



CLINICAL RESEARCH

Clinical research on navel application of *Shehuang Paste* combined with Chinese herbal colon dialysis in treatment of refractory cirrhotic ascites complicated with azotemia

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Abstract

AIM: To explore the efficacy and mechanism of a novel therapeutic method of traditional Chinese medicine in patients with refractory cirrhotic ascites complicated with azotemia.

METHODS: Seventy-five cases of refractory cirrhotic ascites complicated with azotemia were randomly divided into 3 groups: comprehensive treatment ($n = 29$), simple treatment ($n = 24$), and control ($n = 22$). The basic treatment methods were the same in all groups, including liver protecting medicines, diuretics and supportive drugs. The control group underwent only the basic treatment. *Shehuang Paste* (SHP) was applied to the navels of the two treatment groups once a day for 30 d. Colon dialysis with Chinese herbs was administered to the comprehensive treatment group once every two days. Before and after treatment, we measured abdominal circumference, BUN, Cr, serum Na^+ , urine Na^+/K^+ , liver function, endotoxin content, NO, and ET-1. Color Doppler ultrasonography was conducted to measure the portal vein blood flow.

RESULTS: The total effective rate for ascites was 72.4% in the comprehensive treatment group, 45.8% in the simple treatment, contrasting with 18.2% in the controls. Between the two treatment groups and the controls, there were significant differences in the effective rates ($P < 0.01$, and $P < 0.05$). There was also a significant difference ($P < 0.05$) between the two treatment groups. Measurements of Cr and BUN showed higher values for the treatment groups, with the comprehensive better than the simple group ($P < 0.05$). Sera Na, urine

Na/K were different, $P < 0.01$ between pre- and post-treatment in the comprehensive group, and $P < 0.05$ in the simple group. The treatment groups' endotoxin content was also significantly reduced ($P < 0.01$, and $P < 0.05$), with the comprehensive group better than the simple group ($P < 0.05$). Portal vein blood flow and NO content significantly reduced ($P < 0.05$), as did ET-1 content ($P < 0.01$). There were no significant changes in the control group ($P > 0.05$). The comprehensive treatment group's pre- and post-treatment portal vein and splenic vein blood flows showed a positive correlation to NO, ET-1 and endotoxin contents.

CONCLUSION: When treating refractory cirrhotic ascites complicated with azotemia, *Shehuang Paste* combined with Chinese herbal dialysis is better than *Shehuang Paste* alone for ascites resolution, azotemia, and endotoxin elimination. However, both methods on their own were also effective for reducing portal and splenic vein blood flow, and lowering the contents of NO, ET-1 in the two treatment groups.

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Key words: Cirrhotic; Refractory ascites; Azotemia; Vasoactive substance

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INTRODUCTION

Cirrhotic ascites is one of a triad related to portal hypertension, which is not difficult to be cured if patients receive early treatment. Only about 10% of patients proceed to develop 'refractory ascites'. The International Ascites Club^[1] definition of refractory cirrhotic ascites is that ascites is not obviously reduced after treatment (mainly by diuretics administration) or that early ascites recurrence can not be prevented by medicines after discharging liquid administration, which was defined by the Chinese experts based on the simple fact that patients' abundant ascites

lasts more than 3 mo^[2]. Approximately 20% of the patients will go on to develop hepatorenal syndrome (HRS) within 1 year^[3]. Once HRS develops, the mortality rate is almost 100%. In their development, hepatopathy and nephropathy interact with each other. Hepatocirrhosis and fluid and sodium retention, easily complicate any dysfunction of the renal blood stream. If treated with diuretics, azotemia may be induced. However, anuria induced by renal dysfunction can aggravate ascites. Thus it is very important that clinical research should be aimed to prevent, to treat early or to stop the development of hepatorenal syndrome^[4].

The pathogenesis of refractory cirrhotic ascites is not well understood. There are many theories, but portal hypertension is generally accepted as the basis of ascetic formation. Neural-tumour reaction is induced by portal hypertension, and an endogenous vessel activity abnormality in which endotoxin, NO and ET-1 play important roles. These factors lead to hyperdynamic circulation and an effective blood capacity deficiency. Renal blood stream kinetic and functional abnormalities are important in the pathogenesis^[5].

The major medicinal treatments are an abundant discharge of liquid, supplemented by a large volume of protein or self-liquid retransfusion. However, it cannot sustain for a long time and a circulatory functional disorder can easily happen after massive liquid discharging. To date, a medicine to completely reverse low perfusion of nephridium has not been determined^[6]. Thus, it is difficult to treat refractory cirrhotic ascites by the normal methods of internal medicine.

There are reports of herbs being applied to the navel for the treatment of cirrhotic ascites^[7], indicating that the application of herbs to the navel for the treatment of cirrhotic ascites is possible. Such treatment can act fast, significantly reduce ascites, improve symptoms while it neither injures patient's right Qi ("life energy" according to the principle of traditional Chinese medicine) nor disturbs the water-electrolyte balance. But there are few reports about the application of herbs to the navel for the treatment of refractory cirrhotic ascites. Chinese herbal colon dialysis has for many years been applied for treating renal failure. The mechanism for this treatment is that the human colon has functions of absorption and secretion. The mucosa of the colon, a semi-dialytic membrane, can selectively absorb or secrete, using the ion grads in dialytic water, discharge poisonous metabolic productions as endotoxins, carbamide, ammonia, and absorb substances useful for human life from herbs. *Da huang* is the herb usually used. Chen HL^[8] added *Fu xi*, *chuan xiong*, *Hua Q*^[9] conjugated *Fu xi*, *Shui zhi*, and *Sheng mu li*, Chen HC^[10] *Jin yin hua*, *Huai hua*, *Pu gong ying*, and *Duan mu li*. These treatments are mostly used to treat chronic renal failure or hemorrhagic fevers of nephritic syndrome complicated with acute renal failure. However, we have found no reports about these treatments being used for cirrhotic ascites complicated with azotemia.

This study used SHP applied to the navel in combination with Chinese herbal colon dialysis. It aimed to observe the clinical effect on 'refractory cirrhotic ascites', measure the levels of endotoxins, NO, ET-1 and portal vein blood flow. We sought to prevent or postpone

the process of hepatorenal syndrome during azotemia.

MATERIALS AND METHODS

Clinical material

All 75 patients enrolled with refractory cirrhotic ascites were inpatients hospitalized in the authors' hospital from July 2002 to June 2005. They were randomly assigned to 3 groups by SAS software: 29 cases to the comprehensive treatment group; 23 male, 6 female; average age 43 ± 10 years; and average disease duration 6.1 ± 3.0 mo. There were 19 cases of hepatitis B-related cirrhosis, 2 of alcohol-related cirrhosis, 1 of blood fluke related cirrhosis, and 1 of autoimmune related cirrhosis; 24 to the simple treatment group, 17 male, 7 female, average age 43 ± 13 years, average disease duration 7.7 ± 3.5 mo. There were 20 cases of hepatitis B-related cirrhosis, 1 of alcohol-related cirrhosis, and 1 of blood fluke related cirrhosis. The level of ascites, Cr, BUN, age, duration of disease, and disease condition between the two treatment groups were comparable, without significant differences ($P > 0.05$).

Diagnostic criteria for refractory cirrhotic ascites

The diagnosis of refractory cirrhotic ascites was made with reference to guidelines contained in the literature. Inclusion criteria^[11]: (1) Patients with a confirmed diagnosis of cirrhotic ascites; (2) Cases of refractory ascites, that is, previous treatments were either not satisfactory in dispelling ascites or there was an unavoidable early recurrence of ascites after discharge and the ascites had lasted more than 3 mo; (3) The patients' serum Na < 130 mmol/L, urine Na < 10 mmol/24 h, urine Na/K < 1 , and glomerular filtrating rate (GRE) were below normal ranges. The level of Cr is 141-211 $\mu\text{mol/L}$ ^[11].

Exclusion criteria

Patients were excluded if one of the following conditions was present: (1) Ascites originating from cirrhosis complicated with a malignant tumor; (2) Complications with acute digestive tract bleeding or hepatic encephalopathy; (3) Complications with primary diseases of cardiovascular, renal and hematopoietic systems, or with mental disease; (4) Anal stricture, internal or external hemorrhoids with active bleeding; and (5) Patients who did not meet the inclusion criteria, did not follow directions about taking medication, medical records were missed, or the effects and safety of the treatment were difficult to be determined.

Therapeutic methods

SHP Ingredients: Each piece of SHP consisted of snail flesh (approximately 30 g), *Moschus* 1 g, artificial *Calculus Bovis* 1 g, *Radix Euphorbiae Kansui* 10 g and *Bulbus Allii Fistulosi* 10 g.

Preparation: *Bulbus Allii Fistulosi* was pressed juice. *Radix Euphorbiae Kansui* was decocted with water twice, at each 2 h, and mixed with *Bulbus Allii Fistulosi* juice that had been filtrated. The mixture of the juice of the 2 herbs was concentrated to a dense paste with a relative density of 1.20. *Moschus* and artificial *Calculus Bovis* were extracted after being recirculated three times in 95% ethanol. Snail

flesh was minced, the dregs removed and then stewed. The extract of *Moschus* and artificial *Calculus Bovis*, the stewed snail product and the dense paste were mixed and then formed into a medicated patch of 3 cm × 3 cm in size (undertaken by the Pharmaceutical Department of Shenzhen Hospital, affiliated to Guangzhou University of TCM, batch No: 030113)^[12]. The patch was placed into a bag and stored at 4°C.

Quality control: Quality control for the SHP was by detecting the content of Ketone musk and Bilirubin, the main ingredients of *Moschus* and artificial *Calculus Bovis*. *Moschus* (Batch No: 030912) and artificial *Calculus Bovis* (Batch No: 031221) were purchased from Shenzhen Branch of the Medicinal Material Company of China. The amount of medicinal paste on each patch was 1.2 g/100 cm². Bilirubin content in *Calculus Bovis* was above 41% (Bilirubin content is noted as being 35% in the 2005 edition of Pharmacopeia of China). Ketone musk in each piece of SHP was 2.73 mg/g^[13] measured by high performance liquid chromatograph (Gillson, France). The method is reliable and stable.

Colon dialysis ingredients: The formula used for colon dialysis consisted of *Rheum Palmatum L*, *Sophora Japonica L*, *Lonicera Japonica Thunb*, *Taraxacum mongolicum*, *Herba-Mazz*, and *Ostrea telienwhanensis Crosse*; 30 g of each.

Preparation: All ingredients in the colon dialysis formula were decocted together twice in a routine way. The 2 juices were mixed, filtrated to 200 mL, and stored at -70°C until use. For use, the mixture was warmed to 38°C (carried out by the Preparation Room, Guangzhou University of Traditional Chinese Medicine affiliated Shenzhen Hospital, No. 030113).

Group treatment

The basic treatment was given to all three groups. Included in this were liver protecting medicines such as Wuzhi Jiaonang (mainly deoxyschizandrin, two tablets given each time, three times a day) and Silybin Meglumine (two tablets each time, three times a day); diuretics furosemide and antisterone at a ratio of 1:2 (80 mg: 160 mg); and supportive drugs such as 20% human albumin at a dosage of 100 mL per day. Ascites were discharged from 1000 mL to 1500 mL the first time and then from 2000 mL to 3000 mL each time for 3 times once every 2 d. Antibiotics (fortum 2.0 g/d) were administered to patients who complicated with peritonitis.

For the simple treatment group, the treatment method was the basic treatment plus SHP applied to the navel. For the comprehensive treatment group, the basic treatment plus SHP on the navel and the herbal colon dialysis. For the control group, only basic treatment.

Treatment procedures

Navel application: One piece of paste was compressed on the navel (Shenque acupoint) every day.

Colon dialysis: The following were the procedures carried out by patients; first, defecate and urinate. Incline on the right while lying down and prop the buttocks up by about 10 cm. Before dialysis, insert a SaveMedical double-cavity tube into the anus, insert the entering end

about 50 cm into the inner anus and the exiting end would then be about 20 cm into the inner anus. Apply 1200 mL mannitol and 1200 mL dialytic fluid as an enema for 2 h. Clear the intestinal tube to maintain the high penetrability to intestinal mucosa. Later, insert 200 mL of the colon dialysis fluid for 30-60 min until an unforced defecation occurs. For the control group, a placebo of flour was applied to the navel, and the colon dialysis fluid was replaced with Sodium Chloride.

Period of treatment: One month made up one course of therapy. The following items were measured before treatment and at the end of treatment: abdominal circumference, BUN, Cr, serum Na⁺, urine Na⁺/K⁺, liver function, endotoxin content, NO, and ET-1 nephritic syndrome. All items were then rechecked every month over a follow-up period of 3 mo.

Observational methods

General condition: Body weight, abdominal circumference, tongue and coating, pulse rate, volume of urine in 24 h, levels of urinary Na⁺ and K⁺, and Na⁺/K⁺ ratio in urine were measured every morning.

Blood Na⁺ and liver function indexes: Blood Na⁺, and indexes of liver functions including alanine transaminase (ALT), and aspartate aminotransferase (AST) were measured. Gamma glutamyl transferase (γ-GT), total bilirubin (TB), albumin (ALB) and albumin/globulin ratio (A/G) and indexes of renal function, including serum Cr: liver function, serum Cr and BUN were checked using an Olympus 27000 (Japan) for routine automatic biochemical analysis once a week.

Levels of endotoxin, NO and ET-1: Levels of endotoxin, NO and ET-1 were measured before and after treatment using 5 mL of fasting (8 h) cubital venous blood drawn in the morning. Plasma was separated and stored at -20°C. Plasma endotoxin was determined by limulus lysate chromogenic test, and NO by indirect colorimetry. The reagents used were provided by the Beijing Bangding Corporation of Biological Medical Science. ET-1 was determined by radio-immunoassay using a testing kit was provided by the East Asia Technological Institute, of the General Hospital of the People's Liberation Army. All tests were conducted by a trained technician using the same device and kits from the same batch.

Blood dynamics: Examination was conducted early in the morning on the day of blood collection. Patients were required to lie supinely and breathe calmly; a dual-function Color Doppler, Fynergy by GE, DIASONICS Corporation of America, with a 35 MHz frequency detector was used to measure the peak velocity of the blood flow (Vp) in the inner diameter (D) of the portal vein trunk and the splenic vein of the hilum. Examinations were carried out by a trained technician with the volume of the sampling as close as possible to that of the diameter of the blood vessel, and the angle between the sound beam and the blood flow as small as possible (less than 60°). All variables were measured twice and averaged. The volume of blood flow (Q) of portal and splenic veins were calculated by the formula $[V_{mean} \times (D/2)^2 \pi \times 60]$ (D means diameter of blood vessel, Vmean means average velocity of blood flow)^[14].

Table 1 Comparison of pre-and post-treatment for general efficacy on ascites *n* (%)

Treatment groups	<i>n</i>	Ascites grade I resolution	Ascites grade II resolution	Ascites grade III resolution	No effect
Comprehensive	29	6 (20.7)	6 (20.7)	9 (31.0)	8 (27)
Simple	24	2 (8.3)	3 (12.5)	6 (25.0)	13 (54.2)
Control	22	0 (0.0)	1 (4.5)	3 (13.6)	18 (81.8)

Table 2 Changes of azotemia (mean \pm SD)

Treatment groups	<i>n</i>		Cr (μ mol/L)	BUN (mmol/L)
Comprehensive	29	Before	162.96 \pm 11.73	10.54 \pm 1.23
		After	113.82 \pm 9.62 ^{b,d}	6.48 \pm 0.61 ^{a,d}
Simple	24	Before	158.32 \pm 17.21	10.41 \pm 1.43
		After	123.54 \pm 23.13 ^{a,c}	7.92 \pm 0.87 ^b
Controls	22	Before	161.51 \pm 11.55	9.09 \pm 1.18
		After	143.41 \pm 9.87	8.28 \pm 0.38

^a*P* < 0.05, ^b*P* < 0.01, pre-treatment *vs* post-treatment; ^c*P* < 0.05, ^d*P* < 0.01 *vs* control group.

Table 3 Pre- and post-treatment liver function changes (mean \pm SD)

Groups	<i>n</i>		ALT (U/L)	AST (U/L)	γ -GT (U/L)	TB (U/L)	ALB (U/L)	A/G (U/L)
Comprehensive	29	Before	81.73 \pm 55.31	96.92 \pm 52.32	177.63 \pm 22.24	59.89 \pm 34.91	28.28 \pm 4.19	0.82 \pm 0.19
		After	53.22 \pm 30.16 ^a	83.56 \pm 63.45	101.12 \pm 44.11 ^a	28.12 \pm 10.23 ^a	34.14 \pm 3.95 ^a	1.17 \pm 0.74 ^a
Simple	24	Before	73.67 \pm 43.13	98.12 \pm 62.26	170.03 \pm 13.45	67.14 \pm 41.39	28.38 \pm 3.21	0.71 \pm 0.18
		After	50.12 \pm 20.43 ^a	84.65 \pm 60.50	88.20 \pm 33.99 ^a	35.22 \pm 9.35 ^a	35.47 \pm 3.69 ^a	1.15 \pm 0.70 ^a
Controls	22	Before	70.16 \pm 37.24	102.12 \pm 60.32	168.26 \pm 118.04	68.81 \pm 41.33	29.78 \pm 3.39	0.72 \pm 0.21
		After	51.02 \pm 18.34 ^a	87.65 \pm 62.12	89.27 \pm 35.19 ^a	33.12 \pm 9.08	34.78 \pm 4.16 ^a	1.11 \pm 0.73

^a*P* < 0.05, pre- and post-treatment comparison.

Efficacy evaluation standards

Using the “Standards for Efficacy Evaluation of TCM on Liver Cirrhosis Ascites” formulated at the Dalian Conference in 1993 by the special committee of Internal Hepatology, the China Association of Chinese Medicine (draft)^[15], the efficacy on ascites was classified into 3 grades. Grade I: complete resolution of ascites, with no abdominal fluid found in ultrasound B examination, and condition stabilized for more than 3 mo; Grade II: most of the ascites disappeared with only slight shifting dull sound upon percussion in a physical examination and ultrasound B shows little ascites; and Grade III: ascites are somewhat diminished and the abdominal circumference at the level of the naval has decreased by more than 30 cm.

Statistic analysis

Variance analysis and χ^2 test were used to analyze all measurement and enumeration data, respectively. Linear correlation regression analysis was used for the relationship among PVQ and SVQ with levels of endotoxin, NO, and ET-1.

RESULTS

General efficacy for ascites in all groups

In most patients symptoms and physical signs improved to various degrees after treatment. Especially, abdominal distension, reduced urine, and abdominal circumference, lower limb swelling apparently improved, and body weight loss. However, fatigue, liver palm, and spider telangiectasia did not show any change.

In Table 1, the total effective rate on ascites in the treatment group is 72.4% (21/29), the simple treatment group 45.8% (11/24), and the control group 18.2% (4/22).

There is no grade I resolution of ascites in the control group. By χ^2 test, there is a significant difference between the control and comprehensive treatment groups (*P* < 0.01), and the control and the simple treatment groups (*P* < 0.05). There is also difference between the two treatment groups (*P* < 0.05).

Changes of azotemia

Table 2 shows statistically significant differences between pre- and post-treatment changes of azotemia in the comprehensive treatment (*P* < 0.01) and simple treatment (*P* < 0.05) groups. The control group has no obvious change (*P* > 0.05). There are distinct differences between each treatment group and the controls (*P* < 0.01, *P* < 0.05). However, there is no difference between the two treatment groups (*P* > 0.05).

Changes of liver function, blood Na⁺ and urine Na⁺/K⁺

Changes of liver function are shown in Table 3. Liver function ALT, TB, ALB, A/G are significant different between pre- and post- treatment stages in all three groups (*P* < 0.05), but there is no significant difference between the treatment and control groups. Changes of serum Na⁺, and Na⁺/K⁺ are shown in Table 4. The serum Na⁺, and Na⁺/K⁺ rates of the control group were increased after treatment, but there was no significant difference (*P* > 0.05). However, there are significant differences between before and after treatment in the comprehensive treatment (*P* < 0.01) and simple treatment (*P* < 0.05) groups. Though there is no statistical difference between the two treatment groups (*P* > 0.05).

Levels of endotoxin, NO, and ET

Endotoxin content decreased in the comprehensive

Table 4 Pre- and post-treatment serum Na⁺ and urine Na⁺/K⁺ changes (mean ± SD)

Groups	n		Serum Na ⁺	Urine Na ⁺ /K ⁺
Comprehensive	29	Before	126.32 ± 5.13	0.86 ± 0.23
		After	133.19 ± 3.21 ^b	1.76 ± 0.65 ^b
Simple	24	Before	127.27 ± 4.13	0.79 ± 0.26
		After	132.43 ± 3.34 ^a	1.65 ± 0.85 ^a
Controls	22	Before	126.16 ± 5.24	0.82 ± 0.32
		After	128.50 ± 7.29	1.25 ± 0.91

^a*P* < 0.05, pre- and post-treatment comparison; ^b*P* < 0.01, pre- and post-treatment comparison.

Table 5 Pre- and Post-treatment changes of endotoxin, NO and ET-1 (mean ± SD)

Groups	n		Endotoxin (ng/L)	NO (μmol/L)	ET-1 (ng/L)
Comprehensive	29	Before	96.71 ± 28.82	15.82 ± 6.41	44.36 ± 7.14
		After	70.56 ± 27.34 ^{b,d}	11.11 ± 6.02 ^{a,c}	33.87 ± 8.95 ^{b,c}
Simple	24	Before	95.27 ± 29.12	15.11 ± 6.99	45.59 ± 7.46
		After	80.69 ± 26.44 ^{a,c}	11.63 ± 6.15 ^{a,c}	36.67 ± 8.58 ^{b,c}
Controls	22	Before	95.34 ± 30.22	15.65 ± 7.34	41.13 ± 8.25
		After	90.14 ± 32.38	14.23 ± 7.03	39.12 ± 8.46

P < 0.05, ^aPre- and post- treatment comparison, ^b*P* < 0.01; ^ccomparison between groups, *P* < 0.05, ^d*P* < 0.01.

Table 6 Pre- and post-treatment blood flow of three groups (mean ± SD)

Groups	n		PV (Portal vein)			SV (Splenic vein)		
			D (cm)	Vp (cm/s)	Q (mL/min)	D (cm)	Vp (cm/s)	Q (mL/min)
Comprehensive	29	Before	1.43 ± 0.18	14.15 ± 3.34	1274 ± 429	1.19 ± 0.22	15.27 ± 4.12	896.5 ± 301.8
		After	1.21 ± 0.22 ^{a,c}	15.27 ± 3.23	906.0 ± 316 ^{a,c}	1.07 ± 0.18	15.13 ± 3.78	592.2 ± 201.8 ^{a,c}
Simple	24	Before	1.42 ± 0.16	14.21 ± 3.06	1249 ± 416	1.20 ± 0.24	14.26 ± 4.10	896.5 ± 301.8
		After	1.23 ± 0.32 ^{a,c}	14.95 ± 3.40	896.0 ± 376 ^{a,c}	1.06 ± 0.25	15.10 ± 3.80	609.2 ± 208.7 ^{a,c}
Controls	22	Before	1.41 ± 0.26	14.20 ± 2.20	1238.2 ± 422.0	1.20 ± 0.22	14.84 ± 2.56	853.1 ± 321.2
		After	1.40 ± 0.22	14.01 ± 2.40	1247.0 ± 364.2	1.19 ± 0.23	14.96 ± 4.00	843.7 ± 341.0

^a*P* < 0.05, comparison of pre- and post-treatment; ^c*P* < 0.05, *vs* control group.

treatment (*P* < 0.01) and simple treatment (*P* < 0.05) groups. NO (*P* < 0.05) and ET-1 (*P* < 0.01) also decreased after treatment. There was no significant difference between the two treatment groups (*P* > 0.05). Endotoxin, NO and ET-1 contents of the control group also showed no statistical difference (*P* > 0.05) (Table 5).

Comparison of blood flow in portal and splenic veins

For both treatment groups, the diameter (D value) and quantity of blood flow (Q value) of the portal and splenic veins decreased significantly after treatment (*P* < 0.05). In the control group, no great change was found after treatment (*P* > 0.05). Comparison of D and Q among the treatment and control groups after treatment found significant differences (*P* < 0.05). But there were no significant difference between the two treatment groups (*P* > 0.05). No significant changes were shown in Vp in all three groups before and after treatment (*P* > 0.05) (Table 6).

Pre- and post-treatment correlations between splenic and portal vein blood flows and endotoxin, NO and ET-1

As shown in Table 7, the PVQ and SVQ show a positive correlation to the pre- and post-treatment endotoxin levels in the 29 cases of the comprehensive treatment group with a pretreatment *r* (PVQ) = 0.67, *r* (SVQ) = 0.73 for *P* < 0.01; and post-treatment *r* (PVQ) = 0.75, *r* (SVQ) = 0.69 for *P* < 0.01. They have a positive correlation to the NO level with a pretreatment *r* (PVQ) = 0.68, *r* (SVQ) = 0.68 for a *P* < 0.01; and a post-treatment *r* (PVQ) = 0.45, *r* (SVQ) = 0.51 for *P* < 0.05. They also have a positive correlation to ET with a pre-treatment *r* (PVQ) = 0.79, *r* (SVQ) = 0.78 for *P* < 0.01; and a post-treatment *r* (PVQ) = 0.73, *r* (SVQ) = 0.74 for *P* < 0.01.

Adverse reactions and follow-up

Five patients in the treatment groups showed papilla, reddening, swelling or itching skin where paste was applied to the naval area. The symptoms were endurable after treatment with dexamethasone acetate, ointment and there was no need to discontinue the paste application. No other kinds of allergic or adverse reactions were seen. Colon dialysis was implemented every two days and all 53 patients completed the treatment.

During the 3 mo follow-up, 7 cases control dropped out (3 cases effectively, 4 ineffectively treated). In 4 effectively treated patients, the ascites returned to the same level as pre-treatment; 2 ineffectively treated cases died because of HSR. In the treatment groups, 13 cases dropped out (8 effectively, 5 ineffectively treated). In 11 effectively treated patients, the ascites returned to the same level as pre-treatment; 20 cases remained in a stable condition; and in 9 cases the ascites increased but was less than before treatment. No patient in the treatment groups was found to suffer from HSR.

DISCUSSION

For a long time, we have been using SHP applied to the navel area to treat refractory cirrhotic ascites, and have achieved good efficacy^[16]. SHP is useful to treat refractory cirrhotic ascites; however, if complicated with azotemia the efficacy is not so good. Therefore, we have combined this with a herbal colon dialysis treatment; in accord with the theory of colon dialysis for treating uremia. The *Moschus* in the SHP aromatically opens orifices, unblocks network vessels and disperses stasis. Modern research shows that it dilates the blood vessels and has the same curative effect as

nitroglycerin^[17]. The Snail ingredient clears heat, disinhibits fluids, and treats jaundice. The artificial *Calculus Bovis* clears the heart and disinhibits the gallbladder; likewise, modern research shows that it safeguards the liver and disinhibits the gallbladder^[17]. Bulbous *Allii Fistulosi* frees Yang (the bright positive masculine principle in Chinese dualistic cosmology), unbinds toxins, and can guide medicinals to the affected site; likewise, modern research shows it has bacteriostatic capabilities^[17]. *Radix Euphorbiae Kansui* drastically precipitates and expels water. The *Rheum Palmatum* L in the colon dialysis formula removes residues in the stomach intestine, reduces the reabsorbing of azotic, restrains decomposition of BUN and Cr, and has bacteriostatic capabilities^[17]. *Lonicera Japonica* Thunb, *Taraxacum Mongolicum* Herba-Mazx have heat-clearing and detoxification effects; again, modern research shows they have broad-spectrum bacteriostatic capabilities^[17]. Sophorage *Japonica* L clears heat and cools the blood; it can improve filtering capabilities of kidneys^[17]. *Ostrea Teliembanensis* Crosse retains Yin (the dark negative feminine principle in Chinese dualistic cosmology) and suppresses yang; it can also absorb toxic substances in the intestines. Both SPH and the colon dialysis formula dissipated blood stasis and disinhibited the gallbladder, clearing away heat and toxins, and eliminating fluid by purging.

In our 75 cases presented here, after the basic treatment that included liver preprotecting, diuretics, human albumin, and antibiotics, liver function ALT, TB, ALB, A/G in all treatment and control groups had obvious improvements. There was no significant difference between each of the treatment and control groups. However applying herbs on the navel plus herbal colon dialysis was found to not improve the liver function compared with the basic treatment.

After the 3 groups underwent treatment, some improvements in some symptoms were seen. Taking the resolution of ascites as the major efficacy standard, the general rate of the effectiveness of the comprehensive treatment was 72.4%, the simple treatment group was 45.8% (11/24), while that of the control group was 18.2% (4/22). No patient reached Grade I for resolution of ascites in the control group. The effective rate of the comprehensive treatment group was higher than that of the simple treatment group ($P < 0.05$). From this we can infer that only using the basic treatment to treat refractory ascites cannot reach the therapeutic goal, putting herbs on the navel as a treatment has some effect on refractory ascites complicating with azotemia, but combining this with herbal colon dialysis can elevate the efficacy. The three-month follow-up here showed the lasting effects. From an assessment of the indexes having relationships with clinical azotemia, such as Cr, BUN, serum Na, and urine Na^+/K^+ , there was no efficacy pre- and post-treatment in the control group. However, there was a significant difference between the simply treatment group and the comprehensive treatment group, which is better than using just SHP in addition to the basic treatment.

The main pathogenesis of refractory cirrhotic ascites is due to portal vein hypertension (PVH). Therefore, this study sought to show the way to lower PVH. PVH forms as a result of mechanical and functional factors.

Table 7 Pre- and post-treatment correlation between splenic and portal vein blood flows and endotoxin, NO and ET-1 (mean \pm SD)

Indexes	n		r	
			PVQ	SVQ
Endotoxin	29	Before	0.67 ^b	0.73 ^b
		After	0.75 ^b	0.69 ^b
NO	29	Before	0.68 ^b	0.68 ^b
		After	0.45 ^a	0.51 ^a
ET-1	29	Before	0.79 ^b	0.78 ^b
		After	0.73 ^b	0.74 ^b

^a $P < 0.05$, ^b $P < 0.01$.

First, patients present increased blood flow resistance and blood volume in the portal vein. Then they exhibit PVH. We observed portal vein trunk hemodynamic changes by color Doppler ultrasonography; showing that the portal vein blood flow was reduced (mainly by decreasing the diameter of the portal vein) in the two treatment groups after treatment; there was no difference between the two treatment groups. We highlighted that the improvements in PVH came mainly because of SHP. SHP possibly activates blood circulation to dissipate blood stasis, and has the effect of reducing platelet coagulation, improving circulation in the liver and decreasing portal vein resistance. Also, SHP can decrease vasoactive substances, slow down hypertension in the mesentery, and work toward decreasing PVH. Thus it appears a real way to reduce ascites.

PVH is also the initiating factor for the release of vasoactive substances. An increase of endotoxin during cirrhosis stimulates iNOS synthesis, which releases a significant quantity of NO^[18]. The increased amount of NO released in the body leads to dilation of the peripheral vascular system, decreased arterial pressure and effective blood capacity. The decrease in arterial pressure then stimulates the sympathetic nervous system and activates the rennin-angiotonin-aldosterone system to alter the compensatory balancing of hemodynamics. As the illness continues, there is further compensation, even excessive compensation that can ultimately cause a decrease in the amount of blood circulating in the body, retention of both fluid and sodium, a redistribution of the renal blood flow, and the appearance of ascites, edema and azotemia^[19]. The peripheral vascular dilation caused by NO inevitably stimulates the body to compensate by synthesizing and releasing large quantities of ET-1. The increase of ET-1 leads to the contraction of blood vessels in the liver and kidneys, aggravating them to ischemia and portal shunting causing increased endotoxins to enter into the circulatory system; thus initiating a vicious cycle^[20]. A reason why refractory ascites is difficult to treat is that as it appears, the amounts of NO, ET-1, and endotoxin also gradually increase^[21]. Our research results also show that ascites have a positive correlation to the amount of portal vein blood flow and vasoactive substances. In refractory ascites patients, NO, ET and endotoxin are at an elevated level, together with the ongoing ascites. With ascites eliminated after treatment, the levels of endotoxin, NO and ET-1 correspondingly decreased.

Refractory cirrhotic ascites easily reduces azotemia, which also has an early role in hepatorenal syndrome. For treatment, it is effective for ascites to improve intrahepatic circulation and decrease portal vein blood flow, but this is not sufficient for ascites associated with azotemia. Thus, along with the application of Shehuang Paste to the navel area, we combined a Chinese herbal colon dialysis. The crucial procedure in the method is that patients undergo dialysis 2 h daily using mannitol and peritoneal dialysis liquid, and then a colon-enema for 30 min with a Chinese herb decoction. The mechanism utilizes the high diosmosis of the colonic semi-permeable membrane caused by a high diosmosis dialysis liquid to absorb other liquids, and Chinese herbs to reduce the release of harmful and vasoactive substances, especially ammonia and endotoxin. All the cases here were refractory cirrhotic ascites complicated with azotemia. The results presented here demonstrated that applications of Shehuang Paste to the navel area in combination with Chinese herbal colon dialysis is superior to Shehuang Paste alone for eliminating ascites, lessening azotemia, and for reducing vasoactive substances such as endotoxin.

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