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RAPID COMMUNICATION

Therapeutic effect of traditional Chinese medicine on coagulation disorder and accompanying intractable jaundice in hepatitis B virus-related liver cirrhosis patients

Yang-Mei Li, Hong-Zhi Yang, Wei-Bing Guan, Qian-Shan Ke, Min Dai, He-Ping Xie, Shi-Jun Zhang

Yang-Mei Li, Hong-Zhi Yang, Wei-Bing Guan, Qian-Shan Ke, Min Dai, He-Ping Xie, Department of TCM, The Third Affiliated Hospital of Sun Yat-Sen University, 600# Tianhe Road, Guangzhou 510630, Guangdong Province, China
Shi-Jun Zhang, Department of TCM, The First Affiliated Hospital of Sun Yat-Sen University, 58# Zhongshan Er Road, Guangzhou 510080, Guangdong Province, China
Author contributions: Li YM and Yang HZ contributed equally to this work, designed and overviewed the research; Li YM, Zhang SJ and Xie HP analyzed the data; Li YM, Ke QS, Guan WB and Dai M performed the research; Li YM wrote the paper.
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Correspondence to: Hong-Zhi Yang, Department of TCM, The Third Affiliated Hospital of Sun Yat-Sen University, 600# Tianhe Road, Guangzhou 510630, Guangdong Province, China. hzyang1960@163.com
Telephone: +86-13318815024 Fax: +86-20-85253336
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Abstract

AIM: To observe the therapeutic effects of new traditional Chinese medicine (TCM) therapy on coagulation disorder and accompanying intractable jaundice in HBV-related liver cirrhosis patients.

METHODS: Using stratified random sampling according to fibrinogen (Fib) levels, 145 liver cirrhosis patients due to hepatitis B complicated by coagulation disorder were treated. Of them, 70 in research group were treated with TCM by "nourishing yin, cooling blood and invigorating blood circulation" and Western medicine, 75 in control group were treated with conventional Western medicine. The indexes of liver function, coagulation function and bleeding events were observed and compared.

RESULTS: The prothrombin time (PT) was shorter and the fibrinogen (Fib) level was higher in the research group than in the control group (Fib = 1.6-2.0 g/L, 1.1-1.5 g/L, and ≤ 1.0 g/L). The total bilirubin (TBIL) level was significantly lower in the research group than in the control group, except for the subgroup of FIB ≤ 1.0 g/L.

CONCLUSION: TCM therapy can improve coagulation function and decrease TBIL.

Key words: Combination of traditional Chinese and Western medicine; Liver cirrhosis; Coagulation disorder; Nourishing yin; Cooling blood and invigorating blood circulation

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INTRODUCTION

About 25% of hepatitis B virus (HBV)-infected patients would die of severe chronic liver diseases such as liver cirrhosis and liver failure[1]. Coagulation disorder is prevalent in patients with chronic liver disease which is usually detected in laboratory tests and characterized by prolonged prothrombin time (PT), decreased fibrinogen (Fib, coagulation factor Ⅰ) level and thrombocytopenia[2]. For the lack of blood products (plasma and coagulation factor) and high medical expenditure, economical and effective treatment modalities for coagulation disorder are demanded. Moreover, intractable jaundice accompanying coagulation disorder in HBV-related liver cirrhosis patients is also a puzzle and there is no effective treatment for it. We have proved in our prophase researches that coagulation function indexes are significantly related to total bilirubin (TBIL). Therefore, this study was to observe the therapeutic effects of traditional Chinese medicine (TCM) on coagulation disorder and accompanying intractable jaundice in HBV-related liver cirrhosis patients.

MATERIALS AND METHODS

Inclusion criteria

Patients with HBV-related liver cirrhosis[3,4], patients with

coagulation disorder (PT > 14.5 s, fib < 2.0 g/L with or without platelets < 100×10^9/L before admission), patients with no bleeding events (such as epistaxis, gum bleeding, hematemesis and hematochezia before admission), and those at the age of 20-75 years, were included in the study.

Exclusion criteria

Patients with coagulation disorders accompanying liver cirrhosis due to different reasons (such as parasitic infection, autoimmune liver disease, intrahepatic cholestasis, alcoholic liver disease, drug-induced liver disease, fatty liver disease, liver hereditary diseases and liver vascular diseases), patients with other hepatovirus superinfection, haemolysis, disseminated intravascular coagulation (DIC), complications of severe diseases (such as cardio-cerebrovascular disease, hematological disease, respiratory disease, urinary disease and psychosis), and those with pregnancy and lactation, patients with poor compliance, incomplete clinical data, hospitalization time < 14 d, were excluded from the study.

All patients were given their informed consent before therapy.

Information about patients

All the 145 patients with HBV-related liver cirrhosis accompanying coagulation disorder were randomly chosen according to their Fib levels from the Third Affiliated Hospital of Sun Yat-Sen University from January 2002 to February 2008. The data were collected and analyzed retrospectively. The 145 patients were assigned to three subgroups

Subgroup A: Sixty patients (Fib = 1.6-2.0 g/L) were divided into in research group and control group (n = 30). There were 20 males and 10 females in the research group, their average age was 49.83 ± 12.32 years and the average hospitalization time was 35.73 ± 24.20 d. There were 21 males and 9 females in the control group, their average age was 44.67 ± 10.34 years and the average hospitalization time was 36.83 ± 18.15 d.

Subgroup B: Sixty patients (Fib = 1.1-1.5 g/L) were divided into research group and control group (n = 30). There were 20 males and 10 females in the research group, their average age was 50.27 ± 11.71 years and the average hospitalization time was 37.10 ± 19.94 d. There were 21 males and 9 females in the control group, their average age was 49.60 ± 10.45 years and the average hospitalization time was 30.37 ± 16.81 d.

Subgroup C: Twenty-five patients (Fib ⩽ 1.0 g/L) were divided into research group (n = 10) and control group (n = 15). There were 7 males and 3 females in the research group, their average age was 40.80 ± 8.92 years and the average hospitalization time was 41.70 ± 27.57 d. There were 10 males and 5 females in the control group, their average age was 43.20 ± 10.17 years and the average hospitalization time was 54.93 ± 37.10 d.

Methods

Control group: Patients in the control group were treated with conventional Western medicine supplemented with coagulation factors and platelets. Artificial liver system therapy and liver transplantation were not performed.

Research group: Patients in the research group were treated with TCM by nourishing yin, cooling blood and invigorating blood circulation (basic prescription: Yiwei Decoction and Dahuang Zhechong Pills: shashen 15 g, maidong 15 g, shengdi 30 g, yuzhu 15 g, dahuang 6-30 g, huangqin 12 g, gancao 6 g, taoren 9 g, xingren 12 g, shaoyao 12 g, shuizhi 6 g, tubiechong 6 g), in combination with conventional Western medicine. The prescription was modified if symptoms changed.

The herbal decoction was taken half an hour after each meal, one dose a day for 2-3 wk according to the severity of liver cirrhosis.

Observation indexes

Observations included serological index, coagulation function (PT, Fib and PLT), liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB) and TBIL], bleeding events and other complications, death rate and side effects during the treatment.

Statistic analysis

Statistical analysis was performed using Spss11.5. Data were expressed as mean ± SD and analyzed by t-test. Numeration data were analyzed by chi square test. $P < 0.05$ (two-sided test) was considered statistically significant.

RESULTS

Analysis of comparability

Fib level was used as the standard for all the patients who were divided into three subgroups. Chi square test and t-test showed that the general conditions of patients in the research and control groups were similar (Table 1). The serological indexes of coagulation function, liver function and the severity of liver cirrhosis were similar in the two groups before treatment (Tables 2-4). Improvement in coagulation function of the three subgroups was comparable.

Analysis of data

PT, Fib and TBIL levels were significantly higher in subgroups (Fib = 1.6-2.0 g/L and Fib = 1.1-1.5 g/L) of the research group than those in subgroup of the control group after treatment. There was no significant difference in ALB and PLT between the groups (Tables 5 and 6).

PT and Fib levels were significantly higher in subgroups (Fib ⩽ 1.0 g/L) of the research group were significantly higher than those in subgroups of the control group after treatment. There was no significant difference in ALB, PLT and TBIL between the two groups (Table 7).

Bleeding events occurred in 3 patients of the

Table 1 Balance test for general information

		Cases (*n*)	Sex (male/female)	Age (mean ± SD)	Days of hospitalization (mean ± SD)
Fib (1.6-2.0 g/L) level	Research group	30	20/10	49.83 ± 12.32	35.73 ± 24.20
	Control group	30	21/9	44.67 ± 10.34	36.83 ± 18.15
	P value		0.781	0.084	0.843
Fib (1.1-1.5 g/L) level	Research group	30	20/10	50.27 ± 11.71	37.10 ± 19.94
	Control group	30	19/11	49.60 ± 10.45	30.37 ± 16.81
	P value		0.787	0.817	0.128
Fib (≤ 1.0 g/L) level	Research group	10	7/3	46.80 ± 8.92	41.70 ± 27.57
	Control group	15	10/5	43.20 ± 10.71	54.93 ± 37.10
	P value		1.000	0.389	0.346

Anyone in the three subgroups divided by the standard Fib level, age, sex and days of hospitalization was balanced between research and control groups before treatment.

Table 2 Balance test for indexes of coagulation function before treatment (mean ± SD)

		Fib (g/L)	PT (s)	PLT (10^9/L)
Fib (1.6-2.0 g/L) level	Research group	1.68 ± 0.18	20.52 ± 3.12	69.07 ± 32.57
	Control group	1.72 ± 0.15	21.01 ± 3.31	83.60 ± 56.41
	P value	0.279	0.563	0.227
Fib (1.1-1.5 g/L) level	Research group	1.25 ± 0.13	22.27 ± 2.18	59.87 ± 29.90
	Control group	1.29 ± 0.11	22.60 ± 5.75	71.67 ± 24.24
	P value	0.138	0.765	0.099
Fib (≤ 1.0 g/L) level	Research group	0.77 ± 0.19	26.59 ± 5.39	62.80 ± 33.19
	Control group	0.79 ± 0.18	31.49 ± 8.68	73.27 ± 57.34
	P value	0.861	0.127	0.608

Anyone in the three subgroups divided by the standard Fib level and the indexes of coagulation function was balanced between research and control groups before treatment.

Table 3 Balance test for indexes of liver function before treatment (mean ± SD)

		ALT (U/L)	AST (U/L)	TBIL (μmol/L)	ALB (g/L)
Fib (1.6-2.0 g/L) level	Research group	180.90 ± 255.59	163.17 ± 176.13	104.51 ± 65.26	32.79 ± 4.69
	Control group	241.87 ± 349.01	190.87 ± 191.11	126.97 ± 61.69	33.47 ± 3.72
	P value	0.089	0.562	0.176	0.537
Fib (1.1-1.5 g/L) level	Research group	118.57 ± 121.99	144.37 ± 113.62	129.71 ± 95.70	31.74 ± 4.69
	Control group	234.07 ± 392.07	232.87 ± 265.04	169.95 ± 156.22	29.59 ± 5.54
	P value	0.129	0.098	0.234	0.111
Fib (≤ 1.0 g/L) level	Research group	74.40 ± 30.89	92.40 ± 78.44	198.40 ± 123.37	29.60 ± 3.82
	Control group	181.67 ± 283.59	142.80 ± 128.34	245.57 ± 193.69	30.15 ± 6.61
	P value	0.249	0.280	0.503	0.817

Anyone in the three subgroups divided by the standard of Fib level and the indexes of liver function was balanced between research and control groups before treatment.

Table 4 Balance test for related clinical materials before treatment

		Combined with ascites liquid	Combined with hepatic encephalopathy	Combined with infection	Combined with liver cancer
Fib (1.6-2.0 g/L) level	Research group	10	0	8	5
	Control group	15	3	15	2
	P value	0.190	0.236	0.063	0.421
Fib (1.1-1.5 g/L) level	Research group	17	1	10	6
	Control group	20	0	13	2
	P value	0.426	1.000	0.426	0.255
Fib (≤ 1.0 g/L) level	Research group	8	1	4	0
	Control group	12	1	5	1
	P value	1.000	1.000	0.734	1.000

Anyone in the three subgroups divided by standard Fib level, and clinical materials such as complications was balanced between research and control groups before treatment.

Table 5 Fib (1.6-2.0 g/L) level and serum index before and after treatment (mean ± SD)

		Fib (g/L)	PT (s)	PLT (10^9/L)	TBIL (μmol/L)	ALB (g/L)
Research group 30 cases	Before treatment	1.68 ± 0.18	20.52 ± 3.12	69.07 ± 32.57	104.51 ± 65.26	32.79 ± 4.69
	After treatment	1.95 ± 0.43	17.66 ± 2.38	80.10 ± 42.12	34.44 ± 17.10	36.32 ± 3.98
Control group 30 cases	Before treatment	1.72 ± 0.15	21.01 ± 3.31	83.60 ± 56.41	126.97 ± 61.69	33.47 ± 3.72
	After treatment	1.64 ± 0.44	19.07 ± 7.13	67.63 ± 42.65	113.60 ± 163.86	35.69 ± 5.21
P value		< 0.0001	< 0.0001	0.259	0.008	0.604

PT, Fib and TBIL were significantly higher in the research group than in the control group after treatment.

Table 6 Fib (1.1-1.5 g/L) level before and after treatment (mean ± SD)

		Fib (g/L)	PT (s)	PLT (10^9/L)	TBIL (μmol/L)	ALB (g/L)
Research group 30 cases	Before treatment	1.25 ± 0.13	22.27 ± 2.18	59.87 ± 29.90	129.71 ± 95.70	31.74 ± 4.69
	After treatment	1.72 ± 0.33	18.45 ± 2.11	59.50 ± 27.86	46.75 ± 19.83	36.46 ± 3.83
Control group 30 cases	Before treatment	1.29 ± 0.11	22.60 ± 5.75	71.67 ± 24.24	169.95 ± 156.22	29.59 ± 5.54
	After treatment	1.29 ± 0.41	20.56 ± 9.99	68.37 ± 27.20	130.95 ± 180.92	35.51 ± 4.75
P value		< 0.0001	0.032	0.217	0.014	0.399

PT, Fib and TBIL were significantly higher in the research group than in the control group after treatment.

Table 7 Fib (≤ 1.0 g/L) level before and after treatment (mean ± SD)

		Fib (g/L)	PT (s)	PLT (10^9/L)	TBIL (μmol/L)	ALB (g/L)
Research group 10 cases	Before treatment	0.77 ± 0.19	26.59 ± 5.39	62.80 ± 33.19	198.40 ± 123.37	29.60 ± 3.82
	After treatment	1.29 ± 0.35	23.29 ± 5.35	54.80 ± 37.42	77.85 ± 39.21	35.31 ± 5.07
Control group 10 cases	Before treatment	0.79 ± 0.18	31.49 ± 8.68	73.27 ± 57.34	245.57 ± 193.69	30.15 ± 6.61
	After treatment	0.90 ± 0.36	39.08 ± 22.78	70.93 ± 54.06	173.47 ± 149.30	35.86 ± 5.71
P value		0.013	0.043	0.421	0.061	0.807

PT and Fib were significantly higher in the research group than in the control group after treatment.

research group and in 19 patients of the control group ($P < 0.0001$).

DISCUSSION

Fib, which has coagulation function, is a kind of protein that is synthesized in the liver. Fib, the most important coagulation factor in human body, is transformed into fibrin in the coagulation process. Fib decrease is a sensitive change in chronic hepatitis patients, which means that the biological enzyme is declined and the coagulation function is abnormal[5]. Fib can also be used to diagnose DIC caused by liver diseases. It was reported that Fib contents are closely related with the damage degree of hepatocytes, the severity and prognosis of liver cirrhosis[6-10]. Therefore, Fib was chosen as a criterion in this research.

TCM believes that the original etiological factor for HBV infection is "damp-heat", which belongs to the category of warm pathogens. By analyzing and differentiating the development of an epidemic febrile disease and by studying conditions of the four systems (Wei, Qi, Ying, Xue) of patients with coagulation disorder, Yingfen syndrome and Xuefen syndrome are diagnosed. As one of the febrile disease characteristics, warm pathogen can injure yin easily, meanwhile "cooling the blood and invigorating blood circulation" is the traditional therapeutic method for Xuefen syndrome. Therefore, we chose TCM to treat liver cirrhosis accompanying coagulation disorder by nourishing yin, cooling the blood and invigorating blood circulation.

This study showed that TCM therapy for liver cirrhosis could improve PT and Fib, and reduce occurrence of bleeding events by improving microcirculation, increasing blood and oxygen supply to the liver, thus promoting regeneration and restoration of hepatocytes. It was reported that this new TCM therapy has anti-thrombosis effects by relieving the microangium spasm and hypercoagulable state in the liver[11-15]. Heat-clearing and blood-cooling drugs can stimulate pituitary-adrenal axis, enhance stress capability, dredge microcirculation, protect vessel wall, and maintain the balance between coagulation and anti-substance[14], suggesting that such drugs can promote cell proliferation and speed up cell cycle progression. This new TCM therapy can alleviate hepatocellular immune injury caused by HBV infection and degenerative necrosis of hepatocytes. It was reported that blood circulation promoting therapy can inhibit cellular and humoral immunity. Herbal medicine for cooling the blood and invigorating blood circulation can alleviate immune injury by inhibiting autoimmune effect and γ-globulin[12,14,15], and damaged hepatocytes and vascular endothelial cells caused by endotoxmia and inflammatory factors. Studies showed that nourishing yin, cooling the blood and invigorating blood circulation can antagonize apoptosis of vascular endothelial cells

induced by endotoxin[16-18]. The reason why PLT does not ameliorate is that coagulation disorder in patients with HBV-related liver cirrhosis is usually accompanied with hypersplenia and PLT is severely destroyed and phagocytosed by the spleen. In addition, PLT does not come from liver but from bone marrow megakaryocytes.

This study also showed that the new TCM therapy could significantly decrease TBIL. TCM believes that jaundice would not regress easily if only the blood circulation is fluent. Since the pathogenesis of jaundice is blood stasis which is one of the pathogenic factors for coagulation disorder in liver cirrhosis patients, the new TCM therapy can achieve the purpose of treating different diseases with the same method. On the one hand, it can improve hepatocyte function by exerting its anti-thrombosis microcirculation effect and by improving the blood circulation of liver. On the other hand, it can promote biliary excretion by inhibiting immunologic reaction, alleviating inflammation of intrahepatic bile ducts, which can improve the coagulation disorder in liver cirrhosis patients and decrease jaundice. The reason why TBIL can be decreased only when Fib > 1.0 g/L, may be due to the impaired liver function, a short course of treatment and a relative small sample.

In conclusion, this new TCM therapy can improve coagulation function indexes, such as PT and Fib in patients with HBV-related liver cirrhosis and reduce bleeding events which can also decrease TBIL.

COMMENTS

Background

Hepatitis B virus (HBV) infection is prevalent all over the world and 2000 million people have been infected with HBV, 350 million of them are chronic HBV carriers and 25% of HBV-infected individuals will die of chronic severe liver diseases. Coagulation disorder is an important clinical feature of chronic liver disease characterized by prolonged PT, decreased Fib and thrombocytopenia. HBV infection usually leads to bleeding, anaemia, decreased granulocytes, thrombosis and even multiple organ failure,*etc*. Plasma infusion can improve coagulation disorder. We performed this study to find a new traditional Chinese medicine (TCM) therapy for coagulation disorder in patients with HBV-related liver cirrhosis.

Research frontiers

Conventional treatment modalities for coagulation disorders in Western medicine are to improve liver function, avoid using drugs which can affect platelet function and aggravate coagulation disorder, and supply vitamin K, coagulation factors and platelets. Due to the disadvantages of blood products, such as limited supply, allergic reaction and virus infection during infusion, the third generation recombinant coagulation factor VIIa (rhVIa) is a highlight and has been used in clinical practice. In the field of TCM, promoting blood circulation to remove blood stasis for coagulation disorder can increase fibrinogen (Fib), improve prothrombin time (PT) and eliminate complications.

Innovations and breakthroughs

Fib level was used as a criterion to observe the new TCM therapeutic effects on coagulation disorder in patients with HBV-related liver cirrhosis. Early treatment of coagulation disorder by nourishing yin, cooling the blood and invigorating blood circulation before occurrence of bleeding events can reduce bleeding events and prevent disseminated intravascular coagulation (DIC). Meanwhile, this TCM therapy could improve coagulation function and decrease total bilirubin (TBIL).

Applications

The present study confirmed that the TCM therapy by nourishing yin, cooling the blood and invigorating blood circulation focusing on the pathogenic factors and pathogenesis of coagulation disorders in patients with HBV-related liver cirrhosis, could improve coagulation function, decrease TBIL. Therefore, it can be used in the treatment of chronic liver diseases.

Peer review

Deterioration of coagulation function is a serious problem in liver cirrhosis patients. This new TCM therapy is encouraging and interesting with satisfactory therapeutic effects on serum prothrombin, fibrinogen and TBil in patients with HBV-related liver cirrhosis.

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