Long Term Results of Balloon-Occluded Retrograde Transvenous Obliteration for Portosystemic Shunt Encephalopathy in Patients with Liver Cirrhosis and Portal Hypertension

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Edited by OSAMU NAKASHIMA

Summary: This study examined 19 patients with portosystemic shunt encephalopathy caused by a splenorenal shunt (SRS), which was treated with balloon-occluded retrograde transvenous obliteration (B-RTO). Long-term treatment outcomes were evaluated based on hepatic functional reserve and vital prognosis. Encephalopathy improved in all patients after shunt embolization and closure. Albumin, serum ammonia, and the Child-Pugh score, a measure of liver function, were significantly improved 3 years after B-RTO, and exacerbation of damage to liver function was avoided (p<0.01). During the follow-up period, three patients died from liver failure and two patients from hepatocellular carcinoma. Patients had a poor prognosis if their albumin levels were less than 2.8 mg/dL before B-RTO (p<0.05). Encephalopathy patients had complete response to B-RTO, but long-term prognosis was affected by hepatic functional reserve before B-RTO and by concurrent hepatocellular carcinoma. The results of this study suggest that in patients with SRS, it is important to perform B-RTO at an early stage when the hepatic functional reserve is still satisfactory.

Key words balloon-occluded retrograde transvenous obliteration, liver cirrhosis, portal hypertension, portosystemic shunt syndrome, portosystemic shunt encephalopathy, splenorenal shunt

INTRODUCTION

Hepatic encephalopathy (HE) is a general term describing neuropsychiatric symptoms, mainly disturbances of consciousness, that develop because of serious impairment of liver function. Generally, HE is grouped into 2 major types: HE caused by necrosis and destruction of hepatocytes and HE caused by the formation of a portosystemic shunt. Acute liver failure such as acute hepatitis represents the former type, in which hepatic parenchymal cells undergo extensive necrosis, resulting in their decreased ability to process and detoxify encephalopathy-causing substances. The latter is a shunt type in which the encephalopathy-causing substances are absorbed in the intestinal tract, move from the portal system to the systemic circulation, and reach the central nervous system, resulting in hepatic encephalopathy. This type of encephalopathy is called shunt encephalopathy [1].

In 1991, Kanagawa et al. [2] introduced balloon-occluded retrograde transvenous obliteration (B-RTO) as a groundbreaking treatment of solitary gastric fun-

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dal varices. Since that time, this treatment has rapidly become prevalent in Japan because it is a simple and safe procedure and produces good results [3-5]. In addition, B-RTO embolizes and closes portosystemic shunts. It is indicated for and has been reported to be highly effective against shunt encephalopathy [6-8]. The B-RTO generally improves the indocyanine green excretion rate at 15 min (ICGR$_{15}$) following the procedure. However, there have been only a small number of reports on long-term prognosis. Our study retrospectively examined the hepatic functional reserve and vital prognosis as the long-term outcomes of B-RTO in patients with portosystemic shunt encephalopathy caused by splenorenal shunt (SRS). This is the most common type of portosystemic shunt encephalopathy [9].

PATIENTS AND METHODS

Patients

Twenty-three (23) patients were admitted to our hospital for the treatment of shunt encephalopathy between July 1999 and June 2012. The patients were diagnosed with hepatic encephalopathy based on the presence of clinical symptoms such as coma, somnolence, disorientation, abnormal behavior, forgetfulness, abnormal sleep rhythm, and flapping tremor; abnormal electroencephalogram such as triphasic wave pat-

tern and slow wave pattern; and hyperammonemia.

B-RTO was indicated in patients who satisfied the following two criteria. First, patients had recurrent hepatic encephalopathy resistant to standard treatments such as administration of non-absorbable antibiotics (neomycin or kanamycin) and branched chain amino acids (BCAAs); oral administration of lactulose, a poorly absorbable synthetic disaccharide; restriction on protein intake; and removal of factors exacerbating hepatic encephalopathy such as constipation and gastrointestinal bleeding. Second, patients had a portosystemic shunt, (i.e., SRS that was confirmed on contrast-enhanced CT). The study was performed according to the principles of the Declaration of Helsinki, and in all subjects, treatment was performed after obtaining written informed consent.

B-RTO

The B-RTO procedure is an angiographic sclerotherapy, as shown in Figure 1. A 6.5 Fr large capacity B-RTO balloon catheter (Create Medic, Japan) or a 6.0 Fr Selecon MP balloon catheter II (Terumo Clinical Supply, Japan) is inserted retrograde to the portosystemic shunt through a draining vessel of the SRS. The insertion is performed via the right femoral vein or right internal jugular vein and normally through a 7 Fr long sheath. If there is bending or torsion of SRS, selective catheterization is used in the gastric variceal
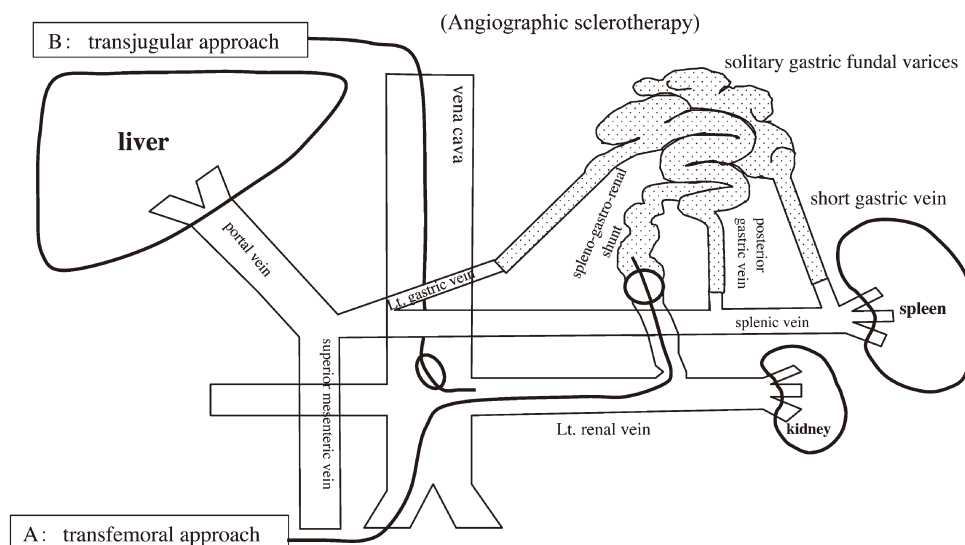

Fig. 1. Schematic representation of B-RTO
The picture shows transfemoral(A) or transjugular(B) approach of balloon catheter through left renal vein into the SRS fed by left, posterior and/or short gastric vein(s). The total SRS is thrombosed and obliterated by injection of 5% EOI as well as the solitary gastric fundal varices. The dotted portion is the area to be thrombosed.
B-RTO, balloon-occluded retrograde transvenous obliteration. SRS, splenorenal shunt.
EOI, ethanolamine oleate with iopamidol.

side. In this procedure, the combined use of micro-catheter and a double coaxial balloon catheter system (CANDIS, Medikit, Japan) are useful [10]. If selective catheterization into the gastric variceal side is difficult or cannot be performed, it is necessary to treat the accessory draining vessels such the inferior phrenic vein and pericardial vein. This treatment includes stepwise injection of 5% ethanolamine oleate with iopamidol (5% EOI) or coil embolization. After accessory draining vessels are treated and SRS becomes the only draining path, the sclerosing agent, 5% EOI, is injected under the balloon occlusion. SRS is embolized and closed overnight, and the balloon catheter is removed on the next day. The dose of 5% EOI should be no more than 0.4 ml/kg per session of B-RTO to prevent complications such as renal dysfunction [11]. We apply the glucose push method (with 50% glucose solution) to advance the sclerosant to the side of the supplying vessel using as small a dose of 5% EOI as possible [12]. This procedure requires no special device and is a useful method to easily reduce the amount of the sclerosing agent used. If a patient requires a dose of 5% EOI that is half the optimal dose for the body weight, drip infusion of haptoglobin (4000 units) is given [13].

Hepatic venous pressure gradient and portal thrombus

The hepatic venous pressure gradient (HVPG) was measured before B-RTO, and the portal venous pressure before B-RTO was evaluated. Contrast-enhanced abdominal CT was performed within 1 week after B-RTO. Evaluation was performed on portal venous thrombus as a complication and on the effect of embolization of SRS.

Evaluation of hepatic functional reserve

The hepatic functional reserve was evaluated by examining the Child-Pugh scores (C-Ps), albumin (Alb), total bilirubin, prothrombin time, $ICGR_{15}$ ascites, encephalopathy, and serum ammonia (NH_3). These items were examined at 0 month as a reference before B-RTO and at 6, 12, 24, and 36 months after B-RTO.

Cumulative survival

The cumulative survival rates were examined 3 years after B-RTO with the focus on hepatic functional reserve.

Statistical analysis

Results are expressed as mean±SD for quantitative data. A paired t-test was used to compare pre- and post-B-RTO values. The Kaplan-Meier method was used to calculate the survival rates. The log-rank test was used to compare the survival rates. The significance level was set at p<0.05. All analyses were performed using Stat-View version 5.0 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Clinical background of patients

Four of the 23 patients were excluded from the analysis. They consisted of 2 patients in whom balloon occlusion could not be performed for anatomical reasons related to the SRS, 1 patient in whom balloon occlusion was possible but multiple shunts were present, and 1 patient in whom B-RTO could not be performed because accessory draining vessels of the major shunt SRS could not be occluded.

The remaining 19 patients were the subjects of this study, and their background information is shown in Table 1. The mean age was 66.9±2.2 years (range: 49-84 years). The men to women ratio was 8:11. The underlying liver diseases were cirrhosis due to HCV in 12 patients, cirrhosis due to HBV in 1 patient, alcoholic cirrhosis in 4 patients, and other underlying disease in 2 patients (schistosomiasis japonica in 1 patient and non-B, non-C liver cirrhosis of unknown cause in 1 patient). Concurrent hepatocellular carcinoma (HCC) was seen in 5 patients. HCC was a single nodule 3 cm or less and had been controlled by non-surgical treatment such as percutaneous radiofrequency ablation or percutaneous ethanol injection.

There was no patient with Child-Pugh grade A liver disease (C-Ps: 6 points or less). There were 14 patients with grade B (C-Ps: 7-9 points) and 5 patients with

TABLE 1.
Background of patients studied (n=19)

Age (years)	66.9±2.2 (49~84)
Sex (M/F)	8 / 11
Cause of cirrhosis HCV/HBV/ALD/others	12 / 1 / 4 / 2
Child-Pugh score	8.7±0.2
Child-Pugh grade A/B/C	0 / 14 / 5
$ICGR_{15}$ (%)	67.3±9.1
Ascites (+/−)	1 / 18
HCC (+/−)	5 / 14
Observation period (month)	28.4±2.4

HCV, hepatitis C virus. HBV, hepatitis B virus. ALD, alcoholic liver disease. $ICGR_{15}$, indocyaninegreen excretion rate at 15 min. HCC, hepatocellular carcinoma.

grade C liver disease (C-Ps: 10-15 points). The mean C-Ps was 8.7±0.2 points. The $ICGR_{15}$ was 67.3±9.1%. Since there was a shunt, the $ICGR_{15}$ values were high overall (normal value: 10% or less). The mean follow-up period was 28.4±2.4 months.

HVPG and portal thrombus of 19 patients

B-RTO was successful in all 19 patients. There was no fatal complication related to the procedure. The mean HVPG before B-RTO was 182.11 mmH_2O (range: 65-480 mmH_2O) (Table 2). One week after B-RTO, contrast-enhanced CT showed that SRS was embolized in all patients, and portal venous thrombus was not observed as a complication in any patient.

Pre- and Post-B-RTO laboratory findings of 19 patients

Table 2 shows the following data of all patients: C-Ps, Alb, and HVPG before B-RTO; ICG_{15} and NH_3 before and after B-RTO; and encephalopathy, ascites, and observation period after B-RTO.

$ICGR_{15}$, encephalopathy and ascites after B-RTO

Table 2 shows post-B-RTO changes in $ICGR_{15}$ and ascites. The mean $ICGR_{15}$ among all patients was 67.3% before B-RTO and 53.2% after B-RTO, indicating a significant decrease (p<0.013). Ascites was observed after B-RTO in 4 patients, of whom only 1 patient required hospitalization for control.

Encephalopathy improved in all patients but one patient (patient #5) died of liver failure at an early stage (6 months) after B-RTO. However, the death was due to encephalopathy from liver failure and not due to shunt encephalopathy. Encephalopathy of another patient (patient #13) improved after B-RTO but SRS regained patency and encephalopathy recurred. In this patient, B-RTO was performed again and encephalopathy improved.

Hepatic functional reserve after B-RTO

Serum ammonia decreased significantly from 146.8±15.6 µg/dL before B-RTO to 91.1±13.0 µg/dL three years after B-RTO (Figure 2, p<0.01). Clinical symptoms of encephalopathy improved as serum am-

TABLE 2.
Pre- and/or post-B-RTO individual data of 19 patients

Patient No.	Sex	Age	C-Ps (point) (Pre)	Alb (g/dL) (Pre)	HVPG (mmH_2O) (Pre)	$ICGR_{15}$ (%) (Pre→Post)	NH_3 (µg/dL) (Pre→Post)	HE (Post)	Ascites (Post)	Observation period (month)
1	F	71	8	2.80	340	58.6→35.4	103→63	(-)	(-)	25+
2	M	49	8	3.70	85	43.0→33.7	114→41	(-)	(-)	36
3	F	53	9	2.80	290	45.8→53.2	125→112	(-)	(-)	36
4	M	66	9	3.09	145	67.9→46.2	125→117	(-)	(-)	36
5	F	62	9	1.72	155	52.3→48.7	160→92	(-)	(+)	6+
6	F	67	10	3.10	230	97.1→69.0	130→87	(-)	(-)	36
7	M	69	8	3.37	95	26.7→22.4	68→28	(-)	(-)	36
8	M	73	9	3.28	240	51.1→44.8	227→98	(-)	(+)	26+
9	F	68	8	3.33	145	60.8→40.4	108→29	(-)	(-)	28
10	F	65	9	2.78	70	34.5→20.0	122→45	(-)	(-)	36
11	F	62	9	2.89	75	78.0→44.5	143→66	(-)	(-)	36
12	F	84	8	3.60	480	62.8→41.0	100→86	(-)	(+)	17+
13*	F	59	7	3.93	195	31.6→18.7	144→93	(-)	(-)	36
14	M	82	10	2.76	70	91.6→44.7	123→120	(-)	(-)	24+
15	M	81	7	2.93	180	20.9→53.0	149→156	(-)	(-)	36
16	F	71	10	2.36	250	81.8→44.2	255→99	(-)	(-)	33
17	M	66	10	2.15	210	88.5→85.0	113→70	(-)	(+)	10+
18	M	70	10	2.29	65	82.9→57.7	116→92	(-)	(-)	36
19	F	54	8	3.29	140	202.0→177.0	364→229	(-)	(-)	12

B-RTO, balloon-occluded retrograde transvenous obliteration. CPs, Child-Pugh score. Alb, albumin. HVPG, hepatic venous pressure gradient. $ICGR_{15}$, indocyanine green excretion rate at 15 min. HE, hepatic encephalopathy. NH_3, serum ammonia. *, recanalized and retreated. +, died.

monia levels improved. The mean albumin level was 2.96±0.13 g/dL before B-RTO and 3.43±0.20 g/dL three years after treatment, indicating a significant increase (Figure 3, p<0.01).

As the albumin level improved and encephalopathy resolved, C-Ps improved significantly from 8.7±0.2 points before B-RTO to 6.7±0.7 points three years after B-RTO (Figure 4, p<0.01). Patient #6 had Child-Pugh grade C liver disease (C-Ps: 10 points) before B-RTO which improved to Child-Pugh grade A (C-Ps: 5-6 points) after B-RTO.

Cumulative survival rate of 19 patients

Two patients died in the early stages after B-RTO: patients #5 and #17 died 6 months and 10 months after B-RTO, respectively. Their Alb levels were very low
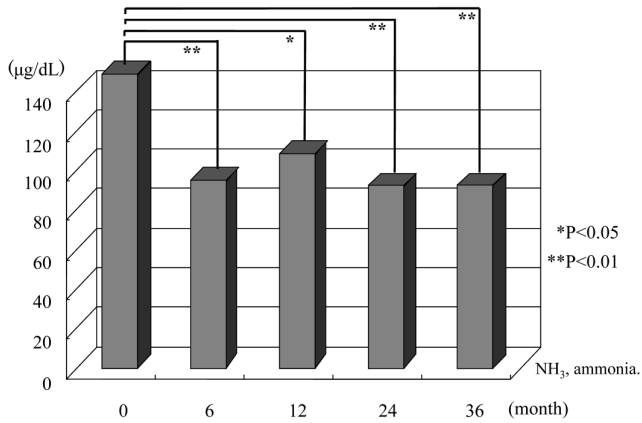

Fig. 2. Changes of serum NH_3 in 3 years after B-RTO

As shunt encephalopathy improved after B-RTO, serum NH_3 levels significantly decreased at all time points compared with the level before B-RTO. The level was 146.8±15.6 µg/dL before B-RTO and 91.1±13.0 µg/dL at 3 years after B-RTO (p<0.01).

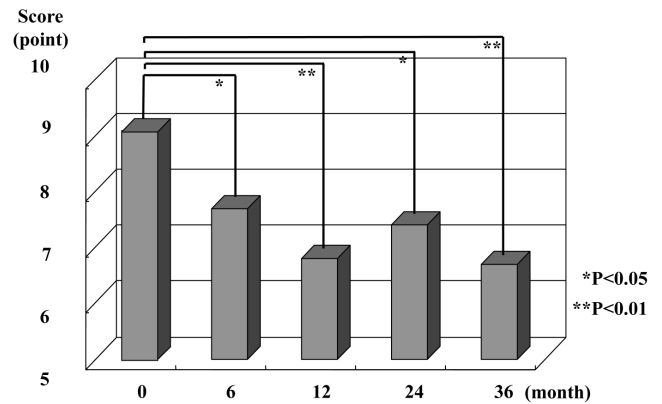NH_3, ammonia. B-RTO, balloon-occluded retrograde transvenous obliteration.

Fig. 4. Changes of Child-Pugh scores in 3 years after B-RTO

As albumin increased and encephalopathy became resolved, Child-Pugh scores significantly improved at all time points compared with the score before B-RTO. The score was 8.7±0.2 points before B-RTO and 6.7±0.7 points at 3 years after B-RTO (p<0.01).

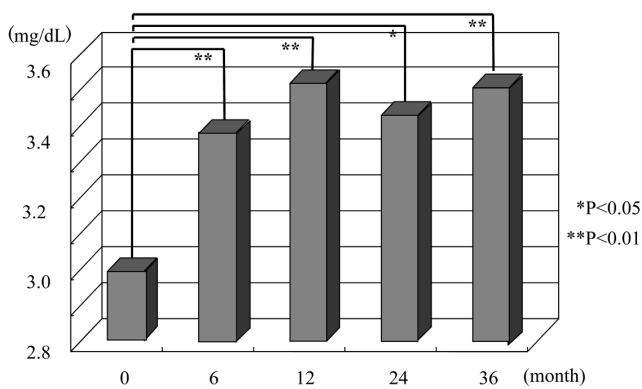B-RTO, balloon-occluded retrograde transvenous obliteration.

Fig. 3. Changes of albumin in 3 years after B-RTO

The mean albumen level was 2.96±0.13 g/dL before B-RTO and significantly increased beginning 6 months after B-RTO. The mean level was 3.43±0.20 g/dL at 3 years after B-RTO, indicating that the level was still significantly higher than that before B-RTO (p<0.01).

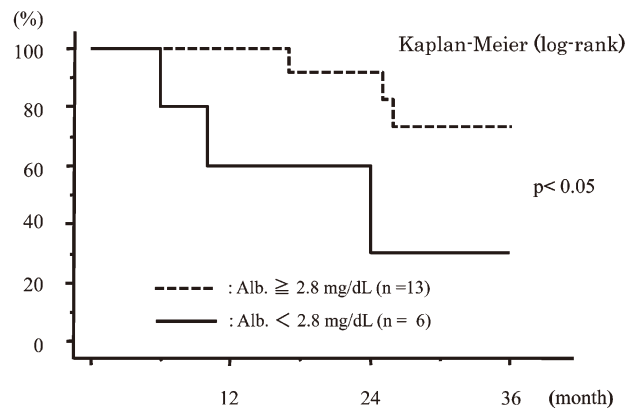B-RTO, balloon-occluded retrograde transvenous obliteration.

Fig. 5. Cumulative survival rates of patients with albumin ≧2.8 mg/dL and <2.8 mg/dL

Cumulative survival rates were examined in patients with an albumin level of 2.8 mg/dL or more and patients with an albumin level of less than this value. The former group had a significantly higher cumulative survival rate (p<0.05).
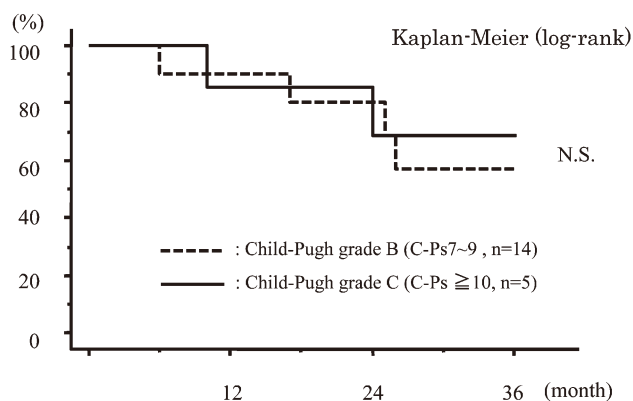
Alb, albumin.

Fig. 6. Cumulative survival rates in patients with Child-Pugh grade B and grade C

Cumulative survival rates were compared between patients with different hepatic function: patients with Child-Pugh grade B liver disease (Child-Pugh scores: 7-9 points) and patients with grade C liver disease (Child-Pugh scores: 10 points or more). There was no significant difference in the cumulative survival rate between these groups of patients.

C-Ps, Child-Pugh score.   N.S., not significant.

before B-RTO, with their pre-B-RTO levels at 1.72 g/dL and 2.15 g/dL, respectively (Table 2).

Figure 5 compares two groups of patients divided based on whether their albumin levels were greater or lesser than 2.8 g/dL, which is approximately the mean albumin level before B-RTO. There was a significant difference in the cumulative survival rate between the two groups (p<0.01). When the patients were divided into a Child-Pugh grade B group and a grade C group, the cumulative survival rate did not differ significantly (Fig. 6).

Cause of death in follow-up

Six patients died, 2 of HCC, 3 of liver failure, and other cause (cerebral infarction) in 1.

DISCUSSION

Portosystemic shunt SRS is a major shunt and can cause portosystemic shunt syndrome (PSS) which includes various syndromes due to portal venous steal. These syndromes mainly involve decreased liver function and decreased survival rate [14]. Shunt encephalopathy is one of the manifestations of PSS. Closure of the portosystemic shunt (i.e., B-RTO preventing the portal venous steal) has been shown to prevent PSS with long-term effects, including a decrease in hepatic functional reserve over time and worsening of vital prognosis [14-16].

Some patients with shunt encephalopathy have frequent repeated bouts or require frequent hospitalization, hindering their daily lives. Such shunt encephalopathy is difficult to control with treatment by medication alone and has been known as an Inose-type hepatic encephalopathy [17]. In this type of portosystemic shunt encephalopathy, treatment with medications can only provide temporary improvement and other treatment is necessary in the long term for the portosystemic shunt [18]. Such encephalopathy used to be treated with shunt ligation and closure via laparotomic surgery. B-RTO is presently the first line treatment for shunt encephalopathy and is effective and minimally invasive [7,18]. B-RTO is an established treatment for solitary gastric fundal varices and was initially developed for embolization, occlusion, and elimination of such varices, which are themselves SRS. B-RTO is also useful in total elimination of SRS. Thus, it became used widely as a good treatment for shunt encephalopathy. In some patients, there are accessory collateral shunts which divert or steal blood flow from SRS. In such cases, B-RTO can become difficult depending on the degree of the accessory collateral shunts outflow. Therefore, it is essential to perform contrast-enhanced CT before B-RTO to fully examine the shunt vascular anatomy and positional relationship.

In all patients in our study, encephalopathy requiring hospitalization was resolved after B-RTO. Improvement in hepatic functional reserve can be expected if hepatopetal portal blood flow increases due to SRS occlusion by B-RTO and if the patient's liver can tolerate it [19-21]. According to Futagawa et al. [22], shunt closure is indicated for patients in whom the increase of portal venous pressure is 50-55% or less after experimental shunt blockage. Tsuruta et al. [23] stated that occlusion can be performed safely if the portal venous pressure is 31 mmH$_2$O (418.5 mmHg) or less after shunt closure. In our study, patient #12 had severe portal hypertension (HVPG of 480 mmH$_2$O) and required repeated and frequent hospitalization due to chronic encephalopathy. Therefore, B-RTO was performed in this patient. Subsequently, the patient did not have recurrence of encephalopathy but developed ascites that required 1 month to control. This patient had severe portal hypertension of 480 mmH$_2$O but B-RTO was performed safely.

In our study, C-Ps and albumin were significantly improved 3 years after B-RTO, indicating that B-RTO prevented the exacerbation of damage to liver function over time. These results were consistent with those of Miyamoto et al. [15]. If patients have reduced liver

volume due to advanced liver cirrhosis, they are unable to tolerate increased hepatopetal portal blood flow. In such patients, there is a concern of development of ascites, liver failure, and varices and of exacerbation of existing varices [18,21,24]. However, we are fortunate that no subjects in our study developed liver failure thought to be caused by B-RTO.

The cumulative survival rate was clearly lower for patients with albumin levels of less than 2.8 mg/dL compared with patients with higher albumin levels. The cumulative survival rate did not differ between patients with Child-Pugh grade B liver disease and those with grade C liver disease. Albumin alone is a primary factor for the liver function. Child-Pugh score consists of 5 factors including albumin, bilirubin, prothrombin time, ascites and encephalopathy. Even in patients with the Child-Pugh grade C, encephalopathy improved and HCC became treatable or liver function improved.

This might be the reason why there was no significant difference in cumulative survival rates between the Child grade B and C. However, it seems that a different study design will be needed to make the difference clear.

In our study, 6 patients died during the mean follow-up period of 28.4±2.4 months. The cause of death was liver failure in 3 patients, HCC in 2 patients, and cerebral infarction in 1 patient. There was no death in the short or long term that was attributable to B-RTO. Two patients died within 1 year after B-RTO. Both patients had HCC and were Child-Pugh grade C cases with low albumin levels at 1.72 mg/dL and 2.15 mg/dL before B-RTO.

If B-RTO is not indicated because of various inappropriate conditions, partial splenic embolization (PSE) is the next choice of treatment. PSE might be performed in the following types of patients: patients having poor hepatic functional reserve or advanced liver cirrhosis and having reduced liver volume due to advanced liver cirrhosis, and patients having shunts that regained patency due to large shunt diameters [25-27]. We had no such patients during the study period.

The results of our present study suggest that if a major portosystemic shunt SRS is present better outcomes can be expected if B-RTO is performed at an early stage when the hepatic functional reserve is still satisfactory. That is, early detection and early treatment of SRS are important.

In conclusion, B-RTO was effective in treating portosystemic shunt encephalopathy due to SRS, and improvement was seen in all patients. However, long-term prognosis was affected by hepatic functional reserve before B-RTO and the presence of HCC. Thus, our results suggest the importance of B-RTO at an early stage when the hepatic functional reserve is still satisfactory.

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