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Multicenter clinical study on Fuzhenghuayu capsule against liver fibrosis due to chronic hepatitis B

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Abstract

AIM: To study the efficacy and safety of Fuzhenghuayu capsule (FZHY capsule, a capsule for strengthening body resistance to remove blood stasis) against liver fibrosis due to chronic hepatitis B.

METHODS: Multicenter, randomized, double blinded and parallel control experiment was conducted in patients (aged from 18 to 65 years) with liver fibrosis due to chronic hepatitis B. Hepatic histologic changes and HBV markers were examined at wk 0 and 24 during treatment. Serologic parameters (HA, LM, P-III-P, IV-C) were determined and B ultrasound examination of the spleen and liver was performed at wk 0, 12 and 24. Liver function (liver function and serologic parameters for liver fibrosis) was observed at wk 0, 6, 12, 18 and 24. Blood and urine routine test, renal function and ECG were examined before and after treatment.

RESULTS: There was no significant difference between experimental group (110 cases) and control group (106 cases) in demographic features, vital signs, course of illness, history for drug anaphylaxis and previous therapy, liver function, serologic parameters for liver fibrosis, liver histologic examination (99 cases in experimental group, 96 cases in control group), HBV markers, and renal function. According to the criteria for liver fibrosis staging, mean score of fibrotic stage(s) in experimental group after treatment (1.80) decreased significantly compared to the previous treatment (2.33, $P<0.05$), but there was no significant difference in mean score of fibrotic stage(s) (2.11 and 2.14 respectively). There was a significant difference in reverse rate between experimental group (52%) and control group (23.3%) in liver biopsy. With marked effect on decreasing the mean value of inflammatory activity and score of inflammation ($P<0.05$), Fuzhenghuayu capsule had rather good effects on inhibiting inflammatory activity and was superior to that of Heluoshugan capsule. Compared to that of pretreatment, there was a significant decrease in HA, LM, P-III-P and IV-C content in experimental group after 12 and 24 wk of treatment. The difference in HA, LM, P-III-P and IV-C content between 12 and 24 wk of treatment and pretreatment in experimental group was significantly greater than that in control group ($P<0.01$-0.05). The effect, defined as two of four parameters lowering more than 30% of the baseline, was 72.7% in experimental group and 27.4% in control group ($P<0.01$). Obvious improvement in serum Alb, ALT, AST and GGT was seen in two groups. Compared to that of control group, marked improvement in GGT and Alb was seen in experimental group ($P<0.05$). The effective rate of improvement in serum ALT was 72.7% in experimental group and 59.4% in control group. No significant difference was seen in blood and urine routine and ECG before and after treatment. There was also no significant difference in stable rate in ALT and serologic parameters for liver fibrosis between experimental group and control group after 12 wk of withdrawal.

CONCLUSION: Fuzhenghuayu capsule has good therapeutic effects on alleviating liver fibrosis due to chronic hepatitis B without any adverse effect and is superior to that of Heluoshugan capsule.

Key words: Chronic hepatitis B; Fuzhenghuayu capsule

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INTRODUCTION

Liver fibrosis, characterized by overproduction and deposition of extracellular matrix in liver tissue, is a healing response to chronic injuries, and through which, chronic hepatitis develops into cirrhosis. Nowadays prevention and reverse of liver fibrosis are a rather important therapeutic strategy, since we still lack the special and effective therapy for primary diseases with liver fibrosis. In the past 20 years, based on the pathogenesis of chronic hepatitis as a dual deficiency of Qi and Yin, static blood blocking vessels and pestilent damp-heat lingering, we composed Fuzhenghuayu recipe directed by the therapeutic method of invigorating blood transforming stasis and boosting essence supplementing deficiency. The previous clinical trials revealed that the recipe could significantly improve clinical symptoms in patients with liver fibrosis due to chronic hepatitis B, improve liver functions, decrease portal pressure and effectively reverse tissue fibrosis[1]. Also, it has been shown that the recipe could enhance serum albumin level in patients with post-hepatitis cirrhosis, improve serum fibrotic markers and adjust immune function[2]. In this study, we conducted a multicenter, randomized, double blinded and parallel control experiment on 216 patients with liver fibrosis due to chronic hepatitis B (110 cases in experimental group, 106 in control group, among them 99 cases in experimental and 96 in control group received histologic diagnosis) in five centers to confirm the efficacy and safety of Fuzhenghuayu recipe against liver fibrosis due to chronic hepatitis B.

MATERIALS AND METHODS

Trial design

Multicenter, randomized, double blinded and parallel control (Heluoshugan capsule) clinical experiment was conducted to investigate the efficacy and safety of Fuzhenghuayu capsule against liver fibrosis due to chronic hepatitis B. Volunteers were selected and enrolled for 24-wk observation. All endpoints were evaluated before and 6, 12, 18 and 24 wk after administration of Fuzhenghuayu capsule respectively.

Case selection

Patients were diagnosed as liver fibrosis due to chronic hepatitis B according to diagnostic standard as follows[3]: (1) History with chronic hepatitis B $\geqslant$6 mo, abnormal ALT $\geqslant$10-folds of normal level and TBil $\leqslant$54 μmol/L; (2) Serum markers for liver fibrosis, including hyaluronic acid (HA), laminin (LM), type III procollagen (P-III-P) and type IV collagen (IV-C) were $\geqslant$normal value±2SD; (3) B ultrasound examination accorded with changes in chronic hepatitis, including increased dense, coarse and enhanced echo of liver; (4) Liver histologic examination accorded with diagnostic criteria for chronic hepatitis, including inflammatory grading degrees (G1-G4) and liver fibrosis staging scores (S1-S4); and (5) symptoms, including pain in hepatic region, fatigue, poor appetite, abdominal distension, liver and spleen tumescence, facies hepatica, liver palm, and spider angioma.

Those satisfied the 1st item and the 2nd item, or the 1st item and the 4th item, or the two positive parameters in the 2nd item could be diagnosed as liver fibrosis due to chronic hepatitis B.

Subject inclusion criteria Patients satisfied diagnostic standard and simultaneously met the qualifications including age (range from 18 to 65 years, no sex limitation) and signing of informed consent form.

Subject exclusion criteria The patients were excluded under the following conditions: (1) TBil $>$54 μmol/L, diagnosed as severe hepatitis B or had the tendency to develop fulminant chronic hepatitis B; (2) Complicated by serious cardiovascular, renal, endocrine, hematologic, nervous and mental disease; (3) Alcoholic, drug induced, infectious, inherited, immune and other viral liver diseases; (4) Women with pregnancy or during lactation; (5) Decompensated post-hepatitis cirrhosis; and (6) Received interferon-γ, antiviral or immunomodulator treatment in the latest 3 mo.

Subject withdrawal criteria Patients failed to follow instructions for administration and observation, or withdrew from therapy without medical reasons, or had incomplete data.

Experimental protocol

Case resource All cases were from inpatient and outpatient department, and various factors for outpatients should be controlled strictly to guarantee planned administration and observation.

Randomization methods Complete randomized principles were employed. Cases were numbered from the 1st to the 240th and divided randomly by SAS software into experimental and control groups. Cases were assigned to five centers according to the admission order.

Protocol for administration With specification of 1.6 g per capsule and Lot# 9912220002 and used as an experimental drug, consisted of *Cordyceps sinesis, Peach kernel, Salvia, Gynostemma, etc*., Fuzhenghuayu capsule was provided by Shanghai Sundise Medicine Technology Development Co. Ltd. With specification of 0.93 g per capsule and used as a control drug, Heluoshugan capsule consisted of *largehead atractylodes rhizome, white peony, nutgrass galingale rhizome, Chinese angelica, papaya, common burreed rhizome, zedoary, turtle shell, Dung beetle, etc.*

Experimental and control drugs were same in appearance, shape, size, color and luster, package and label, *etc*. Two drugs were numbered randomly and five capsules were taken orally once, thrice a day. After 24 wk of treatment, patients were followed up for 12 wk. Patients were forbidden to take any kind of medications that could affect therapeutic effect on liver fibrosis.

Blinding method

Blinding methods included double blind, results were disclosed blindly twice and medications were dispensed according to randomization charts.

Parameters observed

In this study, efficacy and safety assessment were performed.

Assessment of efficacy

Efficacy was assessed from the following aspects:

Primary parameters

Histologic examination Liver biopsy was conducted before and after treatment. Grade and stage scoring were conducted in accordance with "1995 viral hepatitis preventing and treating protocol"[1] and "protocol for scoring activity and degree of fibrosis due to chronic hepatitis"[2]. Liver tissues were embedded in paraffin and stained with HE, reticular fiber staining and collagen staining (VG) were microscopically observed by three pathologists respectively, then histologic diagnosis was established if at least two experts reached an agreement.

Serum markers for hepatic fibrosis Serum markers including HA, LM, P-III-P, and IV-C were measured before treatment, after 12 and 24 wk of treatment and at 12 wk of follow up. Serum samples were assayed with the same batch kit at the same clinical center. HA and LM were assayed by radioimmunoassay (RIA) with the kit from Institute of Naval Medicine, IV-C by ELISA with the kit produced by Shanghai Shigao Biotech Company and P-III-P by RIA with the kit from Orion Company (Finland).

Second parameters

B ultrasound examination and liver function B ultrasound examination and serum parameters of liver function, including AST, ALT, GGT and ALP activity, Alb and TBil/Dbil content determination, were performed before and after 12 and 24 wk of treatment, and at the end of 12 wk of follow up. Serum HBV markers, including HBeAg, HBeAb and HBcAg, were detected with RIA and ELISA, and HBV-DNA with dot blot or PCR.

Safety assessment

Clinical findings manifested as rash, fever, diarrhea, nausea and poor appetite due to administration were carefully evaluated. Blood and urine routine, renal function (BUN and Cr) and ECG were examined before and after treatment.

Requirements for observation and record

Personnel carrying out clinical test should have substantial clinical and research backgrounds in this field and at least intermediate professional title. Appointed technicians performed the laboratory assays. Except for routine examination, blood and liver tissue samples with the size of 0.2 cm×1.5 cm or five hepatic lobules should be obtained before and after treatment. Liver samples were fixed in 100 mL/L neutral formalin. Patients with 10-folds of ALT activity than the upper threshold of normal level after 4 wk of treatment should take enzyme-deactivating drugs, which had no effect on liver fibrosis until termination of treatment. Patients with high ALT levels (10-folds of the upper threshold of normal level) and high TBil contents (more than 85.5 μmol/L) after 1.5 mo should withdraw from therapy and their treatment protocol should be modified.

Summarization of data

At the end of trial, all original data were submitted to statistical experts for further analysis.

Criterion for short-term therapeutic effect Very effective after treatment, liver fibrotic stage decreased by two or more scores, two among the four serum fibrotic markers (IV-C, HA, LM and P-III-P) decreased by more than 30% of the values before treatment and serum ALT returned to normal. Effective: After treatment, liver fibrotic stage decreased by one score, two out of the four serum fibrotic markers (IV-C, HA, LM and P-III-P) decreased by more than 20% of the values before treatment and ALT lowered to 50% of the value before treatment. Ineffective: No obvious improvement was seen.

Criterion for assessing long-term therapeutic effect After 12 wk of follow up, fibrotic markers, liver function and TCM syndromes were observed, long-term therapeutic effect was defined as stability or instability. Stability referred to the increase of fibrotic markers and serum ALT level being less than 20% at the end of treatment, while instability meant that the fibrotic markers and ALT levels increased more than 20% at the end of treatment.

Statistical analysis

Statistical analysis was performed with 6.12 SAS software. χ^2 test, t test and non-parametric statistical test were employed for comparison between two groups before experiment. For self-comparison in each group, variance and non-parametric statistical test were employed to compare therapeutic effect before and after administration in experimental and control groups. For comparison between two groups including comparison of efficacy and safety, central effect oriented variance analysis model (double factors) was employed for quantitative data and central effect-oriented CMH method was employed for classified data. Descriptive analysis was used for safety analysis.

Drugs in each group were known only after statistical analysis was finished.

RESULTS

General condition of the subjects

Enrolment and fulfilment The withdrawal rate of patients (six patients) was 2.7%, a total of 222 subjects were enrolled according to the protocol and among them 216 fulfilled the trial. All the subjects enrolled were eligible for the entry criteria.

Comparison between two groups before treatment There was no significant difference between experimental group (110 cases) and control group (106 cases) in demographic features, vital signs, disease history and seriousness (liver function, serum fibrotic markers, liver histological examination, HBV markers, and ultrasound scores, *etc.*). Blood, and urine routine and ECG were normal in all subjects before treatment (Tables 1-4).

Histologic changes

Variation of inflammation and fibrosis in liver biopsy A total of 195 cases received liver biopsy (99 in experimental group and 96 in control group) before treatment, among them 93 cases received the second biopsy after therapy (50 in trial group, 43 in control group). There was no difference

Table 1 General information in two groups before treatment (mean±SD)

Group	*n*	Sex M/F	Age (yr)	Marriage single/married	Weight (kg)	Previous treatment (case)	Treated with other drugs (case)
Experimental	110	95/15	37.7±9.2	21/89	64.30±8.25	11	26
Control	106	89/17	38.5±8.9	15/91	64.09±6.64	17	26
P		0.848	0.512	0.361	0.844	0.155	0.174

Table 2 Blood and renal routine and PT in two groups before treatment (mean±SD)

Group	*n*	RBC (10^{12}/L)	Hemoglobin (g/L)	WBC (10^9/L)	Platelet (10^9/L)	BUN (mmol/L)	Cr (μmol/L)	PT (s)
Experimental	110	4.6±0.7	139.8±16.7	5.1±1.4	137.1±86.0	4.4±1.3	84.1±17.4	13.6±1.9
Control	106	4.5±0.7	138.9±16.5	5.0±1.4	117.8±48.1	4.7±1.6	86.9±21.0	13.5±1.7
P		0.499	0.761	0.499	0.054	0.193	0.441	0.168

PT: prothrombin time, BUN: blood urea nitrogen, Cr: creatinine.

in inflammation grade and fibrosis stage between two groups before treatment (Table 5). However, in experimental group, liver inflammation grades and fibrosis stage decreased markedly after treatment, whereas no obvious improvement was seen in control group.

Score of liver inflammation and fibrosis Half-quantitative scoring of inflammation activity and fibrosis in liver biopsy in 68 cases (37 cases in experimental group and 31 cases in control) was carried out. There was no difference in grading and staging scores between two groups before treatment (Tables 5 and 6). However, in experimental group, liver inflammation and fibrosis scores decreased markedly after treatment, but no obvious improvement was observed in control group (Tables 7 and 8).

Efficacy on histologic changes The total effective rate was 52% in experimental group and 23.2% in control group according to the set criteria (Table 9).

Changes of serum markers for liver fibrosis There was no significant difference in serum HA, LM, P-III-P and IV-C contents between two groups before treatment, while compared to previous treatment, HA, IV-C, LM and P-III-P decreased significantly in experimental group after treatment (Tables 10-1-3).

Effective rate for fibrosis The effective rate for liver fibrosis was significantly higher in experimental group (72.7%) than in control group (27.4%) ($P<0.01$) (Table 11).

Liver function parameters Experimental group, with a total effective rate of 72.7%, showed a better improvement in liver function than control group with an effective rate of 59.4% ($\chi^2 = 4.263$, $P<0.05$) (Tables 12 and 13).

Changes in ultrasound examination before and after treatment There was no significant difference in B ultrasound scoring, liver size, diameter of stem hepatic portal vein, thickness of spleen, diameter of splenic vein and size of gallbladder in two groups. But compared to those before treatment, there was a significant decrease in hepatic portal vein (after 12 and 24 wk of treatment) in experimental group, diameter of spleen (after 12 wk of treatment in experimental group and 24 wk treatment in control group) and diameter of splenic vein (after 24 wk of treatment in experimental group and 12 and 24 wk of treatment in control group) ($P<0.05$-0.01) (Table 14).

Changes in serum viral markers The positive rates of HBsAg, HBeAg, HBc-IgM and HBV-DNA in experimental and control groups were 100%/100%, 43.64%/45.28%, 40.40%/36.46% and 34.55%/30.91% before treatment, and the negative reverse rates of the above markers were 4.55%/4.76%, 11.82%/11.43%, 11.1%/8.42% and 12.84%/13.33% after treatment. There was no significant difference between two groups before and after treatment.

Efficacy evaluation in follow up

One hundred and four patients were followed up for 12 wk after treatment and emphasis was on observing serum markers for liver fibrosis, ALT and TCM patterns. Results

Table 3 Inflammation grading and fibrosis staging of biopsies in two groups before treatment

Group	*n*	Inflammation (G)				Fibrosis (S)			
		1	2	3	4	1	2	3	4
Experimental	99	12	49	29	9	22	39	21	17
Control	96	22	39	27	8	33	31	20	12
P			0.277				0.121		

Table 4 Serum viral markers in two groups (cases) before treatment

Group	*n*	HBsAg	HBsAb	HBeAg	HBeAb	HBcAb	HBcAb-IM	HBV-DNA
Experimental	110	110	3	48	48	105	40	38
Control	106	106	2	48	56	100	35	37
P			1.000	0.891	0.220	0.765	0.659	1.000

Table 5 Comparison of inflammation activity (G) in two groups in liver biopsy

Group	*n*	Pretreatment					Post-treatment					*P*
		1	2	3	4	mean	1	2	3	4	mean	
Experimental	50	5	25	15	5	2.40	18	20	11	1	1.9	0.001
Control	43	10	19	12	2	2.14	11	17	10	5	2.21	0.583
P				0.277					0.004			

Table 6 Comparison of liver fibrosis staging (S) in two groups in liver biopsy

Group	*n*	Pretreatment						After treatment						*P*
		0	1	2	3	4	mean	0	1	2	3	4	mean	
Experimental	50	0	8	23	10	9	2.40	1	23	14	9	3	1.80	0.001
Control	43	0	11	20	7	5	2.14	2	8	22	4	7	2.14	1.000
P				0.121						0.001				

showed that serum ALT and some markers for liver fibrosis were stable, there was no significant difference between the two groups (Table 15).

Changes of safety parameters

Blood routine and renal function There was an increase in count of RBC, WBC and platelets in two groups after treatment. There was a significant difference in count of RBC in control group, content of Hb in experimental group and count of WBC in two groups after treatment ($P<0.05$). There were changes in BUN in experimental group, Cr and PT after treatment in control group before and after treatment. However, all changes were within normal range and of no clinical significance.

Urine routine, ECG and α-fetoprotein (AFP) No abnormality was seen in urine routine, ECG and X-ray examination in two groups before and after treatment. There was a slight increase in serum AFP in some cases in the two groups. However, the change was in accordance with the characteristics of chronic hepatitis and of no clinical significance.

Adverse reaction No obvious adverse reaction was observed in experimental group, mild reaction (increased exhaust which disappeared after withdrawal) was seen in one case in control group and the adverse reaction rate was 0.9%.

DISCUSSION

Chronic hepatitis B is a common and prevalent disease endangering people's health seriously in China[4,5]. Liver fibrosis, through which chronic hepatitis B develops into cirrhosis, is a common pathologic process for almost all chronic liver diseases, so searching for new medications to prevent and reverse liver fibrosis is an urgent task for hepatologists.

Fuzhenghuayu capsule is a new medication formulated on the basic pathogenesis of liver fibrosis and cirrhosis-*body resistance weakness and stasis blocking vessels*. Previous studies[6-9] have revealed that this medication has good effects on improving liver function and serum fibrotic parameters and cirrhosis, decreasing portal pressure, regulating immune function and amino acids balance. *In vitro* study showed that the underlying mechanism of the medication against liver fibrosis was to inhibit of stellate cell proliferation, collagen synthesis, lipid peroxidation, collagen and transforming growth factor-β1 gene expression and improvement in matrix metalloproteinases activity.

In this study, a multicenter, randomized, double blinded and parallel control method was employed to observe the efficacy and safety of Fuzhenghuayu capsules on 216 cases of liver fibrosis due to chronic hepatitis B at five centers. In accordance with previous trials, a rather good reproducible result is expected.

Fuzhenghuayu capsule can effectively alleviate liver fibrosis in chronic hepatitis B

Liver biopsy examination is a gold standard for diagnosis

Table 7 Inflammation activity scoring in liver biopsy before and after treatment (mean±SD)

Group	*n*	Pretreatment	Post-treatment	*P*
Experimental	37	8.8±3.9	6.6±4.7	0.001
Control	31	7.3±4.1	7.4±4.1	0.978
P		0.185 (P_1)	0.036 (P_2)	

Table 8 Fibrosis scoring in liver biopsy before and after treatment (mean±SD)

Group	*n*	Pretreatment	Post-treatment	*P*
Experimental	37	8.1±5.6	6.0±5.4	0.001
Control	31	7.2±5.5	8.1±6.3	0.413
P		0.433 (P_1)	0.007 (P_2)	

Table 9 Efficacy in two groups in histologic changes of liver fibrosis

Group	*n*	Very effective cases (%)	Effective cases (%)	Ineffective cases (%)	*P*
Experimental	50	4 (8.0)	22 (44.0)	24 (48.0)	0.008
Control	43	1 (2.4)	9 (20.9)	33 (76.7)	

Table 10-1 Changes in serum HA, LM, P-III-P and IV-C contents (mean±SD)

Parameter	Group	*n*	Pretreatment	12 wk of treatment	24 wk of treatment
HA (μg/L)	Experimental	110	303.6±235.7	178.9±158.0[b]	147.9±131.3[b]
	Control	106	276.3±234.9	258.9±243.2[a]	261.8±253.6[b]
LM (μg/L)	Trial	110	137.0±84.6	127.5±92.7[a]	122.4±96.5[b]
	Control	106	134.1±98.6	128.4±55.7	121.2±48.9
P-III-P (μg/L)	Experimental	110	11.1±5.0	8.8±4.9[b]	7.4±4.4[b]
	Control	106	9.6±5.6	9.7±6.6	9.4±6.9
IV-C (μg/L)	Trial	110	119.1±132.5	74.5±88.4[b]	64.5±82.5[b]
	Control	106	91.8±76.7	71.4±57.8	62.4±54.7[b]

[a]$P<0.05$, [b]$P<0.01$ *vs* the same group.

Table 10-2 Difference in serum HA, LM, P-III-P and IV-C contents between two groups before and after treatment

Time points	Group	*n*	HA (μg/L)			LM (μg/L)		
			Median of difference	Standard deviation	Percent of difference	Median of difference	Standard deviation	Percent of difference
12-wk treatment	Experimental	110	-75.6[b]	196.5	-36.3	-10.0[a]	58.3	-8.1
	Control	106	-19.8	222.6	-12.8	3.0	102.2	2.0
24-wk treatment	Experimental	110	-96.1[b]	201.5	-48.5	-17.0	69.3	-13.0
	Control	106	-26.0	254.6	-15.9	-4.5	108.0	-4.5

[a]$P<0.05$, [b]$P<0.01$ *vs* control.

Table 10-3 Changes in serum P-III-P, IV-C contents between two groups before and after treatment

Time points	Group	*n*	P-III-P (μg/L)			IV-C (μg/L)		
			Median of differential	Standard deviation	Percent of difference	Median of difference	Standard deviation	Percent of difference
12-wk treatment	Experimental	110	-2.2[b]	5.0	-20.1	-25.0[a]	128.2	-39.3
	Control	106	-0.0	5.0	-1.3	-6.5	87.0	-9.1
24-wk treatment	Experimental	110	-2.9[b]	4.6	-33.9	-33.0[a]	139.1	-48.3
	Control	106	-0.3	5.5	-3.0	-14.0	80.4	-18.6

[a]$P<0.05$, [b]$P<0.01$ *vs* control.

and evaluation of efficacy on liver fibrosis. In this study, liver biopsies showed that Fuzhenghuayu capsule was superior to Heluoshugan capsule in reversing liver fibrosis. Histologic examination also revealed that Fuzhenghuayu capsule had rather good effects on inhibiting hepatic inflammation. Superior to that in control group, a significant decrease in mean value of degree of inflammatory activity and inflammatory score was seen in experimental group after treatment. This reveals that Fuzhenghuayu capsule has good effects on alleviating inflammatory infiltration and/or hepatic cell necrosis.

Fuzhenghuayu capsule can significantly improve serum fibrotic markers in liver fibrosis due to chronic hepatitis B

It has been widely accepted that serum HA, LM, P-III-P and IV-C are useful markers to evaluate liver fibrosis, especially serum HA and IV-C contents, so multi-parameter determination is advocated for diagnosing and evaluating liver fibrosis in clinic[10-13]. In this study, there was no significant difference in serum HA, LM, P-III-P and IV-C contents between the two groups before treatment. All markers in experimental group showed a consistent and stepwise decrease after 12 and 24 wk of treatment, and before and after treatment, the difference in serum HA and IV-C contents in experimental group were obviously greater than that of control group.

The effective rate was 72.7% in experimental group and 27.4% in control group, indicating that there was a significant difference between the two groups. From this point of view, we conclude that Fuzhenghuayu capsule is superior to Heluoshugan capsule in inhibiting liver fibrosis due to chronic hepatitis B.

Table 11 Efficacy on liver fibrosis in two groups

Group	*n*	Very effective cases (%)	Effective cases (%)	Ineffective cases (%)	*P*
Experimental	110	80 (72.7)	2 (1.8)	28 (25.5)	0.001
Control	106	29 (27.4)	2 (1.9)	75 (70.7)	

Central effect-oriented CMH method was employed in comparison of efficacy between two groups, Q of statistics was Q_{CMH}.

Table 12 Changes in liver function of two groups before and after treatment (mean±SD)

Parameter	Group	Pretreatment	6 wk of treatment	12 wk of treatment	18 wk of treatment	24 wk of treatment
Alb (g/L)	Experimental	40.1±5.2	42.6±5.0[b]	43.2±4.7[b]	43.3±4.3[bc]	43.5±5.7[bc]
	Control	41.0±5.9	42.6±5.3[b]	43.3±5.3[b]	42.8±4.9[b]	43.1±5.2[b]
Glo (g/L)	Experimental	30.1±6.4	29.8±6.1	30.8±6.5	31.3±5.7	31.3±5.8
	Control	29.2±5.1	30.9±5.7[b]	30.9±6.0[a]	31.9±5.6[b]	31.9±6.6[b]
ALT (U/L)	Experimental	116.0±74.6	57.5±56.0[bc]	50.9±39.0[bc]	50.1±43.6[bc]	49.4±41.2[bc]
	Control	96.7±55.0	59.5±52.0[b]	58.9±54.4[b]	61.8±58.5[b]	51.2±39.0[b]
AST (U/L)	Experimental	78.4±59.3	55.5±47.7[b]	54.2±47.4[b]	46.2±29.2[bc]	48.2±35.0[b]
	Control	68.5±53.1	53.8±39.1[b]	59.3±50.2[a]	55.8±39.4[a]	51.9±51.6[b]
GGT (U/L)	Experimental	92.0±71.4	75.3±64.9[b]	67.9±75.8[b]	67.4±70.1[b]	56.4±51.8[b,d]
	Control	86.8±68.6	68.6±52.9[b]	67.7±59.9[b]	70.4±48.0[a]	67.3±58. 2[b]
ALP (U/L)	Experimental	100.6±38.2	96.4±47.3[a]	100.3±52.2	97.9±47.1	93.5±38.8[a]
	Control	95.1±41.9	97.0±43.6	93.1±42.1	91.1±36.5	92.9±41.5
TBil (μmol/L)	Experimental	17.8±7.9	15.8±5.9[b]	15.9±6.4[b]	15.5±9.5[bc]	15.5±5.8[bc]
	Control	16.9±8.4	16.4±8.2	17.1±8.6	18.5±12.1	18.5±13.5
DBil (μmol/L)	Experimental	5.9±5.5	4.7±3.0[b]	4.6±3.0[bc]	4.5±2.5[bc]	4.6±2.7[b,d]
	Control	5.2±4.4	4.8±3.7	5.1±3.7	5.3±3.6	5.9±5.4

[a]$P<0.05$, [b]$P<0.01$ *vs* the same group; [c]$P<0.05$, [d]$P<0.01$ *vs* difference between different time points value and previous treatment in two groups.

Table 13 Efficacy in ALT activity between two groups before and after treatment

Group	*n*	Effectual (%)	Effective (%)	Noneffective (%)	*P*
Experimental	110	64 (58.2)	16 (14.5)	30 (27.3)	0.105
Control	106	54 (50.9)	9 (8.5)	43 (40.6)	

In comparison of efficacy between two groups, central effect-oriented CMH method was employed. *Q* of statistics was Q_{CMH}.

Fuzhenghuayu capsule can significantly improve liver function in liver fibrosis due to chronic hepatitis B

Parameters of liver function improved significantly in both groups after treatment, indicating that both medications have protective effects on liver injury. Compared to those of pretreatment, there was a significant decrease in TBil and DBil in experimental group at different time points after treatment. The difference in TBil and DBil between 18 and 24 wk of treatment and pretreatment in experimental group was significantly higher than that in control group. Comprehensively, compared to Heluoshugan capsule, we draw a conclusion that Fuzhenghuayu capsule has some advantages in improving liver function in patients with chronic hepatitis B.

Table 14 Changes in diameter of stem hepatic portal vein, thickness of spleen and diameter of splenic vein before and after treatment in two groups (mean±SD)

Parameters	Group	*n*	Pretreatment	12-wk treatment	24-wk treatment
Diameter of stem	Experimental	110	12.34±1.94	11.96±1.69[b,d]	12.03±1.61[a]
hepatic vein (mm)	Control	106	12.30±1.75	12.37±1.76	12.06±1.51
Diameter of	Experimental	110	42.77±9.23	41.10±8.11[b]	41.77±7.88
spleen (mm)	Control	106	42.45±9.94	42.12±9.90	41.32±8.28[a]
Diameter of	Experimental	110	7.57±1.86	7.41±1.84	7.28±1.52[a]
splenic vein (mm)	Control	106	7.67±1.94	7.43±1.80[a]	7.39±2.00[a]

[a]$P<0.05$, [b]$P<0.01$ *vs* treatment, [d]$P<0.01$ *vs* different time point and pretreatment between groups.

Table 15 Comparison of stable rate (%) between two groups in follow up

Group	Stable cases/follow up cases (stable rate%)				
	HA	LM	P-III-P	IV-C	ALT
Experimental	18/29 (62.07)	29/34 (85.29)	14/29 (48.28)	30/34 (88.24)	49/50 (98.00)
Control	16/28 (57.14)	25/37 (67.57)	15/25 (60.00)	34/37 (91.89)	54/54 (100.00)
P	0.790	0.100	0.425	0.703	0.481

Fisher precise probability calculation was employed in comparison of stable rates between the two groups.

No obvious anti-virus effect of Fuzhenghuayu capsule was found. Based on the results available from serum parameters for liver fibrosis and ALT activity in follow-up cases, there was no obvious difference in stable rate 12 wk after withdrawal of the drug in two groups.

No change in laboratory examination and ECG after 24 wk of treatment was seen in two groups. No obvious adverse reaction was seen in experimental group. Digestive tract reaction disappeared after withdrawal of the drug was seen in one case only (0.9%) in control group. These indicate that both medications are rather safe.

In conclusion, Fuzhenghuayu capsule can effectively alleviate hepatic fibrosis and decrease serologic fibrotic parameters due to chronic hepatitis B. Since the reverse rate of Fuzhenghuayu capsule is higher than that of Heluoshugan capsule, the medication has excellent effects on reversing liver fibrosis. Thus, Fuzhenghuayu capsule is a safe and effective medication against liver fibrosis due to chronic hepatitis B.

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