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

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Oxymatrine therapy for chronic hepatitis B: A randomized double-blind and placebo-controlled multi-center trial

Lun-Gen Lu, Min-De Zeng, Yi-Min Mao, Ji-Qiang Li, Mo-Bin Wan, Cheng-Zhong Li, Cheng-Wei Chen, Qing-Chun 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

Lun-Gen Lu, Min-De Zeng, Yi-Min Mao, Ji-Qiang Li, 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-Chun Fu, Liver Disease Research Center, Nanjing Military Command, 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 200062, 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
Supported by the Key Project of Shanghai Medical Development Foundation (NO: 99ZDI001) and grants from 1999 Foundation of Chinese Liver Diseases Association for Yong Scholars
Correspondence to: Lun-Gen Lu, MD, Shanghai Institute of Digestive Disease, Renji Hospital, Shanghai Second Medical University, Shanghai 200001, China. lulungen@online.sh.cn
Telephone: +86-21-33070834 **Fax:** +86-21-63364118
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Abstract

AIM: To evaluate the efficacy and safety of capsule oxymatrine in the treatment of chronic hepatitis B.

METHODS: A randomised double-blind and placebo-controlled multicenter trial was conducted. Injection of oxymatrine was used as positive-control drug. A total of 216 patients with chronic hepatitis B entered the study for 24 weeks, of them 108 received capsule oxymatrine, 36 received injection of oxymatrine, and 72 received placebo. After and before the treatment, clinical symptoms, liver function, serum hepatitis B virus markers, and adverse drug reaction were observed.

RESULTS: Among the 216 patients, six were dropped off, and 11 inconsistent with the standard were excluded. Therefore, the efficacy and safety of oxymatrine in patients were analysed. In the capsule treated patients, 76.47 % became normal in ALT level, 38.61 % and 31.91 % became negative both in HBV DNA and in HBeAg. In the injection treated patients, 83.33 % became normal in ALT level, 43.33 % and 39.29 % became negative both in HBV DNA and in HBeAg. In the placebo treated patients, 40.00 % became normal in ALT level, 7.46 % and 6.45 % became negative both in HBV DNA and in HBeAg. The rates of complete response and partial response were 24.51 % and 57.84 % in the capsule treated patients, and 33.33 % and 50.00 % in the injection treated patients, and 2.99 % and 41.79 % in the placebo treated patients, respectively. There was no significance between the two groups of patients, but both were significantly higher than the placebo. The adverse drug reaction rates of the capsule, injection and placebo were 7.77 %, 6.67 % and 8.82 %, respectively. There was no statistically significant difference among them.

CONCLUSION: Oxymatrine is an effective and safe agent for the treatment of chronic hepatitis B.

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INTRODUCTION

Oxymatrine is a kind of alkaloid extracted from a Chinese herb *Sophora alopecuraides L.*[1]. Basic and clinical researches suggested that oxymatrine had the following pharmacological effects such as anti-virus, protecting hepatocytes, anti-hepatic fibrosis, immune regulation, etc[2-7]. In particular, wide attention was paid to its inhibitory effect on hepatitis B virus (HBV) in recent years. Oxymatrine has been proved to have distinct anti-virus effect in the treatment of chronic hepatitis B (CHB)[8-11]. But no information is available about the therapeutic efficacy and safety of oxymatrine capsule treated CHB. In this paper, we evaluated the therapeutic efficacy and safety of oxymatrine (kurorinone) capsule in the treatment of CHB based on a randomized multi-centre, double-blind and placebo-controlled clinical trial.

MATERIALS AND METHODS

Research design

This study was a clinical trial characterized by multi-centre, randomization, double blinding and placebo-control, which was fulfilled by Renji Hospital of Shanghai Second Medical University, Zhongshan Hospital of Fudan University, Changhai Hospital of Second Military Medical University.

Selection of subjects

Enrolled criteria: Age: 18-65 years old, regardless of sex, positiveness of serum HBsAg and HBV DNA for at least 6 months before enrolling, positiveness of serum HBeAg for at least 6 months before enrolling, abnormal serum value of alanine transaminase (ALT) twice or more with a value 1.2 times greater than normal upper limit and a duration more than 8 weeks between two tests within 6 months before enrolling, the serum

level of ALT was more than normal upper limit when screening, total serum bilirubin (TB) level less than or equal to 85.5 μmol/L, non-history of administrating antiviral and immunoregulating drugs, signing in the informed consent form, promising not to receive other drugs in clinical trial and systemic anti-viral agents, cytotoxic agents, hormone, immunoregulators, drugs capable of reducing serum enzyme activity and bilirubin level and Chinese traditional medicines, etc.

Exclusion criteria Patients with positive laboratory test of HIV, positiveness of serum anti-HCV and/or HCV RNA, uncompensable liver diseases, suggestive of autoimmune diseases with antinuclear antibody (ANA) titer greater than a 1:160 dilution, abnormality of serum creatinine with a value of 1.5 times greater than normal, concurrence of other associated severe diseases which might affect the present treatment, hypersensitive to oxymatrine capsule, women with pregnancy and during breast-feeding period.

Treatment procedures and drugs

A total of 216 selected patients were randomly divided into 3 groups: 108 in capsule oxymatrine group, 36 in injection oxymatrine group and 72 in placebo group. Both capsule oxymatrine and injection oxymatrine were provided by Ningxia Pharmaceutic Institute, Ningxia, China (Batch numbers 990426 and 990325, respectively). The magnitude, colour, shape and taste of the vacant placebo capsule were consistent with capsule oxymatrine. Capsule oxymatrine group: 300 mg oxymatrine capsules orally 3 times a day. Injection oxymatrine group: 400 mg intramuscularly once a day. Placebo group: 3 tablets, three times a day. Treatment course of the 3 groups was 24 weeks. After completion of selection and assessment, qualified subjects were allocated randomly into capsule oxymatrine group, injection oxymatrine group and placebo group for a treatment course of 24 weeks according to the treatment code based on stratified randomization.

Observing indexes and assessment

Clinical manifestations Weakness, pain in hepatic region, jaundice, hepatomegaly, splenomegaly, etc.

Liver function indexes Serum levels of total protein, albumin, ratio of albumin and globulin, ALT, aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), total bilirubin (TB), direct bilirubin (DB) and alkaline phosphatase (ALP).

Detection of serum markers of HBV HBV DNA was measured by dot blotting assay. HBsAg, anti-HBsAg, anti-HBc, HBeAg and anti-HBe were measured by Abbott kit before the treatment, 12 and 24 weeks after the treatment.

Analysis of blood and urine All parameters including electrolytes and renal function were measured before the treatment, 12 and 24 weeks after the treatment.

Assessment criteria of therapeutic effect and safety

Mainly evaluated indexes were negatively converting rate of serum HBV DNA and HbeAg, and the normalization rate of serum ALT. The assessment criteria of therapeutic effect were as follow. Complete response: negative conversion of HBeAg and HBV DNA, and normalization of serum ALT. Partial response: negative conversion of HBeAg and HBV DNA or normalization of serum ALT. Nonresponse: the effect didn' t reach the above criteria. Any abnormal clinical manifestations and laboratory tests occurred during the treatment were recorded and filled in a report form of side effects in time whether they were associated with drugs for trial or not.

Statistical analysis

Statistical analysis of the data was performed with SAS 6.12 software kit.

RESULTS

Number of subjects

A total of 216 patients were enrolled in the study, of them 108 in capsule oxymatrine group, 36 in injection oxymatrine group, and 72 in placebo control group. Twelve cases withdrew, and the withdrawal rate was 2.78 %. Eleven cases were excluded for not conforming selection criteria, and the excluding rate was 5.09 %. One hundred and ninety-nine cases entered statistical analysis of therapeutic effect included 102 cases in capsule oxymatrine group, 30 cases in injection oxymatrine group, and 67 cases in placebo control group.

General state of patients in three groups before treatment

Before treatment, the following data were similar among three groups (P>0.05, respectively), including sex, age, duration of hepatitis, abnormality of serum ALT and AST 2-fold higher than normal elevation, etc. There were no significant differences among three groups in symptoms and signs before treatment (P>0.05).

Negative conversion of serum virus markers

Negative conversion rate of serum HBsAg in capsule oxymatrine group, injection oxymatrine group and placebo group was 1.98 %, 3.33 %, and 0.00 %, respectively (Table 1). There were no obvious differences among 3 groups (P=0.269). The negative conversion rate of HBV DNA was 38.61 %, 43.33 % and 7.46 % respectively in the above groups. There were obvious differences between capsule oxymatrine group and placebo group or between injection oxymatrine group and placebo group (P=0.001), but there were no significant difference between capsule oxymatrine group and injection oxymatrine group (P=0.643). The negative conversion rate of serum HBeAg was 31.91 %, 39.29 % and 6.45 % respectively in the above groups. There was an obvious difference between capsule oxymatrine group and placebo group or between injection oxymatrine group and placebo group (P=0.001), but no significant difference between capsule oxymatrine group and injection oxymatrine group (P=0.469).

Normalization rate of serum ALT

The normalization rate of serum ALT in capsule oxymatrine group, injection oxymatrine group and placebo group was 76.47 %, 83.33 % and 40.00 %, respectively. There was an obvious difference between capsule oxymatrine group and placebo group or between injection oxymatrine group and placebo group (P=0.001, Table 2), but no significant difference between capsule oxymatrine group and injection oxymatrine group (P=0.425).

Comparison of therapeutic effect among 3 groups of chronic hepatitis B

The complete and partial response rates were 24.51 % and 57.84 % in capsule oxymatrine group, 33.33 % and 50.00 % in injection oxymatrine group, 2.99 % and 41.79 % in placebo group. There was an with obvious difference between capsule oxymatrine group and placebo group or between injection oxymatrine group and placebo group (P=0.001, Table 3), but no significant difference between capsule oxymatrine group and injection oxymatrine group (P=0.4589).

Adverse effects

In this study, 8 patients had adverse effects in capsule oxymatrine group with an incidence of 7.77 %, 2 patients in injection oxymatrine group with an incidence of 6.67 %, and 6 patients in placebo group with an incidence of 8.82 %. The difference among 3 groups had no statistical significance

Table 1 Negative conversion rates of serum HBsAg and comparison among capsule oxymatrine group, injection oxymatrine group and placebo group

Index	Group	Positive number	Number of negative conversion	Negative conversion rate (%)	Comparison among 3 groups	
					χ^2	*P* value
HBsAg	Capsule	101	2	1.98		
	Injection	30	1	3.33		0.269
	Placebo	67	0	0.00		
HBV DNA	Capsule	101	39	38.61		
	Injection	30	13	43.33	22.716	0.001
	Placebo	67	5	7.46		
HBeAg	Capsule	94	30	31.91		
	Injection	28	11	39.29	17.042	0.001
	Placebo	62	4	6.45		

The comparison of negative conversion rates of serum HBsAg, HBV DNA and HBeAg was performed with chi-square test, statistic was χ^2.

Table 2 Normalization rate of serum ALT and comparison among capsule oxymatrine group, injection oxymatrine group and placebo group

Group	Number of ALT abnormality before treatment	Number of ALT normalization after treatment	Normalization rate (%)	Comparison among 3 groups	
				χ^2	*P* value
Capsule	102	78	76.47		
Injection	30	25	83.33	28.352	0.001
Placebo	65	26	40.00		

The comparison of ALT normalization rate was performed with chi-square test, statistic was χ^2.

Table 3 Comparison of therapeutic effect among 3 groups with chronic hepatitis B

Group	Complete response	Partial response	Non-response	Comparison among 3 groups	
				χ^2	*P* value
Capusle (*n*=102)	25 (24.51 %)	59 (57.84 %)	18 (17.65 %)		
Injection (*n*=30)	10 (33.33 %)	15 (50.00 %)	5 (16.67 %)	35.957	0.0001
Placebo (*n*=67)	2 (2.99 %)	28 (41.79 %)	37(55.22 %)		

The comparison of therapeutic effect among 3 groups was performed with K-W test, statistic was χ^2.

(*P*=0.931). The adverse effects were mild or moderate and mainly manifested as symptoms of upper alimentary tract, rash, bad taste. No severe adverse effect occurred. The statistical analysis of adverse effects included 2 cases withdrawn because of side effects.

DISCUSSION

Hepatitis B virus is a DNA virus that produces both acute and chronic infections of the liver in humans. It has been estimated that over 300 million people worldwide are chronically infected with HBV and that over 250 000 people would die each year due to HBV-associated complications of cirrhosis and primary hepatocellular carcinoma[12-18]. For many years, alpha interferon has been the only approved therapy for chronic HBV infection in most countries. Interferon was effective in 30-40 % of patients, and it must be given by injection and was frequently associated with fever and influenza-like symptoms[19-23]. Recently, lamivudine was approved for the treatment of chronic HBV infection in many regions of the world. Although convenient and well-tolerated, lamivudine' s efficacy rate was similar to interferon and prolonged administration of lamivudine was associated with development of resistance[24-30]. New agents, such as adefovir dipivoxil, offered a promise either alone or in combination with lamivudine in the treatment of individuals who were ' treatment naï ve' have developed lamivudine resistance[31-33]. Up to date, no specific therapy is available for chronic hepatitis B. The following factors may be associated with its pathogenesis such as virulence of HBV strains, number of infected hepatocytes and host immune response, antiviral agents, immunomodulators and drugs might be capable of improving liver function[12-15,34-41].

Traditional Chinese medicine has been widely used for the treatment of liver disease in China[11]. Oxymatrine extracted from *Sophora alopecuraides L.* has been shown to have a remarkable HBV suppressing effect with 40 % serum conversion rate for HBeAg and HBV DNA, similar to that of alpha interferon[8,9,11]. Experiment *in vitro* indicated that oxymatrine had an inhibitory role in the secretion of HBsAg and HBeAg by 2.2.15 cell line transfected with HBV DNA and the inhibitory rates increased gradually following increased oxymatrine concentration and the extension of effect time within a definite range[42]. *In vivo* study of HBV transgenic mouse showed that when mice were injected intraperitoneally oxymatrine at 100 mg/kg, 200 mg/kg and 300 mg/kg once a day for 30 days, the quantity of HBsAg and HBeAg in the liver decreased obviously compared with control group, and there was no significant difference among 3 doses[10]. Clinical research suggested that the normalization rates of serum ALT and TB, and the negative conversion rates of serum HBsAg and HBV DNA were similar to alpha interferon when oxymatrine was applied to treatment of chronic hepatitis B. The results in

present study were similar to the therapeutic effect of interferon in the treatment of chronic hepatitis B at home and abroad[9,11,17,43], indicating that capsule oxymatrine is an effective and safe agent for treatment of chronic hepatitis B.

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