Combination with portosystemic shunt occlusion and antiviral therapy improves prognosis of decompensated cirrhosis

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Abstract

Background and Aim: Portosystemic shunt occlusion using endovascular treatment can transiently improve liver function in patients with decompensated cirrhosis. In recent years, viral hepatitis can be easily controlled. The present study aimed to clarify the safety and efficacy of endovascular treatment in decompensated cirrhotic patients, and to elucidate whether viral treatment improves the prognosis after shunt occlusion.

Methods: Among 98 cirrhotic patients who received portosystemic shunt occlusion from January 2007 to June 2016, we retrospectively analyzed 61 decompensated cirrhotic patients.

Results: Forty-five patients had viral hepatitis. Recovery rates of liver function to Child A within 6 months in viral hepatitis, non-viral hepatitis, and overall were 78% (35/45), 81% (13/16), and 79% (48/61), respectively. Recovery rates according to baseline Child-Pugh score were as follows: score 7, 88% (15/17); score 8, 89% (24/27); score 9, 69% (9/13); and score ≥10, 0% (0/4). Three-year repregexpres the liver function of patients with decompensated cirrhosis.1–5 However, the improved liver function after endovascular treatment is transient (lasting 6–12 months),3 and whether these endovascular procedures can improve the prognosis of patients with decompensated cirrhosis remains unknown.

In recent years, treatments for chronic viral hepatitis have undergone marked development. Nucleoside analogs (NAs) for patients with hepatitis B virus (HBV) can suppress the replication of HBV-DNA for a long time without appearance of resistant mutants,6,7 and direct-acting antiviral agents (DAAs) for patients with hepatitis C virus (HCV) can easily achieve sustained virological response (SVR) at rates exceeding 95% even in real-world settings.8 However, decompensated cirrhosis has been a contraindication for DAA therapy in Japan, and HCV management guidelines of

Introduction

The prognosis of patients with decompensated cirrhosis is particularly poor, with a 5-year survival rate reportedly around 25%.1 The cause of death in cirrhotic patients is mostly liver-related death, such as liver failure, gastrointestinal bleeding, or hepatocellular carcinoma. Large portosystemic shunt growth due to portal hypertension causes hepatic encephalopathy and chronic liver failure because of hepatic blood flow depletion, and representing a severe problem that worsens the prognosis.2

Portosystemic shunt occlusion using endovascular treatment such as balloon-occluded retrograde transvenous obliteration (BRTO) or percutaneous transhepatic obliteration (PTO) has already been established as one of the therapies for gastric varices or hepatic encephalopathy, and these therapies can improve
Western countries have also noted that treatment regimens including a protease inhibitor must not be used in patients with Child-Pugh class B or C decompensated cirrhosis.\textsuperscript{9,10} If decompensated cirrhosis can be recovered to compensated cirrhosis by portosystemic shunt occlusion using endovascular treatment, use of DAAs therapy will be allowed, and the prognosis may thus be improved. However, there is no report about analyzing the influence of viral treatment on prognosis of decompensated cirrhotic patients who received shunt occlusion therapy. The present study aimed to clarify the safety and efficacy of portosystemic shunt occlusion using endovascular treatment in decompensated cirrhotic patients, and to elucidate whether viral treatment improves the prognosis after shunt occlusion.

Material and methods

Patients. A total 98 cirrhotic patients underwent portosystemic shunt occlusion using endovascular treatment such as BRTO and/or PTO in our hospital between January 2007 and June 2016. Indications for endovascular treatment in each case were decided as the consensus decision of hepatologists and interventional radiologists. All endovascular procedures were performed by interventional radiologists.\textsuperscript{4,11,12} When some portosystemic shunts were found on imaging, a dominant shunt that would be the cause of varices bleeding, hepatic encephalopathy, or decreased liver function was occluded. Of these 98 patients, 37 patients were excluded from the present study evaluating improvement of liver function and prognosis in patients with decompensated cirrhosis, comprising: 26 patients with compensated cirrhosis, 8 patients with endovascular treatment failure, 2 patients lost to follow-up, and 1 patient with in-hospital death. Finally, 61 patients with decompensated cirrhotic were retrospectively analyzed. Treatment response was evaluated using changes in laboratory data and diameter of the umbilical portion of portal vein on contrast computed tomography (CT) images, albumin-bilirubin (ALBI) score,\textsuperscript{13} and the recovery rate to Child A.\textsuperscript{14} The sustained viral negativity (SVN) of patients infected with HCV was defined as serum HCV-RNA level remaining negative for >24 weeks after the end of antiviral therapy. SVN in patients infected with HBV was defined as the maintenance of serum HBV-DNA level below the sensitivity of detection by lifelong administration of NA therapy. Patients were classified into three groups: SVN, non-SVN, and non-viral groups. This retrospective study was approved by our institutional review board, and the need for informed consent was waived.

Statistical analysis. Significant changes in laboratory data and diameter of the umbilical portion of the portal vein at 1 month after endovascular treatment were tested using the Mann–Whitney U test. The Kruskal-Wallis test was used to assess for significant differences in ALBI score among patient’s groups. Cumulative reprogression rates to decompensated cirrhosis, aggravation rates of esophageal varices, and survival rates after endovascular treatment according to patient group classification were computed using the Kaplan–Meier method and compared using the log-rank test. Uni- and multivariate analyses for factors contributing to survival were performed using Cox proportional hazards regression modeling. Results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Values of $P < 0.05$ were considered significant for all analyses using the SPSS 21.0 software package (SPSS, Chicago, IL, USA).

Results

Patient characteristics. Baseline characteristics of patients are summarized in Table 1. Although there were 29 patients with a history of HCC treatment in this study, no patient with concurrent HCC was included. There were 39 HCV, 6 HBV, and 16 non-viral patients in this study. Antiviral treatments were performed in 26 patients before or after endovascular treatment, comprising NA in 5 patients, interferon (IFN)-based therapy in 7 patients, and DAAs in 14 patients. One HBV patient was not treated by NA treatment because of low HBV-DNA and normal transaminase levels. The treatment profiles are summarized in Table 2. SVN was achieved in all patients who received antiviral treatment. Seven of 26 SVN patients achieved SVN before endovascular treatment; there were 4 HBV and 3 HCV patients. The median period from start of antiviral therapy until shunt occlusion was 499 days, and ranged from 42 to 4551 days. Remaining 19 viral patients were treated after endovascular treatment. The median period from shunt occlusion until start of antiviral therapy was 172 days, and ranged from 30 to 865 days.

Adverse events during hospital stay after endovascular treatment. Adverse events during hospital stay after endovascular treatment appeared in 18 patients (29.5%), in the form of ascites in 6 patients, pleural effusion in 3 patients, ascites and pleural effusion in 4 patients, portal vein thrombosis in 3 patients, and intraperitoneal bleeding in 2 patients. All cases of ascites and pleural effusion could be controlled using oral diuretics.

Table 1 Baseline characteristics of patients

|                        | N = 61 |
|------------------------|--------|
| Age, years (range)     | 68 (42–81) |
| Sex, male/female       | 37/24 |
| HCV/HBV/Non-virus      | 39/6/16 |
| Child B/C              | 57/4 |
| Child-Pugh score (7/8/9/10/11) | 17/2713/3/1 |
| Purpose of shunt occlusion (recovery of liver function/varices) | 48/13 |
| BRTO/PTO/BRTO + PTO    | 58/3/1 |
| GR shunt/SR shunt/other shunts | 20/24/17 |
| History of HCC treatment (%) | 29 (48%) |
| Esophageal varices (%)  | 42 (69%) |
| Gastric varices (%)     | 21 (34%) |
| History of esophageal varices treatment (%) | 21 (34%) |
| History of splenomegaly (%) | 6 (10%) |
| Antiviral treatment (NA for HBV/IFN-based/DAAs) | 57/14 |

Values are expressed as median (range) or number (percentage).

BRTO, balloon-occluded retrograde transvenous obliteration; DAA, direct-acting anti-viral agent; GR, gastro-renal; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HBV, hepatitis C virus; IFN, interferon; NA, nucleoside analog; PTO, percutaneous transhepatic obliteration; SR, splenorenal.
Treatment response after endovascular treatment.
To evaluate the efficacy by only shunt occlusion, changes in laboratory data and portal vein diameter at the umbilical portion at 1 month after endovascular treatment are analyzed. Those were summarized in Table 3. Recovery rates of liver function to Child A within 6 months after endovascular treatment in viral hepatitis, non-viral hepatitis, and overall were 78% (35/45), 81% (13/16), and 79% (48/61), respectively. Recovery rates according to baseline Child-Pugh score were as follows: score 7, 88% (15/17); score 8, 89% (24/27); score 9, 69% (9/13); and score ≥ 10, 0% (0/4). Of the four patients with Child C, none showed recovery of liver function to Child A. However, liver function improved in two patients from Child C to B within 6 months. To evaluate the influence of viral suppression on liver function after shunt occlusion, change of ALBI score within 6 months after endovascular treatment was compared among three groups. The comparison was shown in Figure 1. ALBI score was significantly lower in non-virus and SVN groups than in non-SVN group. (at 3 months; \( P = 0.048 \), \( P = 0.002 \), SVN vs. non-SVN; \( P = 0.002 \)).

Reprogression to decompensated cirrhosis after endovascular treatment. Cumulative re-progression rates to decompensated cirrhosis after endovascular treatment according to patient group are shown in Figure 2. Three-year re-progression rates to decompensated cirrhosis in non-virus, non-SVN, and SVN groups were 23, 100, and 0%, respectively (non-virus vs. non-SVN; \( P = 0.002 \), SVN vs. non-virus; \( P = 0.016 \), SVN vs. non-SVN; \( P < 0.001 \)).

Aggravation of esophageal varices after endovascular treatment. Cumulative aggravation rates of esophageal varices after endovascular treatment according to patient group are shown in Figure 3. Three-year aggravation rates of esophageal varices in non-virus, non-SVN, and SVN groups were 37, 44, and 46%, respectively. No significant differences were evident among patient groups. Three-year aggravation rates for HBV and HCV patients in SVN group were 60 and 40%, respectively (\( P = 0.392 \)). Rupture of esophageal varices occurred in three patients. Two of these patients belonged to non-SVN group, and one patient was in SVN group. Six patients received splenectomy before endovascular treatment. Two of each patient belonged to three patient group. Among the six patients, aggravation of esophageal varices was observed in two patients during the observation period.

Survival and factors contributing to survival. Cumulative survival rates after endovascular treatment according to patient group are shown in Figure 4. Three-year survival rates

| Treatment                        | N = 26 |
|---------------------------------|--------|
| Nucleoside analogue (for HBV)   | 5      |
| Entecavir                       | 4      |
| Lamivudine plus tenofovir       | 1      |
| IFN-based therapy (for HCV)     | 7      |
| Pegylated IFN monotherapy       | 3      |
| Pegylated IFN plus ribavirin    | 2      |
| Simeprevir triple therapy       | 2      |
| DAAs (for HCV)                  | 14     |
| Sofosbuvir plus ledipasvir      | 10     |
| Daclatasvir plus asunaprevir    | 3      |
| Sofosbuvir plus ribavirin       | 1      |

DAA, direct-acting anti-viral agent; HBV, hepatitis B virus; HCV, hepatitis C virus; IFN, interferon.

| Ammonia (µg/dL)    | Baseline       | After 1 month | P      |
|-------------------|----------------|---------------|--------|
|                   | 117 (25–387)   | 56 (12–181)   | <0.001 |
| Total bilirubin   | 1.4 (0.7–3.4)  | 1.3 (0.5–2.6) | 0.010  |
| (mg/dL)           |                |               |        |
| Albumin (g/dL)    | 2.9 (2.1–4.4)  | 3.2 (2.4–4.3) | <0.001 |
| Prothrombin time  | 61.6 (37.8–85.6)| 71.2 (33.7–84.0) | <0.001 |
| (%)               |                |               |        |
| ALBI score        | –1.55 (–3.03 to 0.86)| –1.84 (–2.86 to 1.00) | <0.001 |
| ALIT (µL)         | 30 (10–102)    | 28 (8–193)    | 0.717  |
| Platelets (x10^3/µm²) | 7.7 (3.2–30) | 6.8 (3.0–21.4) | 0.093  |
| Diameter of umbilical portion (mm) | 6.0 (1.5–14.6) | 7.2 (1.5–13.5) | <0.001 |

Values are expressed as median (range) or number (percentage). ALBI, ALT, alanine aminotransferase.
for non-virus, non-SVN, and SVN groups were 63, 62, and 91%, respectively. The survival rate was significantly higher in SVN group than in non-virus or non-SVN group (SVN vs. non-virus, \( P = 0.003 \); SVN vs. non-SVN, \( P = 0.001 \)). No significant difference was seen between non-virus and non-SVN group (\( P = 0.576 \)). The 8-year survival rate of the SVN group was also maintained at 91%. \( \cdots \), SVN (\( n = 27 \)); \( \cdots \cdots \), Non-SVN (\( n = 18 \)); \( \cdots \cdots \cdots \), Non-virus (\( n = 16 \))

### Discussion

This was a retrospective cohort study of patients with decompensated cirrhosis and large shunt who underwent shunt occlusion by endovascular treatment. The safety and efficacy of shunt occlusion using endovascular treatment, and prognosis after shunt occlusion were evaluated in the present study. As a result, the present study clarified that the recovered liver function by shunt occlusion was maintained for a long time in SVN patients, and the better prognosis was confirmed.

Regarding efficacy of shunt occlusion, recovery rate to Child A within 6 months after shunt occlusion was high (around 80%) regardless of hepatitis etiology. As another change after shunt occlusion, portal vein diameter at the umbilical portion was also significantly expanded only 1 month later. Kako et al. demonstrated using perfusion CT before and after shunt occlusion that shunt occlusion increased portal venous blood flow and decreased hepatic arterial blood.\(^{15}\) Dilatation of portal vein diameter would almost certainly mean an elevation of portal vein pressure, and the improvement in liver function would be
attributable to the increase in effective liver blood flow. Accordingly, decompensated cirrhotic patients with portal vein narrowing because of large portosystemic shunt growth would be good candidates for shunt occlusion in the sense that effective liver blood flow is poor.

In terms of safety, aggravation of ascites, pleural effusion, and esophageal varices after BRTO has been reported as mainly mild to moderate, but the frequency was high. In the present study, although all cases of ascites and pleural effusion were controllable by diuretics, aggravation of esophageal varices was observed in around 40% regardless of the etiology or SVN. Choi et al. reported on the natural history of coexisting esophageal varices after BRTO for gastric varices. They demonstrated that the incidence of esophageal varices bleeding was significantly higher in the BRTO group than in the control group at 7 years (90.7% vs. 50.6%, P < 0.01). Upper gastrointestinal endoscopy should therefore be performed before shunt occlusion, and careful follow-up using endoscopy is needed. On the other hand, Chikamori et al. performed combination therapy with BRTO and splenic artery embolization (PSE) to reduce the risk of aggravation of esophageal varices after BRTO. Their results indicate that PSE or splenectomy may be effective to suppress excessive elevation of portal vein pressure after BRTO. Tanihata et al. indicated that a portal systemic pressure gradient (PSPG) >5 mmHg after BRTO is a risk factor contributing to the aggravation of esophageal varices. Accordingly, PSE or splenectomy might have to be performed for patients with excessive elevation of portal vein pressure after shunt occlusion.

Regarding prognosis after shunt occlusion, Kumanoto et al. studied long-term effects after BRTO to a large splenorenal shunt. They demonstrated no significant difference in survival between the large shunt group treated with BRTO and the group without large shunt, and the cumulative survival rate was significantly higher for the large shunt group than for the large shunt group without BRTO. However, reported 5-year survival rates of patients after BRTO have ranged widely (39–69%). In the present study, independent contributors to survival were age, baseline liver function, baseline ammonia level, and SVN. SVN was strongly associated with preservation of liver function after shunt occlusion. In fact, although the recovered liver function in all non-SVN patients reprogressed to decompensated stage within 3 years, that in all SVN patients was preserved for a long time. On the other hand, although the reprogression rate to decompensated cirrhosis for non-virus group was also significantly lower than that for the non-SVN group, no significant difference was seen in prognosis between the two groups. This discrepancy may be due to the contributions of hepatic reserve, hepatic etiology, effect of hepatitis treatment, or other factors such as hepatocellular carcinoma or age. In fact, the incidence of hepatic failure death for non-virus group was lower than that for non-SVN group. According to these results, if chronic hepatitis of patients can be controlled irrespective of etiology, the recovered liver function by shunt occlusion would be probably maintained. Shunt occlusion alone is not enough to improve prognosis, and preservation of the recovered liver function seems to improve the long prognosis after shunt occlusion.

In the new era of oral NAs and DAAs, hepatitis viruses can be safely and easily eradicated or suppressed for a long time. Therapy with sofosbuvir plus velpatasvir was recently approved for the treatment of decompensated cirrhosis due to HCV in Japan. However, liver function was not improved in all SVN patients. Only 26% (24/91) showed improvements in Child-Pugh class, and 2% (2/91) worsened from baseline to post-treatment patients. Only 26% (24/91) showed improvements in Child-Pugh class, and 2% (2/91) worsened from baseline to post-treatment week 12. Fernandez et al. reported that baseline model for end-stage liver disease (MELD) score alone (cut-off, 18) offered the best predictor of survival for SVR patients with compensated cirrhosis. As described, although it was already reported that antiviral therapy can improve hepatic function, some decompensated cirrhotic patients would thus not show improvements in liver function with antiviral therapy alone. In fact, 4 HBV and 3 HCV patients with compensated cirrhosis who achieved SVN before endovascular treatment were included in

| Table 4  | Uni- and multivariate analyses of factors contributing to survival |
|----------|---------------------------------------------------------------------|
|          | Univariate analysis | Multivariate analysis |
|          | P      | HR | 95% CI | P      | HR | 95% CI |
| Age (years) | 0.028 | 1.099 | 1.010–1.195 | 0.024 | 1.112 | 1.014–1.219 |
| Sex (female) | 0.302 | 1.683 | 0.627–4.515 | 0.225 | 1.301 | 0.401–4.430 |
| Purpose of shunt occlusion (recovery of liver function) | 0.080 | 0.402 | 0.145–1.114 | 0.087 | 0.405 | 0.145–1.114 |
| History of HCC treatment | 0.889 | 1.074 | 0.395–2.921 | 0.672 | 1.184 | 0.397–3.660 |
| History of EV treatment | 0.434 | 1.488 | 0.550–4.029 | 0.384 | 1.398 | 0.499–3.980 |
| Platelets (x10^3/µL) | 0.788 | 0.984 | 0.874–1.108 | 0.468 | 0.744 | 0.550–1.000 |
| Heparin level (IU/L) | 0.768 | 1.036 | 0.821–1.307 | 0.151 | 1.019 | 0.993–1.044 |
| ALT (IU/L) | 0.957 | 1.012 | 0.885–1.157 | 0.468 | 1.441 | 0.537–3.864 |
| Child B | 0.005 | 0.162 | 0.045–0.584 | 0.006 | 0.098 | 0.018–0.521 |
| Ammonia (µg/dL) | 0.023 | 0.990 | 0.981–0.999 | 0.053 | 0.988 | 0.976–1.000 |
| SVN | 0.003 | 0.100 | 0.022–0.447 | 0.001 | 0.071 | 0.015–0.336 |
| Recovery to Child A after shunt occlusion | 0.255 | 0.541 | 0.188–1.558 | 0.005 | 0.099 | 0.018–0.521 |
| Exacerbation of EV | 0.468 | 1.441 | 0.537–3.864 | 0.468 | 1.441 | 0.537–3.864 |

ALT, alanine aminotransferase; CI, confidence interval; EV, esophageal varices; HCC, hepatocellular carcinoma; HR, hazard ratio; SVN, sustained viral negativity.
the present study. The recovered liver function of these patients did not drop for a long time after shunt occlusion. From our results, it appears that the achievement of both SVN by antiviral treatment and liver function recovery by shunt occlusion is crucial for improving liver function and the prognosis of decompensated cirrhotic patients with large portosystemic shunt. Therefore, it can be suggested that shunt occlusion therapy should be performed for decompensated cirrhotic patients with large portosystemic shunt and HCV before antiviral treatment, and antiviral therapy should be performed as soon as possible after recovery of liver function. Because there are a lot of DAA options for patients with compensated cirrhosis, and DAA therapy can be performed with safer condition. In addition, it can be also suggested that shunt occlusion therapy should be considered for patients with decompensated cirrhosis and large portosystemic shunt who already achieved SVN. However, future investigations need to clarify which treatment is better for decompensated viral cirrhosis, anti-viral treatment only or combined antiviral treatment and shunt occlusion.

Some limitations to the present study must be considered. First, the number of patients in the present study was small. Second, as this study used a retrospective design, selection biases would exist. Third, our study population is highly ununiform, and no matched control group was included in the present study. Therefore, the rationale of the present study is weak, and it is difficult to interpret our results. Fourth, the influences of splenectomy, shunt recurrence, and treatment on prognosis could not be evaluated. Fifth, renal dysfunction is a powerful prognostic marker. However, as this study used a retrospective design, selection biases would exist. Third, our study population is highly ununiform, and no matched control group was included in the present study. Therefore, the rationale of the present study is weak, and it is difficult to interpret our results. Fourth, the influences of splenectomy, shunt recurrence, and treatment on prognosis could not be evaluated. Fifth, renal dysfunction is a powerful prognostic marker.

In conclusion, the present study clarified that SVN influences the prognosis of patients with decompensated cirrhosis after portosystemic shunt occlusion using endovascular treatment. SVN in patients with viral hepatitis appears prerequisite to maintaining recovered liver function by shunt occlusion and to improving prognosis. Combination therapy with shunt occlusion and antiviral treatment should thus be considered as a first-line treatment for decompensated cirrhotic patients with viral hepatitis and large portosystemic shunt growth.

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