

Clinical and experimental study of effect of *Raondix Salviae Militiorrhiza* and other blood-activating and stasis-eliminating Chinese herbs on hemodynamics of portal hypertension

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Subject headings hypertension, portal; liver cirrhosis; hemodynamics; drugs, Chinese herbal; blood activating and stasis eliminating

Abstract

AIM To study the effects of *Radix Salviae Militiorrhiza* (RSM), other blood-activating and stasis-eliminating Chinese herbs on hemodynamics of portal hypertension.

METHODS Portal pressure of cirrhotic dogs after chronic common bile duct ligation was measured directly; portal blood flow in patients with liver cirrhosis were detected by ultrasound Doppler.

RESULTS After administration of RSM and *Radix Angelicae Sinensis* (RAS) by intravenous infusion in cirrhosis dogs, the portal venous pressure (Ppv), wedge hepatic venous pressure (WHVP), hepatic venous pressure gradient (HVPg), were significantly decreased ($P < 0.05-0.01$), but the mean arterial pressure (MAP), and the heart rate (HR) remained unchanged. When nifedipine was used, Ppv, WHVP, MAP and HR were significantly decreased ($P < 0.05$), and the MHPg unchanged ($P < 0.05$). After administration of RSM, RSM+nifedipine and RSM+Hirudin+Nifedipine for 10-12 weeks, the diameter of portal vein (Dpv), spleen vein (Dsv), the portal venous flow (Qpv) and splenic venous flow (Qsv) in patients with hepatic cirrhosis were significantly lowered ($P < 0.05-0.01$), and the effect of RAS was weaker.

CONCLUSIONS The efficacy of decreasing Ppv by Chinese herbs—RSM, RAS, etc. as compared

with nifedipine, demonstrated that the Chinese herbs were slower in action than that of nifedipine, but more long-lasting and without side effects. Hence, long-term administration of Chinese herbs, would be more beneficial.

INTRODUCTION

There has been no long-lasting and side effects free drugs to lower the portal hypertension in patients with liver cirrhosis so far. The blood vessel constrictive drugs can reduce the volume of blood flow and lower the portal pressure by contracting visceral blood vessels but can not improve the prognosis of the patients obviously because of their bad dynamic effects, whereas drugs dilating blood vessels such as calcium antagonist—nifedipine can lead to hypotension at large doses although it is effective for portal hemodynamics^[1]. Yigan infusion which contains blood-activating and stasis-eliminating herbs such as large doses of RSM and RAM has some effects of shrinking the liver and spleen; and some of blood-activating and stasis-eliminating herbs can prevent and cure hepatic fibrosis^[2-5]. Therefore, the effects of RAM and RSM in portal and systemic dynamics were investigated in the present study.

MATERIALS AND METHODS

Animal model

Sixteen healthy mixed bred dogs, female and male, weighing 12.5kg - 20kg, were divided into two groups randomly: portal hypertension model group ($n = 12$) made by chronic bile duct ligation method described by Boschj *et al* and control group ($n = 4$).

Drugs and administration route

RSM injection (40%), nifedipine injection (50%) (the Ninth Shanghai Pharmaceutical Factory (batch no 940712123, original drug 1.5g/mL). The dosage for dogs is 20 times higher than for adult people. The dosage by intravenous drip (1/3 of oral doses) of RSM 6g/kg body weight, RAS 3mg/kg body weight, nifedipine 0.3mg/kg body weight in 10% glucose were infused through thigh vein in 10

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Received 1998-05-06

minutes, according to our earlier studies. The time was calculated after the infusion. The dogs were paralyzed with pentobarbital intravenous anesthesia at fast for 12h in 8-11 weeks after bile duct ligation, and tubes were inserted through vein for infusion, through femoral artery for measuring the mean arterial pressure and heart rate, through femoral vein to inferior vena cava for icvp, through mesentery vein to portal vein for Ppv and from right external jugular vein to hepatic vein for FHVP and HVPg. The tubes were washed by heparin to prevent from grume. The indexes were recorded by physiological recorder (RM-6200) synchronously before and 10, 30 and 60 minutes after administration of drugs according to Latin rank principle, 3 times per day, each drug being used for 90min-120min. The results were analyzed by *F* test and *q* test.

Clinical study

Patients Fifty-nine patients with hepatic cirrhosis (hepatitis B, 58 cases; hepatitis C, 1; female 21, male 38, mean age 45.5 years mean course 106 years) were included in. All patients were consonant with the following conditions: patients with hard hepato-splenomegaly and esophagogastric varices; patients with portal diameter >1.4cm with slight or without ascites, no upper digestive tract bleeding and hepatic encephalopathy. The patients who took vaso-active drugs such as propranolol, nifedipine and diuretics recently were asked to stop taking these medicines for a week before entering this study.

Grouping and course of treatment

All patients were divided into 4 groups. Group 1, RSM, 60g/day, 21 patients; group 2, RAS 30g, 15 patients; group 3, RSM 60g/day + nifedipine 30 mg/day, 12 patients; and group 4, RSM 60 g/day + nifedipine 30 mg/day + bloodsucker 3g/day, 11 patients. A whole day dose of RSM and RAS were added with 200ml water and immersed for 20 minutes and then added 600ml water, cooked with low intensity of fire for three times into 100ml and taken orally bid. Leech was baked and ground to fine powder and put in to capsules and taken orally, bid. Nifedipine 30mg, tid, was administered for 10 to 12 weeks.

Experimental apparatus and methods

The patients were examined by color Doppler ultrasoundography (detector head 3.5MHz) at dorsal position quietly at fast. The Dpv, Vpv, Dsv and Vsv were measured before and 2.6 and 10 weeks after treatment. Qpv and Qsv were calculated by the formula: $Q = \pi R^2 \cdot V \cdot 60$. Q: quantity of blood flow, R: half vein diameter (D/2), V: mean velocity of blood stream.

RESULTS

Animal model

Two of 12 dogs died at week 2 and 3 respectively due to infection and 3 dogs died between week 7 to 8 due to hepatic failure. Seven of 12 dogs developed into liver cirrhosis with ascites and abdominal varices, with body weight loss by 1/4 after bile duct ligation at week 5. All dogs had liver cirrhosis with a large amount of ascites, vein of greater omentum congested and abnormal liver function (Bil $83.5 \mu\text{mol/L} \pm 4.95 \mu\text{mol/L}$, ALT $211.67 \text{ U} \pm 44.8 \text{ U}$), there was a significant difference compared with normal animal, $P < 0.01$. The special characters of anatomy and histology were coincided to these of billiary cirrhosis. The mean portal pressure ($2.56 \text{ kPa} \pm 0.30 \text{ kPa}$) with cirrhosis were increased significantly compared with normal dogs (1.18 ± 0.02 , $P < 0.001$).

Effects of RSM and RAS on hemodynamics in health dogs

The portal and systemic circulation index in healthy dogs were not affected by intravenous administration of RSM and RAS. The MAP of dogs were lowered 5 - 10 minutes after RAS administration, but returned normal 60 minutes later. The portal pressure and MAP were decreased significantly 60 minutes after administration of nifedipine compared with those before the drug administration (Ppv $1.50 \text{ kPa} \pm 0.45 \text{ kPa}$ vs $1.27 \text{ kPa} \pm 0.61 \text{ kPa}$, $P < 0.05$; MAP $16.5 \text{ kPa} \pm 0.71 \text{ kPa}$ vs $16.21 \text{ kPa} \pm 0.19 \text{ kPa}$, $P < 0.05$).

Effects of RSM and RAS on hemodynamics in dogs with liver cirrhosis

The Ppv, WHVP and HVPg were decreased significantly in dogs with liver cirrhosis 60 minutes after administration of RSM and RAS ($P < 0.05$ - 0.01). The other indexes were not changed significantly, $P < 0.05$. The Ppv, MAP and HR decreased significantly 60 minutes after administration of nifedipine ($P < 0.01$), but HVPg was not changed significantly ($P > 0.05$). This result showed that RSM and RAS have selective effects on portal system in dogs with cirrhosis but without effects on blood pressure and HR, while nifedipine had effects on blood pressure, Ppv and HR (Table 1).

Comparison in effects of RSM, RAS and nifedipine on Ppv and HVPg

The Ppv in dogs with liver cirrhosis were decreased significantly 10 minutes after administration of RSM and nifedipine as compared with that before ($2.62 \text{ kPa} \pm 0.27 \text{ kPa}$ vs $2.45 \text{ kPa} \pm 0.28 \text{ kPa}$, $P < 0.05$, $2.42 \text{ kPa} \pm 0.05 \text{ kPa}$ vs $2.05 \text{ kPa} \pm 0.24 \text{ kPa}$, $P < 0.05$). Although RSM could lower Ppv but not statistically ($2.56 \text{ kPa} \pm 0.30 \text{ kPa}$ vs $2.43 \text{ kPa} \pm 0.39 \text{ kPa}$, $P > 0.05$).

Table 1 Effect of RSM, RAS and nifedipine on hemodynamics in dogs with liver cirrhosis(KPa)

	RSM treatment group		RAS treatment group	
	Before	After 60 min	Before	After 60 min
Ppv	2.56±0.30	1.82±0.33 ^b	2.42±0.05	1.38±0.32 ^b
FHVP	1.39±0.47	1.10±0.28	0.98±0.15	0.94±0.06
WHVP	2.17±0.36	1.70±0.30 ^b	2.33±0.09	1.90±0.33
HVPG	0.93±0.33	0.60±0.43 ^b	1.35±0.16	0.97±0.30
ICVP	1.02±0.34	0.99±0.29	1.05±0.35	1.02±0.32
MAP	13.75±2.40	13.30±2.34	14.07±3.18	13.13±2.48
HR(beat/min)	134.00±1.72	147.80±22.36	138.75±28.39	137.00±28.02

^a*P*<0.05, ^b*P*<0.01 *vs* compared with pretreatment.**Table 2** Comparison among the effect of RSM, RAS on Dpv HVPG

	RSM <i>vs</i> RAS		RSM <i>vs</i> nifedipine		RSM <i>vs</i> nifedipine	
	Ppv	HVPG	Ppv	HVPG	Ppv	HVPG
Treatment						
30 min	1.29	1.96	3.06	2.30	4.13 ^a	4.26 ^a
60 min	2.51		3.57 ^a		5.95 ^a	

^a*P*<0.05, *P*<0.01 *vs* compared in any two group.**Table 3** The effect of RSM, RAS and other drugs on portal hemodynamics in patients with liver cirrhosis

Group	Dpv (mm)		Dsv (m)		Qpv (ml/min)		Qsv (ml/min)	
	Before	10 weeks	Before	10 weeks	Before	10 weeks	Before	10 weeks
1	14.84±1.03	13.06±1.58 ^c	12.20±1.92	10.03±1.93 ^c	2346.95±1592.29	1686.93±1056.05 ^b	2065.50±1209.17	1421.38±924.99 ^b
2	14.80±0.92	14.37±0.09 ^b	11.10±1.67	10.38±0.186 ^b	1673.42±203.19	1564.49±267.08	1717.60±919.34	1099.04±744.82 ^a
3	15.03±1.29	13.62±0.09 ^c	11.78±3.16	10.97±0.28 ^b	2117.47±676.31	1753.40±593.46 ^a	1825.89±1151.13	1312.28±780.56 ^b
4	14.75±1.39	13.05±0.65 ^b	11.58±2.31	9.87±2.05 ^a	1794.74±641.06	1226.08±321.16 ^a	1781.92±1197.19	1087.74±70.45 ^a

Group 1: RSM; group 2: RAS; group 3: RSM nifedipine; group 4: RSM+bloodsucker+ nifedipine, compared in any two group ^a*P*<0.05 ^b*P*<0.01 ^c*P*<0.01.**Table 4** Comparison of the used drugs on Dpv

	Group 1-2	Group 1-3	Group 1-4	Group 2-3	Group 2-4	Group 3-4
Administration						
2 weeks	-0.254	-4.220 ^c	-2.637 ^a	-3.633 ^c	-2.265 ^a	0.881
6 weeks	3.042 ^b	-0.153	-2.635	-2.917 ^b	-2.941 ^b	-0.415
10 weeks	4.563 ^c	1.217	-0.098	-3.055 ^b	-3.628 ^c	-0.982

Group 1: RSM; group 2: RAS; group 3: RSM+nifedipine; group 4: RSM+leach+ nifedipine, compared in any two group.

^a*P*<0.05 ^b*P*<0.01 ^c*P*<0.01.

Table 2 shows that RAS has a more powerful effect in Ppv and HVPG 30 minutes after treatment than nifedipine ($P < 0.05$) whereas there was no significant difference in effects for Ppv and HVPG among RSM, RAS and nifedipine ($P > 0.05$). It is worthy noticing that RSM and RAS were more effective for Ppv 60 minutes after administration than nifedipine ($P < 0.05$), but there was no significant difference between RSM and RAS. The result demonstrated that the action of nifedipine on portal and blood pressure is quick and short whereas RSM and RAS last long in action but without effects on MAP and HR.

Clinical study

Effects of RSM and RAS on portal hemodynamics in patients with cirrhosis

The Qpv, Dsv, Qpv and Qsv in patients with cirrhosis were lowered significantly after using RSM ($P < 0.01-0.001$), while Dpv, Dsv and Qsv were decreased markedly after using RAS ($P = 0.05-0.01$), but no significant effects on Qpv ($P > 0.05$). The Dpv, Dsv, Dpv and Qsv were all decreased significantly in the groups of RSM + nifedipine and RSM + bloodsucker + nifedipine 10 weeks after treatment ($P < 0.05-0.01$). The velocity of blood flow of portal and spleen vein were not changed significantly ($P > 0.05$) (Table 3).

Comparison of effects of RSM, RAS on Dpv

Dpv decreased significantly in 2 weeks after treatment in the group RSM + nifedipine and group RSM + leech + nifedipine. The rank order in effect from strong to weak is RSM + leech + nifedipine > RSM and RSM + nifedipine > RAS ($P < 0.05-0.01$). (Table 4)

Side effects

There was no side effects in the group taking the medicinal herbs. A few patients had headache, dizziness and so on in the group taking herbs and nifedipine in combination, but all recovered after termination of medicine.

DISCUSSION

Calcium antagonist—nifedipine is one of the most common drugs used to lower portal hypertension, but it can also lower the blood pressure at large oral doses and some patients had bad tolerance to it. More and more attention has been paid to the better effect of RSM and RAS in portal hemodynamics in patients with hepatic cirrhosis. The present study showed that RSM and RAS used intravenously could lower Ppv (kPa, 2.56 ± 0.30 , 1.82 ± 0.33 , 2.43 ± 0.05 , 1.38 ± 0.32 , $P < 0.01$), WHVP (kPa, 2.17 ± 0.36 , 1.70 ± 0.30 ; 2.33 ± 0.09 , 1.90 ± 0.33), and HVPG (kPa, 0.93 ± 0.33 , 0.60 ± 0.43 ; 1.35 ± 0.16 , 0.97 ± 0.30) in dogs with experimental liver cirrhosis, but without any influence on MAP and HR in normal dogs. Although nifedipine could

reduce Ppv, WHVP and HR in dogs with liver cirrhosis, RSM and RAS had more powerful effects in lowering portal hypertension and without effect on systemic pressure as compared with nifedipine. The combination of RSM, RAS, RSM + nifedipine, RSM + nifedipine + leech could reduce Dpv, Dsv, Qpv and Qsv in patients with liver cirrhosis. RSM and RAS could also improve the patients' symptoms and liver function. Rapid and prolonged effects could be obtained, when combined therapy of the herbal medicine and western drugs was used. This should be further studied. The effects of nifedipine in lowering portal hypertension is rapid, which appeared 10 minutes after intravenous and 2 weeks oral administration but with the disadvantage of reducing the blood pressure and HR. The effect of intravenous RAS in reducing Ppv in dogs with liver cirrhosis became stronger than nifedipine with the prolonged time of drug administration ($P < 0.05$), but without changes of blood pressure and HR. Although the effect of RSM in reducing portal hypertension appeared in 30 minutes intravenously and 6 weeks orally it last longer and became stronger, and peaking at 60 minutes intravenously ($2.56 \text{ kPa} \pm 0.30 \text{ kPa}$, $1.82 \text{ kPa} \pm 0.33 \text{ kPa}$, $P < 0.01$) and 10 weeks orally ($14.84 \text{ kPa} \pm 1.03 \text{ kPa}$, $13.06 \text{ kPa} \pm 1.58 \text{ kPa}$, $P < 0.001$). The result showed a long course of treatment or intravenous administration is necessary in RSM. The effect of combination of RSM, leech and nifedipine in treatment of portal hypertension appeared rapidly and more powerful, which is a drug regimen of choice for patients with high Ppv.

The mechanism of RSM and RAS in lowering portal hypertension has not been well understood yet. RSM can prevent from liver fibrosis if it is used for a long time. It was reported that RSM can inhibit fibroblast cells. Large doses of RSM can activate collagenase and help blockage the extracellular matrix^[4]. The value P-III-P and lamin were decreased in patients with liver disease after oral treatment of RSM. The present study demonstrated that long-term oral treatment of RSM for 10-12 weeks can reduce the portal vein and spleen diameters and blood flow, but the velocity of blood flow did not change. The effect become more and more powerful with time. The present study suggested that combination of RSM, RAS, leech and nifedipine is effective in lowering hypertension and without side effects in treatment of liver cirrhosis.

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