Indian J Gastroenterol (September–October 2017) 36(5):411–419
DOI 10.1007/s12664-017-0787-8

ORIGINAL ARTICLE

Shunt occlusion for portosystemic shunt syndrome related refractory hepatic encephalopathy—A single-center experience in 21 patients from Kerala

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Received: 30 July 2017 / Accepted: 8 September 2017 / Published online: 10 November 2017

Abstract

Introduction Large spontaneous portosystemic shunts (SPSS) are seen in a subset of patients with liver disease and medically refractory recurrent/persistent hepatic encephalopathy (MRHE). Shunt occlusion has been shown to improve clinical outcomes.

Methods We retrospectively analyzed patient characteristics, SPSS attributes, procedural features, baseline clinical and investigational parameters, neurological outcomes, adverse effects (procedure and portal hypertension related), and risk factors predicting outcomes in liver disease patients undergoing shunt occlusion procedure for MRHE.

Results Between October 2016 and July 2017, 21 patients (Child-Pugh score, CTP 6 to 13) with mean model of end-stage liver disease (MELD) and MELD-sodium scores 15.7 and 19.3 respectively with MRHE [3-cirrhotic Parkinsonism (CP)] were diagnosed to have single or multiple large SPSSs. A total of 29 shunts were occluded (1 surgical, 20 non-surgical). Recurrent and persistent HE and CP markedly improved in the short (n=20, 1 to 3 months), intermediate (n=12, 3 to 6 months), and long (n=7, 6 to 9 months) follow up. None had spontaneous or persistent HE at a median follow up 105 (30 to 329) days (p<0.05). Motor, speech, sleep abnormalities, daily activities of living, and liver disease severity scores improved significantly on follow up. Baseline arterial ammonia showed a statistically significant reduction in all time periods of follow up after shunt occlusion (p<0.05). CTP >11 predicted mortality post shunt occlusion (p=0.04). Embolization of large SPSS in liver disease patients with MRHE and modestly preserved liver function is safe and efficacious and associated with improved quality of life and can function as a bridge to liver transplantation in accurately selected patients.

Keywords Balloon-occluded retrograde transvenous occlusion · Coil-assisted retrograde transvenous occlusion · Cirrhosis · Cyanoacrylate glue · Hepatic encephalopathy · Plug-assisted retrograde transvenous occlusion · Portal hypertension · Portosystemic shunt syndrome

Introduction

Hepatic encephalopathy (HE) can be broadly classified into two forms, one type related to hepatic (synthetic and metabolic) failure and the other related to portosystemic shunts that can be spontaneous or iatrogenic such as surgical or transjugular intrahepatic portosystemic shunt (TIPS). Large spontaneous portosystemic shunts (SPS) related recurrent or persistent HE is seen in 46% to 71% of cirrhosis patients [1]. The latter can also lead to a condition known as hepatic or cirrhotic Parkinsonism. In these patients, the HE is medically refractory leading to poor quality of life and heavy financial burden with frequent hospitalization and home-based medical care [2]. Cirrhosis patients with SPS have relatively preserved liver function and lower model for end-stage liver disease (MELD) scores and are not ideal candidates for liver

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12664-017-0787-8) contains supplementary material, which is available to authorized users.

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transplantation. The term "portosystemic shunt syndrome" (PSS) was coined by Kumamoto et al. in-cirrhosis patients with SPS and describes the gradual worsening of liver function (increasing Child-Pugh scores) over 5 years, in comparison to cirrhotics without or obliterated large SPS [3]. Further elaboration of this syndrome was made by Saad et al. In the Saad classification, three stages were described. In the early stage (A), the patient is asymptomatic with well-preserved hepatic function and large SPS. In the late stage (B), the patient is symptomatic with recurrent/persistent HE and fairly-preserved hepatic function. In the terminal/end stage (C), HE related to both shunt and declining synthetic function, liver atrophy, thrombosis of the portal vein (due to a larger fraction of shunted blood), ascites, and jaundice is seen. Thrombocytopenia (seen in >90%) and indirect hyperbilirubinemia (due to shunt hemolysis, 10% post TIPS) are noticeable events in PSS [4, 5]. Sakurabayashi and colleagues initially showed that embolization of large PSS in cirrhotics decreased HE, lowered ammonia, and improved quality of life [6]. Further case reports, hospital series, and a multicenter effort proved the same. Studies from India are only a couple, single-center-based small patient cohort mostly from the North. We present the largest single-center study of large PSS occlusion in liver disease patients with refractory HE, from a tertiary care hospital based in Kerala, in South India.

Methods

This retrospective study was conducted at PVS Memorial Hospital and initiated after approval of the Medical Services Hospital Review Board. Patients were classified based on the etiology, time course, and severity of their HE by updated joint American Association for the Study of Liver Diseases–European Association for the Study of the Liver guidelines [7]. Inclusion criteria for the study were patients with liver disease and recurrent or persistent hepatic encephalopathy (grade ≥2) and documented large portosystemic shunts and no response to medical management. SPSSs were identified by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Depending on the anatomy of the predominant SPSS and preference of the interventional radiologist, the approach and type of intervention was determined. Baseline data including age, sex, etiology of cirrhosis, shunt type and size, procedural approach, and methods of embolization—coil-assisted retrograde transvenous occlusion (CARTO), plug-assisted retrograde transvenous occlusion (PARTO), balloon-occluded retrograde transvenous occlusion (BRTO) with or without cyanoacrylate glue embolization, or a combination of these were analyzed. Evaluation of patients was done, 1 to 3 months (short-term), 3 to 6 months (intermediate term), and 6 to 9 months (long-term) post procedure. Days of hospitalization, new or worsening sequela of portal hypertension post procedure, Child-Pugh-Score (CTP), MELD and MELD-sodium (MELD-Na) score, ammonia level, improvement in clinical grades of HE and neurological symptoms (as per UPDRS), quality of life score (Schwab and England Activities of Daily Living Scale), and mortality post shunt occlusion were studied. Safety was assessed by evaluating immediate post procedure complications and in the long-term by monitoring portal hypertensive complications or death. A complete list of definitions is given in Supplementary Document 1.

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software (Ostend, Belgium). Data are given as mean and standard deviation or as median and range between brackets as applicable. The Fischer's exact or chi-square test was used for evaluation of categorical data. Correlation analyses to measure the strength of the relationship between two non-parametric measures were done using Kendall's tau rank correlation coefficient. The Wilcoxon rank test was used for pairwise comparison between baseline and post interventional data. The discrimination ability of a variable to predict mortality was evaluated using the area under a receiver operating characteristic (ROC) curve. The Youden index was used to capture the best cut-off point. $P<0.05$ was considered statistically significant.

Results

Patient characteristics and related outcomes

Between October 2016 and July 2017, a total of 1728 liver disease patients were admitted to the intensive unit, of which 1008 (58.3%) had admission related to HE. One hundred and eight patients (10.7%) were admitted due to recurrence of HE and large PSS were found in 36 (33.3%). Thirteen patients (n=36) had medical control of HE after optimization of ammonia lowering measures, and two patients underwent shunt embolization for HE and associated gastric variceal bleeding. Twenty-one patients (n=1008, 2.08%) underwent shunt occlusion for medically refractory HE (Fig. 1). Seventeen (n=21, 81%) were male and mean age was 56.6±10.6 years. All were cirrhotics, except a 24-year-old woman with congenital hepatic fibrosis (CHF) and recanalized paraumbilical vein with severe sleep reversal, poor concentration in college, and thrombosis of intrahepatic portal vein radicles. The etiology of cirrhosis was nonalcoholic steatohepatitis in 13 (61.9%) and alcohol in 6 (28.6%) patients. Diabetes mellitus was seen in 57.1% (n=12), hypertension in 28.6% (n=6), and obesity in 52.4% (n=11). Two patients died (9.5%), one during the procedure (due to hemoperitoneum) and another (due to

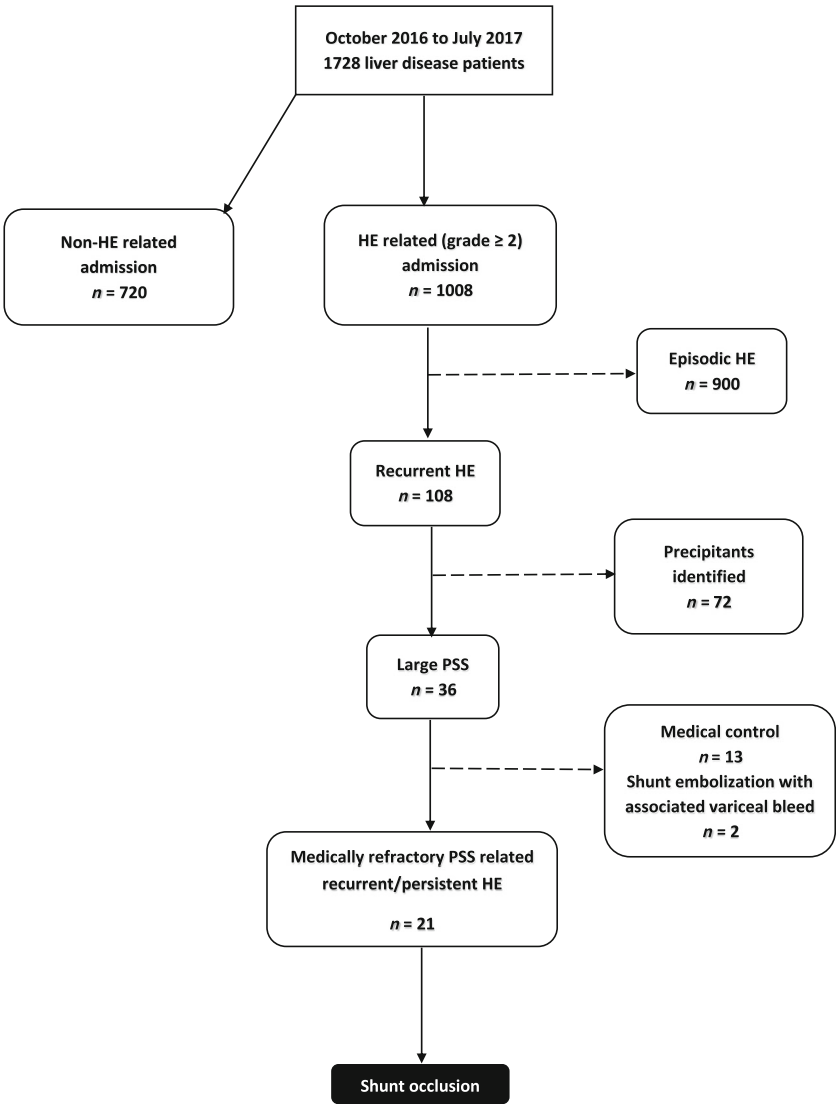


Fig. 1 Consort diagram of patients enrolled into the study

complications of portal hypertension) at 206 days of follow up. The median duration of hospital stay (*n*=20) was 2 (1–18) days. The median duration of follow up was 105 (minimum–maximum, 30–329) days (*n*=20). All patients completed short-term, 12 patients intermediate, and 7 patients long-term follow up. Age, sex, and presence of comorbidities did not affect the outcome.

Shunt characteristics and procedures

A total of 31 shunts were identified in 21 patients of which 29 shunts were occluded. The approach (*n*=21) was transjugular in 15 (71.4%), transhepatic in 4 (19%), transfemoral in one (4.8%), and by laparoscopic surgery in 1 (4.8%). Lienorenal shunt (LRS) was the commonest, seen in 17 (54.8%), followed by mesocaval shunt (MCS) in 7 (22.6%). Others included left gastric vein and short gastric vein to gastric varices, left coronary vein to azygous vein, leinocaval, mesoiliac shunt, and recanalized paraumbilical vein (Fig. 2). Multiple shunts (≥2) were seen in seven (33.3%) patients. The median shunt size was 13.3 mm (6–42). CARTO or PARTO were done in six (28.6%) patients each; CARTO+BRTO in one, CARTO+cyanoacrylate glue in three, CARTO and PARTO in three, and CARTO+ PARTO+BRTO in one patient (Fig. 3). Percutaneous approach for shunt occlusion in a patient with CHF and recanalized paraumbilical vein failed due to intrahepatic portal radicle thrombosis and hence, a laparoscopic shunt occlusion was performed. Only one patient underwent a repeat occlusion, 32 days after the initial procedure. The overall technical success rate was 95.2%.

Clinical and investigational characteristics and related outcomes

The important baseline and follow up clinical and investigational characteristics of the study cohort are shown in Table 1.

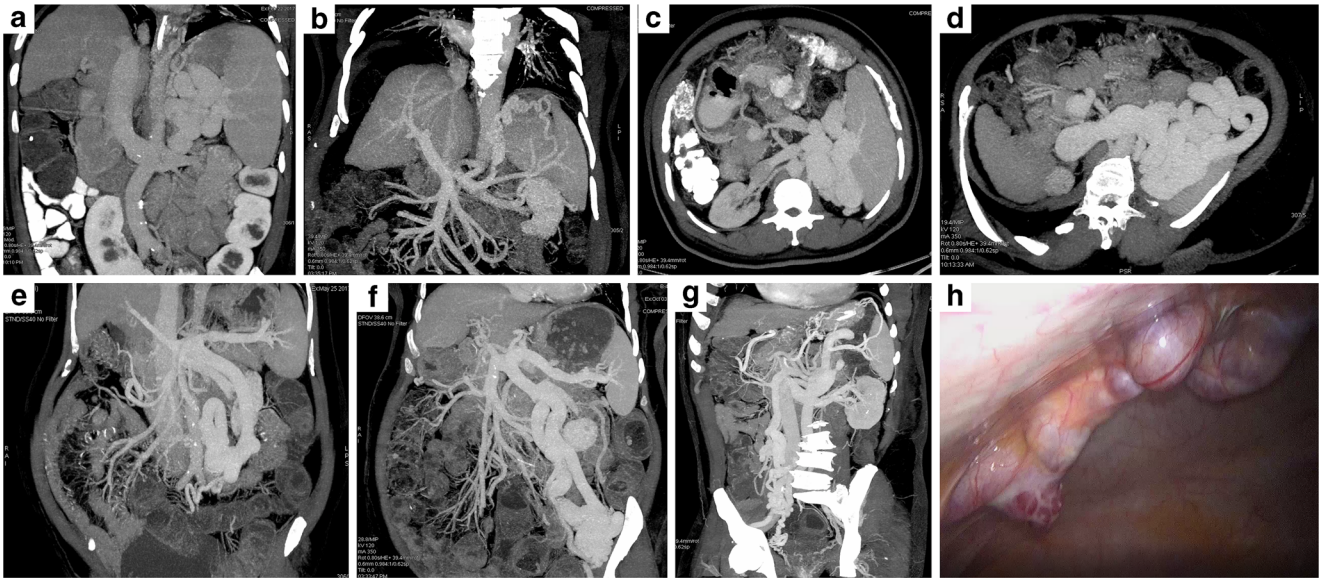


Fig. 2 Computed tomography portography showing large tortuous lienorenal shunt (**a**); left gastric vein to short gastric vein shunt (**b**); double lienorenal shunt (**c**); lienorenal and mesocaval shunt (**d**); large tortuous mesocaval shunt (**e**); serpiginous mesocaval shunt with pelvic extension (**f**); triple shunts including lienorenal, mesocaval, and mesoiliac shunt (**g**); and laparoscopic image of tortuous recanalized paraumbilical vein

Hepatic encephalopathy (Fig. 4) At baseline, recurrent HE was seen in 13 (61.9%), persistent in 8 (38.1%), and hepatic Parkinsonism in 7 (33.3%) patients. The WHC grade 2 HE was seen in 14 (66.7%) and grade 3 and 4 in (14.3%) patients before the procedure. Significant reduction in HE from baseline was seen post shunt occlusion. Post procedure, on short-term follow up (n=20), HE was absent in 75% (n=15, p<0.0001). Of the patients who had HE, grade 3 and 4 were seen in none. In the intermediate (n=12) and long-term (n=7), HE was absent in nine (75%, p=0.001) and five (71.4%,

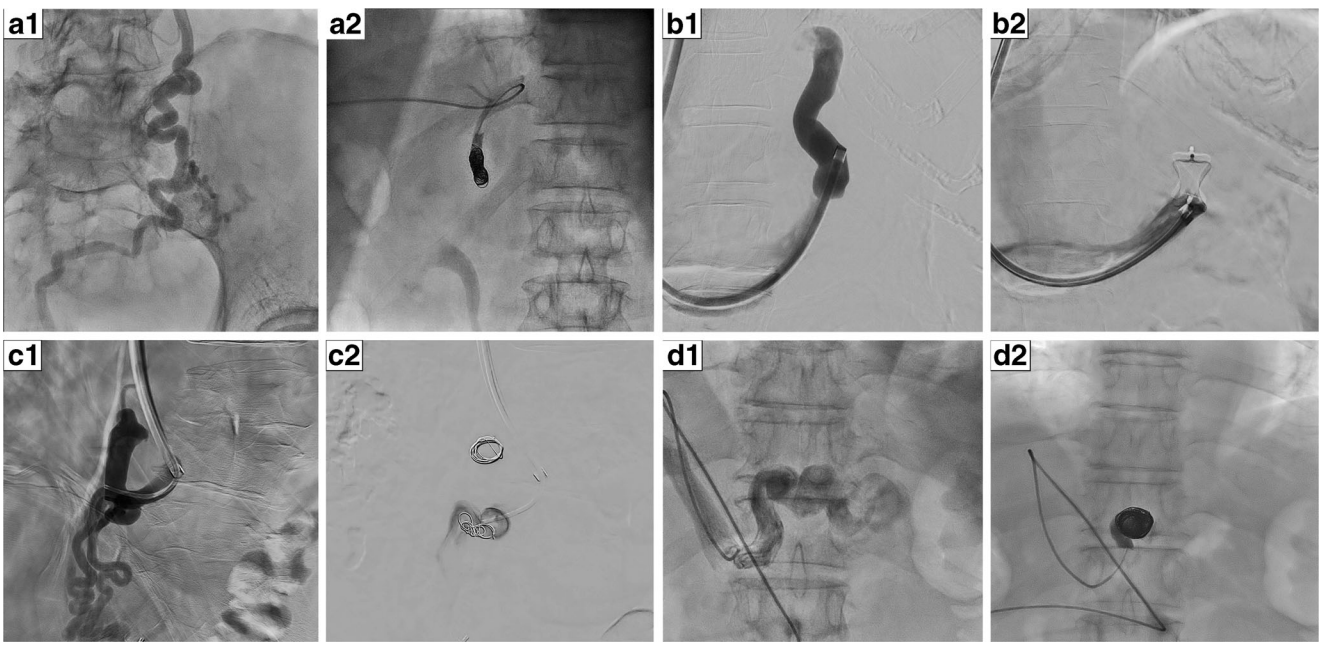


Fig. 3 Fluoroscopy and digital subtraction images of shunt occlusion procedures. Transhepatic antegrade coil assisted occlusion of patent tortuous umbilical vein into internal iliac veins (A1 and A2); Amplatzer™ plug-assisted occlusion of large lienorenal shunt (B1 and B2); coil, Amplatzer™ plug and balloon retrograde transvenous occlusion with cyanoacrylate glue injection assisted shunt occlusion of large lienorenal, mesocaval, and mesoiliac shunts (C1 and C2); transhepatic antegrade coiling and cyanoacrylate glue injection of tortuous left gastric vein to azygous vein collaterals (D1 and D2)

Table 1 Baseline and follow up parameters of patients undergoing portosystemic shunt occlusion

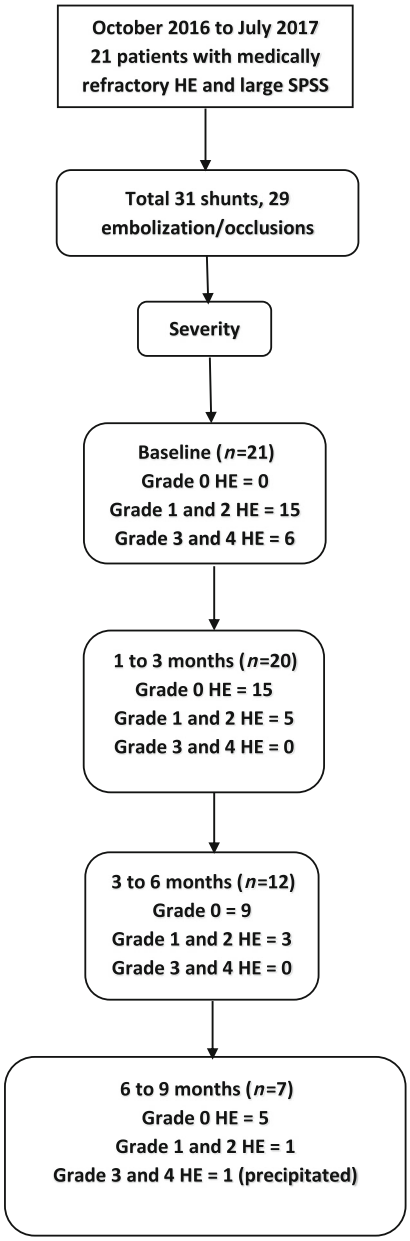
	N	Mean	SD	Median	Minimum	Maximum
Age	21	56.6	10.6	56	24	74
Hemoglobin at baseline (Hb)	21	11.6	1.67	11.5	8.76	16.2
Total leukocyte count at baseline	21	5.2	1.64	5.3	2.2	8.9
Platelet count at baseline	21	0.78	0.25	0.8	0.42	1.31
Platelet count at 1 to 3 months	20	0.99	0.48	0.92	0.28	2.40
Platelet count at 3 to 6 months	12	0.89	0.18	0.93	0.48	1.10
Platelet count at 6 to 9 months	7	0.89	0.23	0.95	0.55	1.20
Serum sodium at baseline	21	133.3	3.53	133.0	127.0	140.0
Serum sodium at 1 to 3 months	20	134.1	3.83	135.0	122.0	140.0
Serum sodium at 3 to 6 months	12	132.2	3.99	133.0	122.0	136.0
Serum sodium at 6 to 9 months	7	131.1	3.62	132.0	127.0	137.0
Serum creatinine at baseline	21	0.94	0.26	1.0	0.5	1.5
Serum creatinine at 1 to 3 months	20	0.96	0.21	0.95	0.6	1.5
Serum creatinine at 3 to 6 months	12	0.96	0.29	0.95	0.5	1.4
Serum creatinine at 6 to 9 months	7	1.1	0.5	0.9	0.6	1.9
Total bilirubin at baseline	21	3.38	2.76	3.1	0.7	14.5
Total bilirubin at 1 to 3 months	20	2.50	1	2.3	0.7	4.800
Total bilirubin at 3 to 6 months	12	2.9	1.6	2.3	0.8	5.9
Total bilirubin at 6 to 9 months	7	4.4	6.3	1.6	1.5	18.7
Prothrombin time at baseline	21	16.5	5.3	16.1	0.2	27.4
Prothrombin time at 1 to 3 months	20	16.5	3.1	15.9	12.3	25.2
Prothrombin time at 3 to 6 months	12	16.6	2.76	16.8	12.7	20.8
Prothrombin time at 6 to 9 months	7	18.1	5.8	19.1	12.0	28.9
INR at baseline	21	2.1	2.6	1.5	1.08	13.3
INR at 1 to 3 months	20	1.41	0.3	1.35	1.04	2.12
INR at 3 to 6 months	12	1.41	0.23	1.41	1.08	1.82
INR at 6 to 9 months	7	1.6	0.51	1.62	1.0	2.47
Serum albumin at baseline	21	2.8	0.69	2.9	1.13	4.4
Serum albumin at 1 to 3 months	20	3.01	0.48	3.05	2.1	4.2
Serum albumin at 3 to 6 months	12	2.95	0.39	3.1	2.1	3.5
Serum albumin at 6 to 9 months	7	2.98	0.53	3.2	2.1	3.5
CTP score at baseline	21	9.66	1.98	10.0	6.0	13.0
CTP score at 1 to 3 months	20	8.25	1.91	8.0	5.0	11.0
CTP score at 3 to 6 months	12	8.25	2.13	8.0	6.0	12.0
CTP score at 6 to 9 months	7	8.57	3.55	7.0	6.0	15.0
MELD score at baseline	21	15.7	4.18	14.0	10.0	26.0
MELD score at 1 to 3 months	20	13.8	3.38	13.0	9.0	20.0
MELD score at 3 to 6 months	12	14.5	3.60	13.5	9.0	20.0
MELD score at 6 to 9 months	7	16.2	9.03	14.0	8.0	34.0
MELD-Na score at baseline	21	19.3	4.43	19.0	12.0	28.0
MELD-Na score at 1 to 3 months	20	17.4	3.83	17.0	11.0	27.0
MELD-Na score at 3 to 6 months	12	18.9	4.64	17.5	12.0	27.0
MELD-Na score at 6 to 9 months	7	21.1	8.45	19.0	12.0	36.0
Ammonia at baseline	21	233.8	84.7	209.0	134.0	456.0
Ammonia at 1 to 3 months	20	104.6	34.2	105.0	32.0	178.0
Ammonia at 3 to 6 months	12	88.3	15.1	93.0	56.0	108.0
Ammonia at 6 to 9 months	7	73.7	20.4	76.0	49.0	106.0

INR International normalized ratio, *CTP* Child-Turcotte-Pugh score, *MELD* model for end-stage liver disease, *MELD-Na* MELD sodium, *Hb in g/L* total leukocyte count in $\times 10^3$ /L, platelet count in $\times 10^5$ /L, sodium in mmol/L, creatinine in mg/dL, albumin in g/dL, and ammonia in mcg/dL

p=0.03) patients, respectively. None of the patients developed spontaneous HE at the end of follow up.

Hepatic parkinsonism Of the seven patients, three had Hoehn and Yahr severity grade 5, and another three patients (14.3%) had severity grades between 3 and 4. All patients survived on median follow up of 193 (42–329) days. Post procedure, the Hoehn and Yahr severity grade improved significantly (p=0.016) to ≤2.5 in five (71.4%) patients and Parkinsonian features fully abated in two (28.5%).

Laboratory parameters The mean platelet count ($\times 10^5$/L) at baseline was 0.78±0.25, with significant improvement on short-term follow up (0.99±0.48, p=0.013). However, the improvement plateaued at intermediate and long-term follow up (0.89±0.18 and 0.89±0.23, p=0.13 and 0.57, respectively). Serum sodium, creatinine, prothrombin time, international normalized ratio, and serum albumin did not show statistically significant changes on short, intermediate, and long-term follow up post shunt occlusion. None of the blood parameters at baseline predicted mortality after shunt occlusion. Baseline



HE hepatic encephalopathy, *SPSS* spontaneous portosystemic shunt

Fig. 4 Severity of hepatic encephalopathy grades before and after shunt occlusion

arterial ammonia level (n=21, 233.8±84.7 mcg/dL) showed statistically significant reduction in the short-term (n=20, 104.6±34.2, p<0.001), intermediate (n=12, 88.3±15.1, p=0.0005), and long-term (n=7, 73.7±20.4, p=0.015) follow up after shunt occlusion in lieu with decreasing HE grades. Higher levels of ammonia did not significantly predict mortality in treated patients.

Liver disease severity The median CTP score of 10 (6–13) at baseline (n=21) improved to 8 (5–11), 8 (6–12), and 7 (6–15) in the short (n=20), intermediate (n=12), and long-term (n=7) follow up periods after shunt occlusion. The MELD and MELD-Na scores showed significant but transient improvement from baseline (n=21, 15.7±4.18/19.3±4.43) at short-term follow up (n=20, 13.8±3.38/17.4±3.83, both p=0.025). There was mild, but insignificant rise in MELD and MELD Na scores in the intermediate and long-term after shunt occlusion. Only baseline CTP score correlated (Kendall tau rank correlation, p=0.006) with death after shunt occlusion [p=0.04, odds ratio 18 (1.02–317.5); cutoff >11; p<0.001 area under the curve 0.974, sensitivity 100, specificity 89.47; Supplementary Fig. 1]. Baseline MELD and MELD-Na scores did not significantly affect outcomes after shunt occlusion.

Neurological outcomes Unified Parkinson's disease rating scale (UPDRS) for walking—15 patients (71.4%) had difficulties in walking before the procedure with 5 (33.3%) patients having severity grade >2. Post shunt occlusion, on follow up, among survivors (n=19), this improved to four (21%) having difficulties with walking and only one patient (5.2%) with severity grade >2 (p=0.002). UPDRS for Falls–17 (80.9%) patients had some degree of frequent falls at baseline with 12 (57.1%) patients having severity grade ≥2. Post procedure, on last follow up, among survivors, only four (n=19, 21.1%) patients had some degree of falls and only one (5.2%) with grade 2 severity (p=0.0001). UPDRS for speech—at baseline, 16 patients (76.2%) had some degree of speech abnormalities with seven (33.3%) having severity grades >2. After procedure, on last follow up among survivors, only six (31.5%) had some form of speech abnormality, with none having severity grade >2 (p=0.0001). Three patients with WHC–HE grade 4 at baseline were evaluated for neurological improvement using GCS in the early short-term (3rd and 7th day of admission). The median GCS was 8 at baseline in all patients, improving to 11 (9–11) and 14 (13–14) on 3rd and 7th-day post shunt occlusion.

At baseline (n=21), the median sleep disturbance severity score on the Epworth sleepiness scale was 14 (10–24), improving to 8 (6–15) on last follow up among survivors (n=19, p<0.0001).

Activities of daily living The means of Schwab and England Activities of Daily Living Scale [minimum 0% (vegetative, bedridden)—maximum 100% (completely independent)] at baseline (n=21) was 0.671±0.32 post procedure (n=19) significant improvement (p=0.0001) in daily activities of living (0.93±0.13) and hence quality of life was noted.

Adverse effects

Procedure-related immediate complications were as follows. Two patients (n=21, 9.52%) developed adverse effects directly related to the procedure. One patient developed grade 1 Common Terminology Criteria for Adverse Events (CTCAE) event (local site hematoma) that was managed

conservatively, while the other developed CTCAE grade 5 (hemoperitoneum and multiple organ failures) events during the procedure, leading to death within 24 h.

Long-term complications related to portal hypertension

At baseline (*n*=21), 23.8% (*n*=5) had no esophageal or gastric varices, 52.4% (*n*=11) had grade 1, and 23.8% (*n*=5) had grade 2 esophageal varices. Post procedure, on last follow up (*n*=20), 25% (*n*=5) had no varices, 45% (*n*=9) had grade 1, and 30% (*n*=6) had grade 2 esophageal varices. This increase in variceal grade was not statistically significant, but one patient (*n*=20, 4.8%) developed non-fatal variceal bleeding, controlled with band ligation 122 days post shunt occlusion.

Sixteen patients (76.2%) did not have ascites at baseline while 19% (*n*=4) and 4.8% (*n*=1) had grade 1 and 2 ascites, respectively. On short-term follow up, (*n*=20), two patients (10%) developed new onset ascites (grade 2), while in the intermediate term (*n*=12), one patient developed new onset grade 2 ascites and another had worsening of ascites from the short-term (grade 3). On long-term follow up (*n*=7), the patient in the intermediate term, who had grade 2 ascites had worsening of ascites (to grade 3) and the patient with grade 3 ascites in the intermediate term had persistence of grade 3 diuretic intractable ascites, later developing mild portopulmonary hypertension (POPH) and has been listed for liver transplant (LTx). The changes in grades of ascites in the three follow up periods did not reach statistical significance. One patient developed spontaneous bacterial peritonitis (SBP) within 100 days after shunt occlusion while three patients (two new onsets) developed SBP, after 100 days of the procedure, one of them (the patient mentioned above with intractable ascites and POPH) who is currently listed for LTx.

Discussion

We present the largest single-center study on PSS embolization in patients with refractory HE in the current literature. Shunt embolization for refractory HE forms an important aspect in improving the quality of life, curbing financial burden associated with repeated hospital admissions, and could help prevent progression of portosystemic shunt syndrome in patients with Saad Type B (late stage) disease. Hepatic encephalopathy has a poor prognosis with a 1-year and 3-year survival rates after the initial episode of 42% and 23%, respectively. Sakurabayashi and co-workers in 1997 showed that transvenous bland coil embolization of large SPSS was safe and efficacious in patients with recurrent HE with HE recurrence rate of 28.6% at 6 months follow up [6]. Most of these studies were single-center based, except one, done by Laleman et al., which was a multicenter study with the largest number of patients (*n*=37) and the longest follow up [mean 697 days] [8]. Several authors have reported on the safety and efficacy of transcatheter embolization of PSS in patients with

Table 2 The safety and efficacy of transcatheter embolization of portosystemic shunt syndrome in patients with refractory hepatic encephalopathy

Year Author [Ref]	Patients (study)	Procedure	Technical success rate (%)	Follow up period	Survival (%)	Spontaneous HE recurrence (%)
1997 Sakurabayashi et al. [6]	7 (single center)	CARTO BRTO	100	3–6 months	–	29
2000 Chikamori et al. [9]	5 (single center)	BRTO	100	17–74 months	80	0
2007 Zidi et al. [16]	7 (single center)	CARTO BRTO	100	8 days to 6 years	42	100
2012 Mukund et al. [14]	7 (single center)	BRTO	86	Mean 4 months	–	0
2013 Laleman et al. [8]	37 (multicenter)	CARTO PARTO Matrix	100	Mean 697 days	–	36
2014 Naeshiro et al. [10]	14 (single center)	BRTO	92.9	Median 27 months	45	7
2014 An et al. [11]	17 (single center)	CARTO PARTO	100	Median 19 months	65	40
2016 Lynn et al. [12]	20 (single center)	CARTO PARTO	100	Median 12 months	–	33
2017 Current study	21 (single center)	CARTO PARTO SSO	95.2	1 to 9 months	90.4	0

Modified from: Takenaga S and Aizawa Y. Interventional Radiol. 2017; 2: 51–58

CARTO coil assisted retrograde transvenous occlusion, *BRTO* balloon occluded retrograde transvenous occlusion, *PARTO* Plug [Amplatzer™ (St Jude Medical, Minnesota, USA)]-assisted retrograde transvenous occlusion, *SSO* surgical shunt occlusion, *PHT* portal hypertension

refractory HE [9–12] (Table 2). The study by Mukund et al., from Delhi, was the first study from India to shed light on safety and efficacy of shunt embolization procedure in seven patients with a mean follow up of 4 months [14]. Recently, Choudhary et al., also from Delhi, reported on shunt embolization for recurrent HE in five patients [15]. Patil et al. performed a systematic review and meta-analysis of studies involving occlusion/embolization of SPSS for medically refractory HE but excluded patients without cirrhosis, surgical shunt occlusions, and follow up less than 6 months. They found that a total of six studies fulfilled inclusion criteria with most patients with Child-Pugh A disease and MELD score <15. Lienorenal shunts were predominant, and 90% of the procedures performed were technically successful and did not result in any procedure-related complications. Improvement in HE was seen in a pooled percentage of 76.2%. De novo variceal disease was seen in 6%, and new onset or worsening ascites was seen in 14%. The authors concluded that PSS occlusion or embolization was safe with minimal complications in patients with adequate functional liver reserve [13].

All these studies, when taken together, showed very few major adverse effects. In the study by Laleman, hemorrhagic shock was seen in one patient, and severe sepsis and peritoneal hemorrhage were seen in two patients in the study by Zidi et al. [16]. Worsening or new onset ascites and variceal disease was seen in all the studies except Mukund et al. (possibly due to shorter duration of follow up) but were clinically insignificant. In the current study, we describe the clinical outcomes of post shunt embolization in 21 patients with liver disease and recurrent HE. We also included patients with severe persistent HE and presence of cirrhotic parkinsonism in the presence of large SPSS. Kang et al. showed that cirrhotic patients had a higher risk of developing Parkinsonism. They, however, did not assess the presence of SPSS in their group of patients [17]. da Rocha et al. showed that Parkinsonism associated with large SPSS could be reversed with shunt embolization [18]. In our patients, in lieu with other studies, we have shown that occlusion of large shunts in patients with liver disease and recurrent/persistent HE ameliorated severity and recurrence of spontaneous HE. We also showed the added benefits on improved motor, speech, and sleep abnormalities; amelioration of Parkinsonian features in patients with persistent HE, and improvement in quality of life and activities of daily living. This was true with regards to progressive and significant decrement in arterial ammonia levels in our patients on follow up. The impact of shunt occlusion procedures on the natural history of the liver disease has been variable in most studies. Laleman et al. had shown that deno novo development of varices and ascites and worsening of portal hypertension in some of their patients, while An et al. showed that residual liver function improved with shunt occlusion (and prevention of progression to Saad Type C or end-stage PSS) with restoration of portal flow (in the absence of portal vein thrombosis) and amelioration of HE. In our study, we found that portal hypertensive complications—both new and worsening pre-existing were transient and did not significantly correlate with outcomes. In our patients, CTP and MELD score improved significantly on short-term, plateauing in the intermediate and long-term follow up after shunt occlusion. The study by Zidi et al. [16] is worth discussing in this regard. In their cohort of patients, even though technical success was achieved in all patients, the clinical results were poor as long-term improvement was obtained in only one patient and HE recurrence was seen in all. Three patients died within 3 months after the procedure from complication of end-stage liver disease. They concluded that the optimal management of patients with cirrhosis and chronic refractory HE is liver transplantation. They also found new PSS development post embolization probably due to inadequate collateral embolization of smaller shunts, that later hypertrophied. In our patients, we obliterated all the significant shunts (≥8 mm) and did not find new PSS or recurrent HE development on follow up. The four patients who died in Zidi et al. study had a CTP score of 10, 10, 9, and 9 without including HE. In our study, we found that inclusive of HE scores, patients with CTP >11 had very high mortality. Patients with CTP score >11 and recurrent/persistent HE was unlikely to benefit from shunt occlusion. In the others, shunt occlusion could improve quality of life and prevent further hospitalizations for HE. The current study specifically defines the poor liver reserve, (evidence by CTP score, that also encompass portal hypertension components) suggested by other authors that is associated with mortality. MELD or MELD-Na scores were not significantly associated with outcomes, probably due to the absence of portal hypertension components in MELD model. Laleman et al. also found that MELD >11 was a significant risk factor for the development of recurrence of HE in the long-term. We could not find such correlation in our patients, mostly because our follow up was shorter in comparison to the Laleman study (mean 127 vs. 697 days).

Our study is unique in many ways. This is the largest single-center series on shunt occlusion in severe recurrent/persistent HE from India. We also shed light on the importance of looking for large SPSS in patients with cirrhosis and persistent HE and atypical parkinsonism features. Embolization of such shunts in the presence of good liver function proved highly beneficial in improving activities of daily living and quality of life in our patients. We included one patient with HE in the absence of cirrhosis who underwent surgical shunt occlusion due to technical difficulty in accessing the portal system percutaneously. We included this patient since she fulfilled the required study criteria and the etiology of the liver disease did not change the primary assessment factor (improvement in HE, neurological status). This patient also showed improved neuropsychological symptoms. As described by previous authors, a recanalized paraumbilical vein must be considered a cause of PSS in the absence of other factors. We present the largest single-center

experience in shunt occlusion for PSS in patients with refractory HE. Our results are in lieu with previous studies, but also shed light on novel baseline prognostic indices that help guide appropriate patient selection for shunt occlusion procedures. Patients with liver disease and medically refractory spontaneous recurrent or persistent HE in the presence or absence of cirrhotic parkinsonism and large SPSS can benefit from shunt embolization/occlusion, which is safe and efficacious in the short, intermediate, and long-term. In the presence of a good residual liver function, portosystemic shunt occlusion decreases severity and frequency of HE; improves motor, speech, and sleep abnormalities; and reverses hepatic parkinsonism features in patients with liver disease. Indeed, long-term benefits of shunt occlusion may be disappointing, but appropriately selected patients can benefit from this procedure as a bridge to liver transplantation. Patients with Child-Pugh score >11 do not benefit from shunt occlusion and must undergo evaluation and listing for liver transplantation at the outset.

Compliance with ethical standards

Conflict of interests CAP, LK, and PA declare that they have no conflict of interests.

Ethics statement All procedures performed in this study, with human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

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