PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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• VIRAL HEPATITIS •

Capsule oxymatrine in treatment of hepatic fibrosis due to chronic viral hepatitis: A randomized, double blind, placebo-controlled, multicenter clinical study

Yi-Min Mao, Min-De Zeng, Lun-Gen Lu, Mo-Bin Wan, Cheng-Zhong Li, Cheng-Wei Chen, Qing-Chuen Fu, Ji-Yao Wang, Wei-Min She, Xiong Cai, Jun Ye, Xia-Qiu Zhou, Hui Wang, Shan-Ming Wu, Mei-Fang Tang, Jin-Shui Zhu, Wei-Xiong Chen, Hui-Quan Zhang

Yi-Min Mao, Min-De Zeng, Lun-Gen Lu, Shanghai Institute of Digestive Disease, Renji Hospital, Shanghai Second Medical University, Shanghai 200001, China
Mo-Bin Wan, Cheng-Zhong Li, Changhai Hospital, Second Military Medical University, Shanghai 200433, China
Cheng-Wei Chen, Qing-Chuen Fu, Nanjing Military Command Liver Disease Research Center, Shanghai 200233, China
Ji-Yao Wang, Wei-Min She, Zhongshan Hospital, Fudan University, Shanghai 200032, China
Xiong Cai, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China
Jun Ye, Shanghai Putuo District Central Hospital, Shanghai 200333, China
Xia-Qiu Zhou, Hui Wang, Ruijin Hospital, Shanghai Second Medical University, Shanghai 200025, China
Shan-Ming Wu, Mei-Fang Tang, Shanghai General Hospital of Infectious Diseases, Shanghai 200083, China
Jin-Shui Zhu, Wei-Xiong Chen, Shanghai No.6 People's Hospital, Shanghai 200230, China
Hui-Quan Zhang, Shanghai Shibei Hospital, Shanghai 200073, China
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Correspondence to: Yi-Min Mao, M.D., Shanghai Institute of Digestive Disease, Renji Hospital, Shanghai Second Medical University, Shanghai 200001, China. maoyimin1@sina.com
Telephone: +86-21-33070834 **Fax:**+86-21-63364118
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Abstract

AIM: To evaluate the efficacy and safety of oxymatrine capsule in treatment of hepatic fibrosis in patients with chronic viral hepatitis.

METHODS: It was a randomized, double blind, placebo-controlled, multicenter clinical study. One hundred and forty-four patients were divided into oxymatrine capsule group (group A) and placebo group (group B).The course was 52 wk. Patients were visited once every 12 wk and the last visit was at 12 wk after cessation of the treatment. All patients had liver biopsy before treatment. part of them had a second biopsy at the end of therapy. Clinical symptoms, liver function test, serum markers of hepatic fibrosis were tested. Ultrasound evaluation was performed before, during and at the end of therapy.

RESULTS: One hundred and forty-four patients enrolled in the study. Of them 132 patients completed the study according to the protocol,49 patients had liver biopsy twice (25 patients in group A and 24 in group B). At the end of therapy, significant improvements in hepatic fibrosis and inflammatory activity based on Semi-quantitative scoring system (SSS) were achieved in group A. The total effective rate of the treatment was 48.00%, much higher than that of 4.17% in group B (P<0.05). Significant improvement in serum markers of hepatic fibrosis such as hyaluronic acid (HA) and type III procollagenic peptide (P III P) in group A was seen (P<0.05). The total effective rate of serum markers at the end of therapy in group A was 68.19%, much higher than that of 34.85% in group B (P<0.05). The total effective rate of noninvasive markers at the end of therapy in group A was 66.67%, much higher than that of 30.30% in group B (P<0.05). The rate of adverse events was similar in two groups.

CONCLUSION: Oxymatrine capsule is effective and safe in treatment of hepatic fibrosis due to chronic viral hepatitis.

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INTRODUCTION

Hepatic fibrosis is a kind of compensating and healing response in the liver to liver injury induced by a variety of causes and also a common pathological process of many chronic liver diseases characterized by hyperplasia and deposition of fibro-connective tissues. It is essential to block the genesis and progress of hepatic fibrosis[1-5,30,31]. Oxymatrine is a kind of alkaloid extracted from a Chinese herb Sophora alopecuraides L. which has been proved to have antihepatic fibrosis effect[6,7,18-20]. In this paper, we reported the clinical study data of oxymatrine capsule in treatment of hepatic fibrosis in patients with chronic viral hepatitis.

MATERIALS AND METHODS

Resarch design

This study was a clinical trial characterized by multicentre, randomization, double blinding, and placebo-control. Enrolled patients were randomly assigned into oxymatrine capsule group (group A) or vacant placebo control group (group B), with 72 cases in each group and a treatment course of 52 wk. This study was conformed to the Good Clinical Practice (GCP) of China. The research protocol was discussed and approved by the Ethic Committee of National Clinical Research Base of Drugs in the Institute of Digestive Disease of Renji Hospital. Informed consent was obtained from each patient.

Selection of subjects

Enrolled criteria were age: 18-65 years regardless of sex; positive serum markers of hepatitis B virus (HBV) and hepatitis C virus (HCV) for at least 6 mo before enrollment; abnormal serum value of alanine transaminase (ALT) twice or more within 6 mo before enrollment; liver biopsy examination during 1 mo before enrollment indicating the stage of hepatic fibrosis from 1 to 4 according to National Criteria of Grading and Staging for chronic

viral hepatitis amended in 1995 and the scores of stage equal or more than 1 assessed by the semi-quantitative scoring system (SSS) of hepatic fibrosis; total serum bilirubin level less than or equal to 85.5 μmol/L; no history of administrating following drugs: antiviral drugs, immunoregulating drugs and other antifibrotic agents; promising not to receive other systemic antiviral agents, cytotoxic agents, immunoregulators, drugs capable of reducing serum enzyme activity and bilirubin level, and Chinese traditional medicines, *etc.* Following situations should be excluded: patients with positive laboratory test of HIV; uncompensable liver diseases; suggestive of autoimmune diseases with antinuclear antibody (ANA) titer greater than a 1:160 dilution; bone marrow inhibition; abnormality of serum creatinine with a value 1.5 times greater than normal; concurrence of other associated diseases which might affect the present treatment such as unstable diabetes, renal insufficiency, unstable angina pectoris, alcoholic liver disease, epilepsy, obvious manifestations of neurosis, drug abuser, psychosis, pancreatitis, disability of absorption and malignant disease, and so on; Having taken other drugs in clinical trial within 30 d before the first medication; hypersensitive to oxymatrine capsule; pregnancy and during breast-feeding period; female conceptive patients not adopting any contraceptives.

Treatment procedures and drugs

After completion of selection and assessment, qualified subjects were allocated into group A or B randomly. The patients in group A took 300 mg oxymatrine capsules orally 3 times a day, and 2 tablets of complex vitamins B and C at the same time for 52 wk. The patients in group B took 3 tablets of vacant capsules instead of oxymatrine capsules and complex vitamins B and C at the same frequency as described above for 52 wk. All patients received follow-up once every 12 wk during treatment and were followed up at out-patient department 12 wk after treatment. Oxymatrine capsule, vacant placebo capsule, complex vitamins B and C tablets were manufactured and provided by Ningxia Pharmaceutic Institute and Shanghai Green Valley Ecological Engineering Co.LTD.

Observation of indexes and assessment

Clinical manifestations Clinical symptoms and signs were divided into grades from 0 to 3 according to the symptomatic grading criteria , evaluated at each follow-up visit, and examined 24 and 52 wk after treatment and 12 wk after drug withdrawal.

Analysis of blood and urine routines and related liver function indexes These indexes were evaluated at each follow-up visit and examined 52 wk after treatment and 12 wk after drug withdrawal.

Analysis of serum markers of hepatic fibrosis Tests of serum hyaluronic acid (HA), laminin (LN), type III procollagenic peptide (p III p), type IV collagen-7S (IV-7S) were fulfilled by Military Clinical Immunologic Research Centre of Changzheng Hospital, Second Military Medical University. The above markers were evaluated before treatment, 24 and 52 wk after treatment, 12 wk after drug withdrawal respectively, and examined 24 and 52 wk after treatment,12 wk after drug withdrawal, respectively.

Imaging examination (type B ultrasound) The detection included 5 indexes: maximal oblique radius of right liver lobe, main trunk diameter of portal vein and its blood flow parameters per minute; width of spleen at the hilus and the diameter of spleenic vein. Ultrasound examination was performed on fixed machines and by fixed operators and the data were recorded and input in computers which were read by experts. All the indexes were evaluated before treatment and 52 wk after therapy, examined 52 wk after drug withdrawal.

Histopathological detection Histopathological specimens were independently observed and assessed based on National Criteria of Grading and Staging for chronic viral hepatitis amended in 1995 and SSS by 3 pathologists from Department of Pathology, Medical College, Fudan University. The observed results were checked by another 3 pathologists who did not anticipate in the study by Kappa test. The reciprocal consistence among the above pathologists was satisfactory. The observed results in all patients were evaluated before therapy and part of them were evaluated 52 wk after therapy. All data were examined 52 wk after therapy.

During treatment and after therapy was terminated, the following events were recorded: combined medication, adverse reactions and the compliance of patients.

Assessment of therapeutic effects

Indexes of histopathology The curative effect was evaluated based on SSS. Distinctly effective: the scores of hepatic fibrosis based on SSS from liver biopsy decreased at least 6 scores compared with that before treatment. Effective: the above scores decreased at least 2 scores. Ineffective: the effect did not meet the effective criteria.

Assessment of indexes of noninvasive tests These indexes were evaluated comprehensively in terms of clinical manifestations, serum liver fibrotic markers and ultrasound detection data. Distinctly effective: any two values among serum liver fibrotic indexes decreased by at least 80% compared with that before treatment, at least the main trunk diameter of portal vein and splenic width returned to normal after treatment, clinical symptoms and signs disappeared or their total scores decreased by at least 75% compared with that before treatment. Effective: any two values among serum liver fibrotic indexes decreased by at least 40% compared with that before treatment, the main trunk diameter of portal vein and splenic width reduced after treatment, clinical symptoms and signs disappeared basically or their total scores decreased by at least 25% compared with that before treatment. Ineffective: the effect did not meet the effective criteria.

Assessment of safety

Any abnormal clinical manifestations and laboratory tests occurred during treatment were recorded and divided into 4 grades according to the criteria published by WHO and the Ministry of Public Health of China in 1994.

Statistical analysis

Statistical analyses were performed by professor Su BH and He QB from Department of Statistics, Shanghai Second Medical University, and SAS 6.12 software kit was used.

RESULTS

Selected patients

A total of 144 patients satisfied the selection criteria. Of them, 12 cases withdrew or were excluded during treatment, 132 cases fulfilled the treatment course according to the required protocol (66 cases in group A and 66 cases in group B). Before treatment, the following general data between two groups were similar (P>0.05, respectively): sex, age, drinking history, duration of hepatitis, duration of abnormality of liver function and a more than 2-fold normal elevation of serum ALT, *etc*. Each qualified patient received liver biopsy before treatment. A total of 49 cases had a second liver biopsy (25 cases in group A and 24 cases in group B).

Analysis of observed indexes

Clinical symptoms and signs Clinical manifestations in group A were obviously improved 52 wk after therapy (P<0.05), except for epistaxis (P = 1.0000). Heptomegaly was also improved significantly after therapy (P = 0.0313), symptoms of gum bleeding

and epistaxis were not improved obviously in group B (P>0.05). Signs of hepatomegaly, splenomegaly and liver palm were significantly improved in group B (P<0.05), improvement of anorexia in group A was greater than that in group B (P = 0.0263).

Liver function Indexes of liver function in group A were significantly improved 52 wk after treatment (P<0.05) except for serum gamma glutamino transpeptidase (GGT) and TB (P>0.05). In group B, indexes such as serum ALT, AST, TB and alkaline phosphatase (ALP) had no obvious difference before and after therapy (P>0.05). Compared with group B, the improvement of ALT and AST in group A was much greater (P = 0.0007 and 0.0025). Fifty-two wk after therapy, the normalization rate of ALT in group A was 70.77%, much higher than 39.68% in group B (P = 0.0003). In groups A and B, 14 out of 46 cases (30.43%) and 12 out of 25 cases (48.00%) had their serum ALT levels returned to normal 52 wk after treatment ,and their serum ALT levels became abnormal again after drug withdrawal.

Liver histologic examination Evaluation of hepatic fibrosis based on SSS: In group A, the scores of hepatic fibrosis after therapy were 4.72±5.63, much smaller than 6.76±6.67 before therapy (P = 0.0001), while the scores in group B after therapy increased significantly (P = 0.0009). There was an obvious difference between two groups (P = 0) (Table 1). Evaluation of histolgic inflammatory activity based on SSS: In group A, the scores of histologic activity decreased from 46.08±3.84 before treatment to 4.00±2.97 after therapy (P = 0.0002), while the scores in group B after therapy did not decrease obviously (P = 0.2344). There was an obvious difference between two groups (P = 0008) (Table 2).

Evaluation of serum markers of hepatic fibrosis In group A, serum levels of HA, LN, p III p and IV-7S decreased significantly 24 and 52 wk after treatment (P<0.05). In group B, serum levels of LN, p III p and IV-7S also decreased obviously after treatment (P<0.05). However, degrees of improvement in HA and p III p between two groups were distinctly different (P<0.05). In group A, except for LN (P = 0.1493), the other 3 liver fibrotic markers increased significantly 12 wk after drug withdrawal compared with that 52 wk after treatment (P<0.05). In group B, except for HA (P = 0.4212), the other markers also increased obviously 12 wk after drug withdrawal compared with that 52 wk after treatment (P<0.05). The increase of HA in group A was more than that in group B (P = 0.0002) and the increase of IV-7S in group B was more than that in group A (P = 0.0048).

Imaging examination After treatment, the average values of main trunk diameters of portal vein and splenic width in group A obviously decreased (P<0.05). However, in group B, the above two parameters and the parameters of blood flow volume per minute of portal vein and diameters of splenic vein all increased significantly compared with those before therapy (P<0.05). The changes in main trunk diameters of portal vein and splenic width between two groups were statistically significant (P<0.05).

Analysis of therapeutic effect

Assessment of histopathology based on SSS After treatment, the rates of distinct effectiveness and effectiveness in group A were both 24.00%, and the total effective rate was 48.00%. In group B, none achieved distinct effectiveness and the effective rate was only 4.17%; Comparison of the rates of distinct effectiveness and effectiveness between two groups had a significant difference (P = 0.004) (Table 3).

Assessment of serum markers of hepatic fibrosis The total effective rate of group A 24 and 52 wk after therapy was 57.43% and 68.19%, more than 24.24% and 34.85% of group B (P = 0.0002 and 0.0004, respectively). Twelve weeks after treatment, the total effective rate of group A was 50.00%, more than 15.16% of group B (P=0.00).

Assessment of noninvasive indexes of hepatic fibrosis After treatment, the rates of distinct effectiveness and effectiveness

Table 1 Liver fibrotic scores before and after therapy based on Semi-quantitative Scoring System

Group	Before	After	Before-after	Comparison before therapy		Comparison within group		Comparison between groups	
				Statistics	*P*	Statistics	*P*	Statistics	*P*
A									
(n = 25)	6.76±6.67	4.72±5.63	2.04±2.59			96.0	0.0001		
B				1.4098	0.1586			4.8834	0
(n = 24)	4.13±2.82	6.33±4.04	-2.21±3.72			83.0	0.0009		

Table 2 Liver histologic activity scores before and after therapy based on Semi-quantitative Scoring System

Group	Before	After	Before-after	Comparison before therapy		Comparison within group		Comparison between groups	
				Statistics	*P*	Statistics	*P*	Statistics	*P*
A									
(n = 25)	6.08±3.84	4.00±2.97	2.08±2.71			69.5	0.0002		
B				0.0407	0.9675			3.3543	0.0008
(n = 24)	6.08±4.06	6.92±4.17	-0.83±3.38			21.5	0.2344		

Table 3 Comparison of histopathology of hepatic fibrosis

Group	Distinctly effective	Effective	Ineffect-ive	Comparison between 2 groups	
				Statitics χ^2	*P*
A	6	6	13		
(n = 25)	(24.00%)	(24.00%)	(52.00%)		
B	0	1	23	12.6970	0.0004
(n = 24)	(0.00%)	(4.17%)	(95.83%)		

Table 4 Comparison of noninvasive markers of hepatic fibrosis

Group	Distinctly effective	Effective	Ineffect-ive	Comparison between 2 groups	
				Statitics χ^2	*P*
A	2	42	22		
(*n* = 66)	(3.03%)	(63.64%)	(33.33%)		
B	0	20	46	16.2494	0.0001
(*n* = 66)	(0.00%)	(30.30%)	(69.70%)		

in group A were respectively 3.03% and 63.64%, and the total effective rate was 66.67%. In group B, the rates of distinct effectiveness and effectiveness were respectively 0% and 30.30%, and the total effective rate was 30.30%.The comparison of the above statistics between two groups had a significant difference ($P = 0.0001$) (Table 4).

Adverse effects

In group A, there were 5 patients who suffered from adverse drug reactions and the incidence was 6.94%. The adverse drug reactions mainly included nausea, rash, chest discomfort, fever, epigastric comfort, diarrhea and poor taste, and most of them were mild or moderate. None of the patients withdrew because of adverse drug reactions. In group B, adverse effects occurred in 7 patients and the incidence was 9.72%. The manifestations were similar to those in group A and 1 patient withdrew because of weakness, anorexia, epigastric discomfort after taking drugs.

DISCUSSION

Hepatic fibrosis, a precuror of cirrhosis, is a consequence of sever liver damage that occurred in many patients with chronic liver disease, and involves the abnormal accumulation of extracellular matrix[3,4,11,12]. Liver fibrosis represents a major worldwide healthcare burden. Current therapy is limited to removing the causal agent. This approach has been successful in some diseases, particularly in haemochromatosis and chronic viral hepatitis[9,10,17,28]. However, for many patients treatment was not possible, while other patients presenting to medical attention were at an advanced stage of fibrosis[8,9]. There is therefore a great need for novel therapies for liver fibrosis. Tremendous insights into the understanding of hepatic fibrosis have taken place over the past ten years. Foremost among these is the recognition that hepatic stellate cells (formerly known as lipocytes, Ito cells, or fat-storing cells) play a central role based on their ability to undergo activation following liver injury of any cause[11,15,16,29]. Hepatic stellate cells have been recognised to be responsible for most of the excess extracellular matrix observed in chronic liver fibrosis. The detailed understanding of hepatic stellate cell biology has allowed the rational design of novel antifibrotic therapies[29]. Effective therapy for hepatic fibrogenesis would probably also be multifactorial, based on the basic mechanisms underlying the fibrogenic process[13,14,21-23].

At present, it is considered that treatment of hepatic fibrosis and antihepatic fibrosis are two different concepts and antifibrotic drugs should act on various parts of the genesis and development of hepatic fibrosis. Firstly, as for etiological treatment, oxymatrine could effectively treat chronic viral hepatitis and promote the serum markers of hepatitis B virus (HBV) and hepatitis C virus (HCV) in chronic hepatitis B and C to convert to negative and reduce serum level of ALT[6,7]. Secondly, oxymatrine could inhibit the proliferation of hepatic stellate cells (HSC) at the concentrations of 0.5-16 μg/mL *in vitro*. In addition, oxygen stress and lipid peroxidation are important mechanisms responsible for hepatic injury and hepatic stellate cell activation. Therefore, inhibition of lipid peroxidation is an essential strategy of antihepatic fibrosis[12-16]. By establishing D-galactosamine-induced rat liver fibrosis model, we observed the effect of oxymatrine on serum and tissue biochemical indexes, content of liver hydroxyline, expression of TGFβ1 mRNA and changes of tissue pathology, the results showed oxymatrine had prophylactic and therapeutic effects on D-galactosamine induced rat liver fibrosis. This was partly by protecting hepatocytes and suppressing fibrosis accumulation through anti-lipoperoxidation[10]. In present study, We found that the scores of hepatic fibrosis after therapy in group A were 4.72±5.63, much smaller than 6.76±6.67 before therapy, and the scores in group B after therapy increased significantly. There was an obvious difference between two groups. The scores of histological inflammatory activity in group A decreased from 46.08±3.84 before treatment to 4.00±2.97 after therapy, and the scores in group B after therapy did not decrease obviously. There was an obvious difference between two groups both in improvement of histopathology and in improvement of noninvasive indexes such as clinical manifestations, serum markers of hepatic fibrosis[24-27]. Associated indexes of liver function and imaging detection indicated that oxymatrine was an ideal drug of antihepatic fibrosis. It is valuable to pay more attentions to the basic and clinical research of oxymatrine in order to explore the accurate mechanisms of its effect on antihepatic fibrosis.

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