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Outcomes of combination treatment with MARS and TIPS for hepatic veno-occlusive disease: a report of 12 cases

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Abstract

Background: In patients with acute liver injury caused by hepatic veno-occlusive disease (HVOD), molecular adsorbent recirculation system (MARS) may be used to improve liver function in conjunction with transjugular intrahepatic portosystemic shunt (TIPS) to reduce portal hypertension.

Methods: Twelve patients were admitted to our hospital following treatment for HVOD for 10 to 21 days at other hospitals. All patients were treated with a combination of MARS and TIPS, and they were evaluated clinically including liver function tests.

Results: After the initial treatment with MARS, liver function improved significantly in all patients. TIPS placement decreased the hepatic venous pressure gradient (HVPG) to 10.17 ± 2.26 mmHg from a pre-TIPS HVPG of 23.58 ± 9.43 mmHg. The outcomes of combination treatment with MARS and TIPS in 12 patients with HVOD were as follows: 1) improvement of various clinical and biological parameters leading to full recovery in 1 year in 6 patients; 2) full recovery following liver transplantation for acute liver failure in three patients; and 3) three patients died due to hepatic failure after TIPS placement.

Conclusion: The combination of MARS and TIPS creation is promising as a potential treatment for acute HVOD, and it showed an improvement in overall survival.

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Hepatic veno-occlusive disease, transjugular intrahepatic portosystemic shunt, molecular adsorbent recirculation system, hepatic venous pressure gradient, portal hypertension, liver failure

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Introduction

Hepatic veno-occlusive disease (HVOD) is characterized by the development of painful hepatomegaly, ascites, weight gain, and jaundice, and these patients have a high risk of mortality.[1] With improvements to medical science, an increasing number of causes of this disease have been found including chemical or radiation toxicity, bone marrow transplantation (BMT) in patients with leukemia,[2] liver transplantation,[3] and plant pyrrolizidine alkaloids.[4]

Currently, the main treatment is the combination of tissue plasminogen activator (t-PA) and heparin,[5] but the mortality rate of patients with severe HVOD is more than 98%.[6] To develop an effective therapy for patients with HVOD, we initiated combination therapy using the molecular adsorbent recirculation system (MARS) and transjugular intrahepatic portosystemic shunt (TIPS) creation. MARS and TIPS creation for HVOD have shown promising results, and therefore, this retrospective study was undertaken to evaluate the safety and efficacy of combination therapy with MARS and TIPS creation in 12 patients with severe HVOD.

Materials and methods

This study was approved by the Research Ethics Committee of Shandong Qianfoshan Hospital, The First Affiliated Hospital of Shandong First Medical University (approval no. 2017S052). Because of the retrospective nature of the study, the requirement for informed consent was waived.

Clinical information

Twelve patients were admitted to our hospital following treatment for HVOD for 10 to 21 days at other hospitals from January 2012 to June 2016.

Clinical diagnosis

All patients had a history of herbal medicine use for joint or bone pain 1 to 4 weeks before HVOD onset. Gynura segetum was used by eight patients, and mixed herbs of unknown ingredients were used by four patients. The patients presented with a severe loss of appetite, ascites, right upper abdominal pain, and tender hepatomegaly. The laboratory studies yielded elevated liver enzyme levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin [TBil]). No history of alcoholism, other drug abuse, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or hepatitis A, B, C, D, or E was observed in the patients. These patients' symptoms were consistent with the Baltimore Diagnostic Criteria,[7] and all the patients had no history of BMT.

Histological diagnosis

All patients underwent percutaneous liver biopsy using the coaxial technique. There were no complications. The liver biopsy needle was a standard type with co-axial

(SAG-18090C, TSK Laboratory, Limu, Japan). The patients were asked to hold their breath in complete expiration, and the needles were quickly advanced and withdrawn from the liver tissue. The liver biopsy specimens were fixed in 10% formalin for histopathologic examination. All histological specimens were examined by the same pathologist. Occlusion of terminal hepatic venules, sinusoidal congestion, centrizonal hemorrhagic necrosis, and sinusoidal fibrosis were found on the pathological section (Figure 1).

Image diagnosis

All of the patients had ascites, hepatomegaly, and a panther-stripe or low-echogenic area in the liver on ultrasound imaging. Liver ultrasound showed a dilated portal vein with slow flow in patients with HVOD. In eight patients, the hepatic veins were poorly visible on the liver ultrasound scan. The hepatic segment of the inferior vena cava was narrow, but the blood flow was unobstructed. Abdominal computerized tomography (CT) revealed multiple uneven low-density lesions in the liver, massive ascites, and indistinct hepatic veins. A multiplanar reconstruction (MPR) image showed localized concentric narrowing of the inferior vena cava at the level of the liver (Figure 2). None of the patients underwent hepatic or wedged hepatic venography before TIPS placement.

Medical care

Because there is no specific treatment modality for HVOD that could serve as a reference, the standard criteria were established based on reported cases, a small series analysis, and our team's experiences. All the patients had severe coagulation disorder, and some also had a hemorrhage in the digestive tract; thus, these patients could not receive t-PA. Our primary goals for treatment were to improve liver function and reduce portal hypertension. Ascites was treated with sodium restriction, human albumin, diuretics, and paracentesis. Severe coagulation disorder was treated with fresh frozen plasma. Reduced glutathione (Laboratorio Farmaceutico C.T.S.r.l., Sanremo, Italy),[8] magnesium isoglycyrrhizinate injection (CCTQ Pharma, Lianyungang, China), and ursodeoxycholic acid capsules (Losan Pharma GmbH, Neueburg, Germany)[9,10] were given as antioxidants and anti-apoptotic agents to

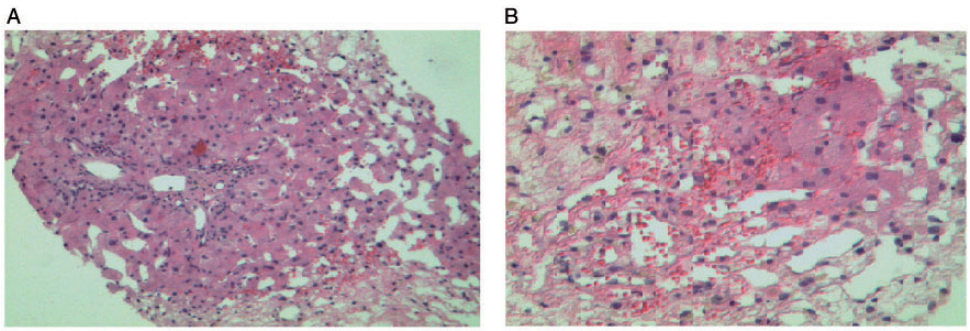

Figure 1. Pathological evaluation of the liver before treatment. (a) Pathological evaluation demonstrated that some regions of liver cells showed necrosis, fibrous tissue hyperplasia, and a small amount of iron-containing hemoglobin deposition, while hepatic sinusoids around the portal area showed obvious expansion and congestion. Hematoxylin–eosin staining, 200×. (b) Erythrocyte infiltration into the liver plate, some liver cell degeneration, and some liver cell regeneration are visible. Hematoxylin–eosin staining, 400×.

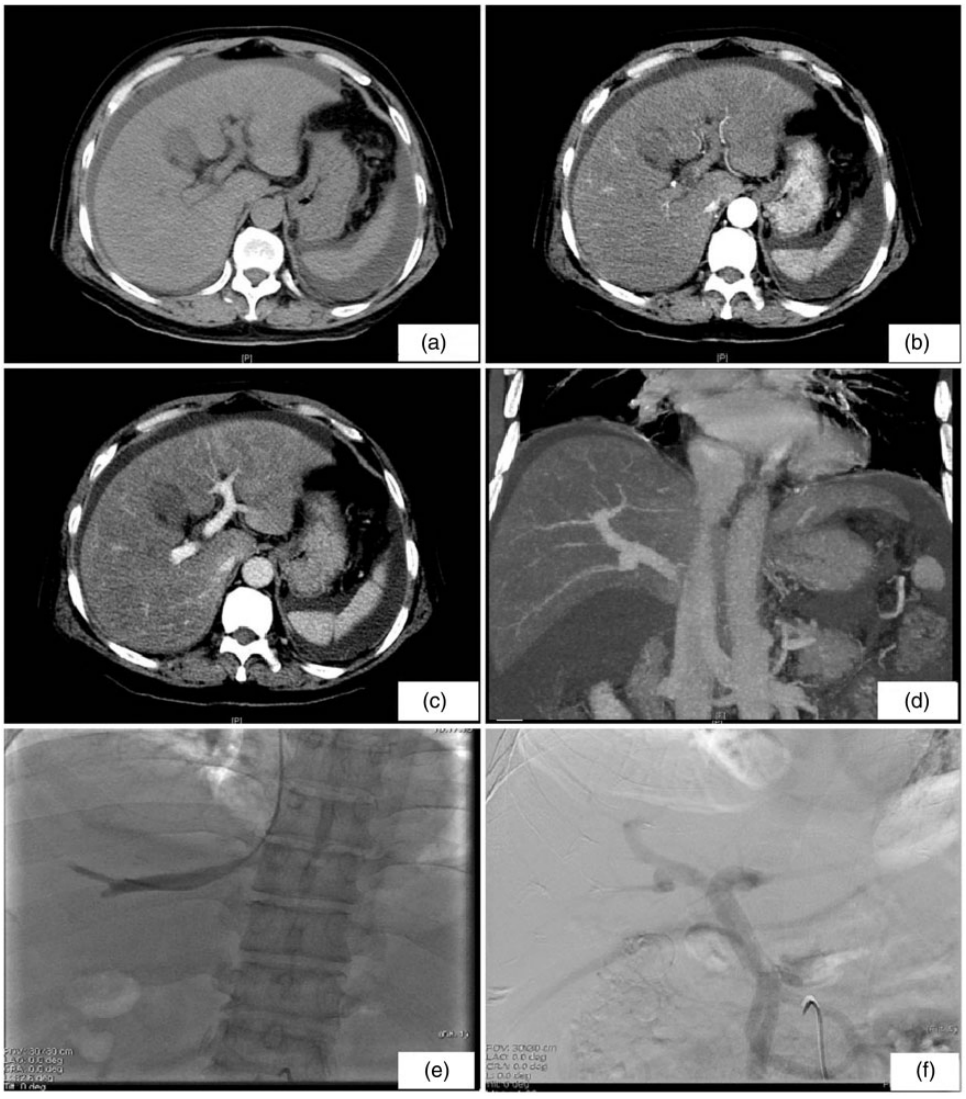

Figure 2. Abdominal computerized tomography and angiographic findings of the liver in patients with hepatic veno-occlusive disease. (a) Plain CT scan showed that the liver density in most patients was reduced, patchy or map-like low density areas were present, and ascites can be observed. (b) Arterial enhancement CT scan showed a transient irregular infusion enhancement region. (c) Portal venous enhancement CT scan showed a typical patchy, map-like enhanced area. (d) MPR image showed that the inferior vena cava was narrow, but there was no expansion at both ends. (e) Hepatophlebography showed that the hepatic vein was normal without any obstruction. (f) Indirect portography showed that the portal vein and superior mesenteric vein were normal without any obstruction.
MARS, molecular adsorbent recirculation system; TIPS, transjugular intrahepatic portosystemic shunt; CT, computed tomography; MPR, multiplanar reconstruction.

reduce injury to liver cells. Lactulose oral solution (Abbott Healthcare Products B.V, Weesp, The Netherlands) and *Clostridium butyricum* granules (Miyarisan Pharmaceutical Co., Ltd, Tokyo, Japan) were administered to avoid bacterial translocation. Esomeprazole sodium (Nexium, AstraZeneca, Sodertalje, Sweden) was used to treat upper gastrointestinal hemorrhage.

MARS support treatment

All of the patients were treated with MARS (GAMBRO, Lund, Sweden) to reduce ALT, AST, and TBil levels, improve liver function, and remove those albumin-bound toxins to maintain systemic homeostasis before TIPS creation. If hepatic encephalopathy (HE) and the patients' liver function did not improve significantly within 3 days after TIPS creation, the patients underwent MARS therapy. Although the coagulation function of those patients remained poor, heparin was still required to prevent thrombus formation in the filter during MARS therapy. Protamine was used to reverse the effects of heparin before the filtered blood was returned to the body to prevent severe bleeding.

TIPS process

All patients received MARS therapy for 3 days before the TIPS procedure. The technique for the TIPS procedure was as follows: 1) The patients fasted for 12 hours before the TIPS procedure. After placing the patient in the supine position, the right side of the neck and groin were prepped and draped in a sterile fashion. The puncture site was anesthetized with 5 mL of 2% lidocaine; 2) After percutaneous catheterization of the right internal jugular vein, the 10-Fr (40 cm) introducer from the RUPS-100 set (Cook Medical, Bloomington, IN, USA) and a 5-Fr selective catheter were advanced into the right hepatic vein to perform hepatic venography; 3) After percutaneous catheterization of the right common femoral artery, a 5-Fr sheath was placed into the femoral artery, and through the sheath, a 5-Fr selective catheter was advanced into the abdominal aorta and then placed into the superior mesenteric artery. The venous phase of the superior mesenteric angiogram visualized the portal vein and its right and left main branches for portal vein targeting from the hepatic vein during TIPS creation; 4) The right main portal vein was punctured from the right hepatic vein using a Rosch–Uchida needle. Once the needle entry into the portal vein was confirmed using an injection of contrast medium, a 0.035-inch stiff guide wire was advanced into the splenic vein and a 5-Fr pigtail catheter was then advanced over the guide wire into the splenic vein. After measuring the portal venous pressure, a splenoportogram was performed. A catheter with a marker was used to determine the length of the stent that was required to stent the hepatic parenchyma between the hepatic vein and the portal vein; and 5) After dilating the parenchymal tract using an angioplasty balloon catheter, the 10-French sheath was advanced into the portal vein. The polytetrafluoroethylene (PTFE)-covered stent (VIATORR TIPS Endoprosthesis, W.L. Gore & Associates, Inc., Flagstaff, AZ, USA) was deployed between the hepatic and the portal veins, and it was then dilated to 8 mm. After measuring the portal venous pressure, a completion portal venogram was obtained.

Statistical analysis

All of the data were analyzed using the Statistical Package for SPSS v18.0 (IBM Corp., Armonk, NY, USA). The data followed a normal distribution, and it was expressed as the mean $\pm$ standard deviation. The data were analyzed using a paired

t-test. A P value <0.05 was considered to be statistically significant.

Results

There were seven men and five women between the ages of 22 and 72 years (mean age, 42.4 years) who were enrolled into this study. The clinical and biological characteristics of the patients are summarized in Table 1.

In accordance with the Baltimore Diagnostic Criteria[7] (which includes the following: bilirubin $>34.2\,\mu mol/L$, hepatomegaly, ascites, and weight gain), all patients had life-threatening severe VOD after intake of Chinese herbal medicines containing pyrrolizidine alkaloids. All of the patients received MARS therapy before TIPS placement. After TIPS creation, two patients (patients 2 and 4) were treated with MARS once, one patient (patient 3) was treated twice, and three patients (patients 9, 11 and 12) were treated three times. After the first MARS treatment, the ALT decreased from $970.2 \pm 701.9\,IU/L$ to $576.9 \pm 329.2\,IU/L$ ($P < 0.01$), AST decreased from $1048.4 \pm 938.9\,IU/L$ to $672.8 \pm 546.8\,IU/L$ ($P < 0.01$), and TBil decreased from $192.4 \pm 136.6\,\mu mol/L$ to $152.0 \pm 110.2\,\mu mol/L$ ($P < 0.001$). These changes in liver function are summarized in Table 2.

TIPS was successfully performed without any TIPS procedure-related complications for all patients. The portal venous pressure decreased significantly from $29.75 \pm 10.09\,mmHg$ to $21.25 \pm 7.1\,mmHg$ following TIPS placement ($P < 0.001$), while the hepatic venous pressure gradient (HVPG) decreased from $23.58 \pm 9.43\,mmHg$ to $10.17 \pm 2.26\,mmHg$ ($P < 0.001$). The changes in hepatic venous pressure, portal vein pressure, and HVPG before and after TIPS are summarized in Table 3. All of the patients underwent liver function tests. Doppler sonography confirmed TIPS patency in all patients during the follow-up period. All the stents were unobstructed. The hepatic venous pressure after TIPS creation was lower than that before TIPS creation in patients 1, 2, 4, and 12. Generally, right atrial and hepatic venous pressure increased after

Table 1. Main clinical and biological characteristics of the 12 patients.

Patients	Sex	Age (years)	PT (s) (normal range 9.8–12.1 s)	PLT (10^9/L) (normal range, 125–350 10^9/L)	ALB (g/L) (normal range, 40–55 g/L)	ALT (U/L) (normal range, 7–40 U/L)	AST (IU/L) (normal range, 13–35 IU/L)	Bilirubin (μmol/L) (normal range, 5–24 μmol/L)
1	Male	39	15.9	189	31	451.2	311.7	165.3
2	Male	72	27.5	55	28	1451	1842.2	321.6
3	Female	45	16.9	75	27	789.4	732.4	467.5
4	Female	61	23.2	56	30	690.1	701.4	234.3
5	Male	22	16.2	203	33	355.3	298.4	56.7
6	Male	54	12.8	187	35	244.3	232.3	36.7
7	Female	26	15.4	112	28	980.5	873.1	167.7
8	Male	22	14.8	189	38	1896.6	2042.4	86.5
9	Female	40	17.3	77	25	544.3	432.8	90.5
10	Female	34	12.1	235	29	328.9	298.9	66.3
11	Male	30	22.5	99	23	2460.5	3250.5	345.6
12	Male	56	14.3	245	31	1450	1565.1	270.2

The table shows the clinical and biological characteristics of the 12 enrolled patients.
Laboratory tests were performed on the day after the patients were hospitalized.
PT, prothrombin time; PLT, platelets; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase.

Table 2. Liver function test results before and after combination treatment with MARS and TIPS.

	ALT (IU/L)					AST (IU/L)					TBil (μmol/L)				
Patients	Admission	Pre TIPS	Post TIPS 3d	Post TIPS 1w	Post TIPS 4w	Admission	Pre TIPS	Post TIPS 3d	Post TIPS 1w	Post TIPS 4w	Admission	Pre TIPS	Post TIPS 3d	Post TIPS 1w	Post TIPS 4w
1	451.2	327.5	410.1	242.5	46.7	311.7	278.6	301	220.5	45.4	165.3	102.4	132.1	89.5	23.6
2	1451	1132.5	2014.2	–	–	1842.2	1344.1	2022.5	–	–	321.6	262.8	416.2	–	–
3	789.4	325.7	466.3	321.4	689.2	732.4	563.1	662.3	442.5	790.2	467.5	367.4	378.5	301.2	345.2
4	690.1	675.8	789.9	–	–	701.4	640.2	885.3	–	–	234.3	201.5	346.3	–	–
5	355.3	256.2	201.4	78.5	32.1	298.4	205.5	145.6	77.6	23.5	56.7	53.2	79.6	66.4	14.5
6	244.3	186.5	178.5	89.3	41.4	232.3	180.4	167.5	77.5	34.6	36.7	33.5	44.6	33.3	15.6
7	980.5	490.2	560.5	340.4	88.4	873.1	422.4	432.5	226.7	67.7	167.7	105.6	112.4	102.4	33.2
8	1896.6	889.1	551.3	320.5	32.5	2042.4	920.6	650.1	430.2	45.6	86.5	65.2	54.6	34.5	16.1
9	544.3	432.4	323.1	233.5	345.6	432.8	360.7	278.6	266.9	345.9	90.5	78.7	76.5	63.4	189.8
10	328.9	301.1	245.6	102.5	23.4	298.9	276.8	206.3	113.5	34.3	66.3	56.7	50.2	45.7	22.3
11	2460.5	1015.4	787.8	654.2	568.9	3250.5	2011.5	1540.6	1650.5	890.7	345.6	289.9	267.5	201.3	234.6
12	1450	890.8	877.9	450.6	761.2	1565.1	870.2	770.5	450.2	678.7	270.2	206.7	212.5	187.5	176.6

Transaminase and bilirubin in most patients decreased significantly after TIPS, and liver function improved gradually. Three patients (patients 2, 4, and 12) died after the combined treatment, and three patients (patients 3, 9, 11) recovered fully after liver transplantation. Nine patients survived until 1 year (1-year survival rate, 75%).
MARS, molecular adsorbent recirculation system; TIPS, transjugular intrahepatic portosystemic shunt; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; d, day; w, week.

Table 3. Hepatic venous and portal venous pressures, and HVPG before and immediately after TIPS placement.

	Hepatic venous pressure (mmHg)		Portal venous pressure (mmHg)		HVPG (mmHg)	
Patient	Pre	Post	Pre	Post	Pre	Post
1	7	4	24	11	17	7
2	14	13	34	29	20	16
3	7	12	34	28	27	16
4	5	3	43	33	38	30
5	6	12	20	16	14	4
6	4	13	24	17	20	4
7	8	11	20	17	12	6
8	3	15	30	18	27	3
9	1	5	18	15	17	10
10	4	13	32	20	28	7
11	9	19	52	30	43	11
12	6	3	26	21	20	18

Patients 2, 4, and 12 died after TIPS placement, and patients 3, 9, and 11 underwent liver transplantation. Three patients who died after TIPS placement had a HVPG of >16 mmHg.
HVPG, hepatic venous pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

TIPS placement. It is unknown why the hepatic venous pressure was lower in patients 1, 2, 4, and 12 after TIPS creation compared with the hepatic venous pressure pre-TIPS because hepatic venous pressure usually increases following TIPS placement. Post-TIPS HVPG was greater than 12 mmHg in patients 2, 3, and 4. Patient 2 died 3 days after undergoing TIPS because of HE and sepsis. Patient 4 died 4 days after TIPS because of multiple organ failure. Patient 12 died 37 days after TIPS because of liver failure and concurrent severe lung infection. Patients 3, 9, and 11 underwent treatment for acute liver failure before TIPS placement, and they underwent liver transplantation on day 43, 45, and 15, respectively, after TIPS. All patients who underwent liver transplantation recovered at home and were followed-up. The rest of the survivors were alive and healthy after a 1-year follow-up period.

Discussion

A diagnosis of HVOD usually involves a typical clinical presentation and exclusion of other causes of liver injury. Many traditional Chinese medicines contain the components of Pas.[11] Chinese people believe that herbal medicines are natural and innocuous, but they can lead to HVOD in many individuals in China.

If severe HVOD develops, it is almost uniformly fatal, and many treatments including the combination of t-PA and heparin are ineffective or unsatisfactory.[12] Because there is a lack of acceptable therapies, the goals of combination therapy for HVOD are to improve liver function by MARS therapy and reduce portal hypertension by TIPS placement.

In the present study, the 1-year survival rate was 75%; nine patients survived following combination therapy (liver transplantation in three patients). Senzolo et al.[13] reported a 20% survival rate in patients with HVOD treated with TIPS. The difference in survival rates between the report by Senzolo et al.[13] and the present study may be because of the difference in the HVOD pathogenesis. In the former, the patients were treated with BMT for

leukemia and some of them had multiorgan failure associated with infection. However, our patients were healthy before they developed HVOD, and they were treated with the combination of MARS and TIPS. The present study results strongly suggest that improvement of the liver function due to MARS therapy before and after TIPS placement results in increased survival of patients with HVOD. The combination of TIPS plus MARS was superior to TIPS alone for treating HVOD, which confirms that the clinical manifestations of severe HVOD do not solely result from portal hypertension.[14,15]

In our report, eight patients had a HVPG that was higher than 20 mmHg before TIPS, and three of them died and two underwent liver transplantation. This was consistent with Bearman et al.'s study,[16] which suggested that patients with HVPG >20 mmHg had a poor prognosis. Patients 3, 9, and 11 underwent liver transplantation after TIPS, and their HVPG after TIPS was higher than 10 mmHg. Compared with the HVPG of survivors and non-survivors, we further found that a HVPG $\geq$10 mmHg after TIPS may be an important factor that affects the survival rate of HVOD patients.

After successful establishment of TIPS using a large number of portal blood diversions into the systemic circulation, the portal blood flow was reduced significantly, causing liver injury, HE, and severe infection.[17] However, the portal pressure was also reduced, which was significant for alleviating the large amount of ascites that was caused by portal hypertension, the pressure was reduced in the hepatic sinusoid, central vein, and interlobular vein. This, in turn, reduced liver cell edema and improved hepatic artery perfusion, which were conducive to liver function recovery.[18]

Senzolo et al.[19] reported two HVOD patients who were treated with TIPS; one of these patients recovered fully with histological amelioration, and the other patient had portal hypertension that resolved, but there was no amelioration in histology at 16 months after TIPS. Similarly, histological changes after TIPS were reported by Fried et al.[20] in six patients, among whom three (50%) showed amelioration of sinusoidal congestion and hemorrhagic necrosis. Combined with our research, all the survivors were healthy during the long follow-up period, suggesting that HVOD is a transient disease process. After experiencing the most severe stage, patients' liver function may recover fully or partially. However, due to the small sample size, further study is required.

Botanicals are self-prescribed, self-administered, and widely available, and unspecified mixed formulas are common in China. Healthcare providers should be advised to obtain accurate information about their patients' use of herbal remedies and ensure that these patients are well-educated about the remedies' potential hepatotoxicity. Although 70% of patients recover spontaneously, the remainder comprise complications that are characterized by severe ascites, impaired sodium excretion, renal insufficiency, and a HVPG of 20 mmHg. This group of patients may benefit from hepatic decompression if the procedure is performed early in the disease course. Thus, we believe that it is important to explore the role of TIPS as an option for patients with progressive VOD, but without other forms of concomitant liver injury, who do not respond to medical therapy. This should be performed before other organ failure occurs, and especially after liver transplantation because no other therapeutic option is available except re-transplantation.[21]

Our study has some limitations. The sample size was relatively small and there was no drug-treated control group. Additionally, a survival analysis was not

performed. Thus, further study should be performed to confirm our study results.

In conclusion, the combined therapy with MARS before and after TIPS placement has shown a survival benefit in patients with HVOD that is caused by herbal medicine in China. Prospective studies are needed to evaluate the safety, efficacy, and long-term benefits of the combined treatment.

Author contributions

Li Deng drafted the manuscript and analyzed patient samples. Xiuli Yin, Yingying Zhao, and Jing Yang assisted with sample analysis. Hongli Yang and Changqing Xu were involved with patient care and analyzed patient samples. Kun Li conceived the study, collected the case data, finalized the manuscript, and acts as the guarantor.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. DeLeve LD, Shulman HM and McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis* 2002; 22: 27–42.
2. Wadleigh M, Ho V, Momtaz P, et al. Hepatic veno-occlusive disease: pathogenesis, diagnosis and treatment. *Curr Opin Hematol* 2003; 10: 451–462.
3. Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2016; 51: 906–912.
4. Wu XW, Wang WQ, Liu B, et al. Hepatic veno-occlusive disease after taking Gynura Rhizome: the value of multidetector computed tomography in diagnosing the disease and evaluating the clinical therapeutic effect. *Hepatol Res* 2012; 42: 304–309.
5. Keating GM. Defibrotide: a review of its use in severe hepatic veno-occlusive disease following haematopoietic stem cell transplantation. *Clin Drug Investig* 2014; 34: 895–904.
6. Kumar S, Deleve LD, Kamath PS, et al. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation. *Mayo Clin Proc* 2003; 78: 589–598.
7. Dignan FL, Wynm, RF, Hadzic N, et al. BCSH/BSNMT guideline: diagnosis and management of veno-occlusive disease(sinusoidal obstruction syndrome)following haematopoietic stem cell transplantation. *Br J Haematol* 2013; 163: 444–457.
8. Goringe AP, Brown S, O'Callaghan U, et al. Glutamine and vitamin E in the treatment of hepatic veno-occlusive disease following high-dose chemotherapy. *Bone Marrow Transplant* 1998; 21: 829–832.
9. Ohashi K, Tanabe J, Watanabe R, et al. The Japanese multicenter open randomized trial of ursodeoxycholic acid prophylaxis for hepatic veno-occlusive disease after stem cell transplantation. *Am J Hematol* 2000; 64: 32–38.
10. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 2015; 50: 781–789.
11. Stegelmeier BL, Edgar JA, Colegate SM, et al. Pyrrolizidine alkaloid plants, metabolism and toxicity. *J Nat Toxins* 1999; 8: 95–116.
12. DeLeve LD, Valla DC and Garcia-Tsao G. Vascular disorders of the liver. *Hepatology* 2009; 49: 1729–1764.

13. Senzolo M, Germani G, Cholongitas E, et al. Veno occlusive disease: update on clinical management. *World J Gastroenterol* 2007; 13: 3918–3924.
14. Shulman HM and Hinterberger W. Hepatic veno-occlusive disease: liver toxicity syndrome after bone marrow transplantation. *Bone Marrow Transplant* 1992; 10: 197–214.
15. DeLeve LD, McCuskey RS, Wang X, et al. Characterization of a reproducible rat model of hepatic veno-occlusive disease. *Hepatology* 1999; 29: 1779–1791.
16. Bearman SI, Anderson GL, Mori M, et al. Venoocclusive disease of the liver: development of a model for predicting fatal outcome after marrow transplantation. *J Clin Oncol* 1993; 11: 1729–1736.
17. Sliva RF, Arroyo PC Jr, Duca WJ, et al. Complications of following transjugular intrahepatic portosystemic shunt: a retrospective analysis. *Transplant Proc* 2004; 36: 926–928.
18. Azoulay D, Castaing D, Lemoine A, et al. Transjugular intrahepatic portosystemic shunt (TIPS) for severe veno-occlusive disease of the liver following bone marrow transplantation. *Bone Marrow Transplant* 2000; 25: 987–992.
19. Senzolo M, Patch D, Cholongitas E, et al. Severe venoocclusive disease after liver transplantation treated with transjugular intrahepatic portosystemic shunt. *Transplantation* 2006; 82: 132–135.
20. Fried MW, Connaghan DG, Sharma S, et al. Transjugular intrahepatic portosystemic shunt for the management of severe venoocclusive disease following bone marrow transplantation. *Hepatology* 1996; 24: 588–591.
21. Senzolo M, Cholongitas E, Patch D, et al. TIPS for veno-occlusive disease: is the contraindication real? *Hepatology* 2005; 42: 240–241.