thrombi at that time. Therefore, we attempted PVE during portography to strengthen the anticancer effects in patients with HCC. Under ultrasound guidance, we used a catheter introducer for the selective puncture of a portal branch and administered a fibrin mixture with added Lipiodol® (Guerbet, Villepinte, France) to the portal vein, using a balloon catheter to prevent scattering of the embolic materials. PVE was performed at the right portal vein, the left portal vein, and the more peripheral part of the intrahepatic portal vein in patients with HCC (fig. 1A–C). In patients with a large liver tumor compressing the first portal branches, transileocecal PVE was performed (fig. 1D). Immediately

after PVE, portal pressure increased from 20 to 140 cm H₂O. Most patients had abdominal discomfort or pain and fever after PVE. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels slightly increased and then decreased within 2 weeks after PVE. We also found that the indocyanine green retention rate at 15 min (ICGR15) slightly increased. On laparotomy, the appearance of the area affected by PVE varied depending on the state of embolization of the portal branch and recanalization of the occluded artery. The embolized area was dark red, which produced a demarcation line between the embolized and nonembolized parts of the liver. Regarding liver specimens, PVE caused necrosis of the extracapsular invasion, portal thrombi, and main tumor. In the noncancerous areas, we observed atrophy of the hepatic cells and dilatation of the sinusoids. In patients with portal thrombi, the portal thrombus was covered by embolic materials after PVE (fig. 2). We also found that the unaffected liver volume increased, especially when the right portal vein was embolized.

Portal Vein Embolization before Major Hepatectomy

To determine whether PVE can extend surgical indications and increase the safety of liver resection, we studied the postoperative course of patients after major liver resection, i.e. right hepatectomy with and without PVE [5]. Serum AST, ALT, and total bilirubin levels and prothrombin time were not different between patients who did or did not undergo PVE. However, the pre- and postoperative changes in serum AST levels and prothrombin time were significantly smaller in patients who underwent PVE than in those who did not. In patients who underwent PVE, the left liver (non-embolized) volume increased after PVE and liver resection; however, when comparing the volume of the left liver at the beginning of treatment and 4 weeks after surgery, the extent of the volume increase in the left liver in patients who underwent PVE was similar to that in those who did not undergo PVE. This indicated that PVE causes regeneration of the left liver in two stages [6, 7].

^{99m}Tc-galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy demonstrated that after PVE, the right receptor index decreased and the left receptor index increased (fig. 3) [8–10]. These results indicated that PVE induces a shift in hepatic function from the embolized to the nonembolized part of the liver, PVE of the right portal vein increases the hepatic functional reserve and left liver volume, and ^{99m}Tc-GSA uptake after PVE may predict the response to liver resection. The status of liver regeneration after PVE can also be evaluated by the erythrocyte polyamine level [9].

The operative mortality after major hepatectomy was significantly lower in patients who underwent PVE than in those who did not. PVE also improved the outcomes after liver resection in patients with HCC [6, 7]. Previous reports have also demonstrated favorable long-term survival rates after PVE and subsequent major hepatectomy in patients with HCC, which were similar or superior to those in patients who did not undergo PVE [7, 10]. However, the recurrence-free survival rates were reportedly similar between patients who did and did not undergo PVE for HCC [7, 10, 11].

Fig. 1. Embolized portal veins: **A** right portal vein, **B** left portal vein, **C** posterior branch, and **D** transileocecal embolization of the right portal vein.

Fig. 2. Histologic finding after portal vein embolization in a patient with portal tumor thrombus. The tumor thrombus is covered by embolic material (arrows).

Beppu et al. [12] reported that even though patients with HCC who underwent preoperative PVE and right-sided hemihepatectomy had a significantly larger resected liver volume on admission, their long-term prognosis was comparable to that of patients who underwent upfront hepatectomy. They also reported that PVE might decrease extrahepatic recurrences.

Despite prior PVE, hepatic failure developed in some patients after major hepatectomy. In some, the portal pressure immediately after PVE was >30 cm H₂O [13]. In others, the prognostic score [14] (calculated by age, parenchymal hepatic resection rate, and ICGR15) 2 weeks after PVE increased to >50 points. Thus, a portal pressure of >30 cm H₂O, i.e. portal hypertension, or a prognostic score of >50 points were significantly associated with postoperative hepatic failure [9]. This means that PVE can act as a tolerance test before major hepatectomy. In such patients with a risk of postoperative hepatic failure, the amount of liver to be resected should probably be limited, or another therapy should be attempted.

A study on the relationship between histologic inflammatory activity and increase in the left liver volume in patients with HCC

and chronic hepatitis showed that histologic inflammatory activity was negatively correlated with increase in left liver volume, indicating that histologic inflammatory activity was the essential factor regulating liver regeneration after PVE in patients with chronic hepatitis [13].

To determine the limitations of PVE preoperatively, we investigated the correlation between serum type IV collagen 7s domain (7s collagen) concentrations and changes in the left liver volume after PVE [15]. The percent increase in the left liver volume negatively correlated with the pre-embolization serum 7s collagen concentration. In some patients with high serum 7s collagen concentrations (>8 ng/ml), the percent increase was <100% and right hepatectomy was not performed. The serum 7s collagen concentration correlated with the histologic activity score (activity of hepatitis) and the histologic fibrosis score (degree of hepatic fibrosis). These results indicate that serum 7s collagen concentration may predict the efficacy of PVE. PVE before right hepatectomy may not be indicated in patients with high serum 7s collagen concentrations because increases in the left liver volume are not expected in such patients.

Experimental Study

For experimental study, we used rats in which the portal branches supplying 70% of the total liver volume were embolized (fig. 4) [16, 17]. Cirrhosis was induced by carbon tetrachloride because the background liver function in patients with HCC is frequently impaired by chronic liver disease such as cirrhosis. We showed that PVE caused an increase in ornithine decarboxylase activity, deoxyribonucleic acid (DNA) synthesis, and mitosis of the hepatocytes, although DNA synthesis was delayed in rats with cirrhosis. Thus, PVE caused cell proliferation and hypertrophy in the nonembolized part of the liver in normal rats and in those with cirrhosis.

We found that PVE enabled liver regeneration to occur in two stages, and prior PVE reduced the overload during the early stage of liver regeneration [17]. During the active phase of liver regeneration after hepatectomy, the basic functions of the hepatocytes such as albumin synthesis are depressed, indicating that the regenerating liver is vulnerable to stress. PVE of the right liver induced a shift in functional capacity from the right to the left liver without affecting total liver function so that when major hepatectomy is conducted, the basic functions of the left liver are already enhanced. PVE also enhanced the defense mechanisms of Kupffer cells. These mechanisms may contribute toward improving the outcome of major hepatectomy.

We then evaluated the effects of PVE in an endotoxin-induced liver injury model using rats. 7 days after PVE, the nonembolized part of the liver was approximately twice the size of the corresponding lobes in intact rats, the Kupffer cell density was doubled, and the hepatic function per unit weight, evaluated by the elimination of ICG, was approximately the same as that in the controls. When endotoxin was intravenously injected 48 h after hepatectomy in rats in whom previous PVE was and was not performed, hepatic dysfunc-

Fig. 3. ^{99m}Tc -galactosyl human serum albumin scintigraphy **A** before and **B** after right portal vein embolization.

Fig. 4. The portal branches perfusing the median and left lateral lobes of the rat liver were embolized.

tion and endotoxin-induced liver injury were significantly less in the PVE + hepatectomy group than in the hepatectomy alone group. These results showed that preoperative PVE can make hepatectomy safer. However, drugs metabolized by cytochrome P450 (CYP) isoforms should be used carefully in patients who undergo major hepatectomy with PVE because the hepatic CYP-dependent drug metabolism by CYP isoforms recovered more slowly [18].

We also studied the effects of 70% PVL in rats. PVL caused increases in ornithine decarboxylase activity, DNA synthesis, and mitosis in the unaffected liver [19]. After PVL, a necrotic area appeared near the central vein, and it spread widely from the central to the intermediate zone of the hepatic lobules [20]. Subsequently, macrophages or Kupffer cells migrated to the extrasinusoidal space and the necrotic cells began to be eliminated by phagocytes. By day 14, the hepatic architecture had been completely restored. Some endothelial cells had lost their pore structures and had developed basement membranes. The Kupffer cell density and their phagocytic activity also decreased. Apoptotic hepatocytes were often

seen. Therefore, the affected liver atrophied, although PVL caused regeneration of the unaffected liver.

Current Indications of Portal Vein Embolization

In the current guidelines, PVE is indicated when the standardized FLR volume (percentage of total estimated liver volume) is $\leq 20\%$ in a normal liver, $\leq 30\%$ in liver with intermediate disease without cirrhosis, and $\leq 40\%$ in liver with cirrhosis [21]. Patients classified as having Child-Pugh class B or C liver disease or those with ICGR15 $> 20\%$ are not candidates for major hepatectomy after PVE. Our previous study showed that the effects of PVE are not seen in patients with severe hepatic fibrosis (serum 7s collagen concentration, > 8 ng/ml) and severe active hepatitis. When the portal pressure is > 30 cm H₂O after PVE, the amount of liver to be resected should probably be limited or another therapy should be attempted.

In patients with biliary obstruction due to tumor progression, biliary decompression before PVE was required to avoid injuring the dilated bile duct. PVE has recently been used before various types of surgeries. Nagino et al. [4] reported the usefulness of additional embolization of segment IV branches in right PVE in patients undergoing right trisectionectomy.

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Additional Indications of Portal Vein Embolization

Bile leakage, one of the most common complications after hepatic resection, is sometimes intractable. Use of PVE has been reported for the treatment of interrupted-type bile leakages to decrease bile production from the embolized part of the liver [22]. We also experienced a case of a patient with intractable bile leakage that was resolved by PVE [23]. In this case, the posterior branch of the bile duct was completely obstructed after anterior sectionectomy. Portal posterior branch embolization stopped the bile leakage. Thus PVE might be a nonsurgical option for the treatment of intractable bile leakage.

Conclusion

Today PVE is used worldwide as a preoperative treatment to make major hepatectomy safer and to increase the number of patients undergoing hepatectomy.

Disclosure Statement

The authors declare no conflict of interest. There is no funding to report.