Hepatitis B patients exhibiting mild alanine aminotransferase elevation: A comparative analysis of treatment with and without Bicyclol tablets

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Abstract. The aim of the present study was to analyze the medicinal effect of Bicyclol tablets on patients with chronic hepatitis B (CHB) and concomitant mild alanine aminotransferase (ALT) elevation (40-80 IU/l). A retrospective cohort study, which included patients from the hospital information system (HIS; established by the Chinese Academy of Medical Sciences) viral hepatitis database comprised of 18 third-grade class A hospitals in China, was performed. Patients were divided into an exposed group (administered with Bicyclol tablets) and a non-exposed group (no administration of Bicyclol tablets). The CHB patients that exhibited mild ALT elevation provided the curative effect analysis data set, and the patients with viral hepatitis who underwent more than two creatinine/hemoglobin/leucocyte examinations served as the safety analysis data set. The factors influencing ALT normalization rate were analyzed and the safety of Bicyclol tablets was assessed. In total, 82 pairs of patients were included in the curative effect analysis, and single factor analysis revealed that the ALT normalization rate of the exposed group was statistically significantly higher than that of the non-exposed group (P=0.040) for patients with mild ALT elevation. After adjusting for patient age, gender, baseline ALT levels, state of illness upon admission, pattern of hospitalization, hospitalization days and drug combination, the odds ratio (95% confidence interval) of the ALT normalization rate of the exposed group was 2.156 (1.103-4.215) when compared with the non-exposed group. During treatment, the occurrence rates of creatinine/hemoglobin/leucocyte level abnormalities of the exposed group, which were included in the safety analysis were statistically significantly lower than those of the non-exposed group (P<0.05). These findings indicate that Bicyclol tablets improve the ALT normalization rate of CHB patients exhibiting mild ALT elevation.

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Introduction

Chronic hepatitis B (CHB), which is defined as persistence of hepatitis B surface antigen for six months or more, is a major public health problem. According to the World Health Organisation, there are an estimated 240 million chronically infected individuals worldwide, particularly in low- and middle-income countries (1). The major complications of CHB are cirrhosis and hepatocellular carcinoma (HCC). Between 20 and 30% of those who become chronically infected will develop these complications, and an estimated 650,000 individuals will succumb due to CHB annually (1). The majority of individuals are unaware of their hepatitis B virus (HBV) infection, and, therefore, often present at an advanced stage of the disease (1). China has been identified as a region with a high prevalence of HBV; based on the National Disease Supervision Information Management System of China, the mean reported incidence of HBV was 84.3 per 100,000 in China between 2005 and 2010 (2). Despite the reduction in the incidence of the HBV infection, there are ~93 million individuals chronically infected with HBV and ~20 million cases of symptomatic CHB in China currently (3). The high prevalence of CHB poses heavy social and financial burdens for China.

The dynamic natural history of CHB infection involves a complex interaction between the host immune system and the virus. Broadly, there are four phases, of varying duration, which are defined as follows: Immune-tolerant, immune-elimination (or immune-clearance), inactive and reactivation (4,5). The immune-tolerant phase is characterized by a high level of HBV replication, HBeAg positivity, and a normal or minimally elevated alanine aminotransferase (ALT) level (6). Low ALT level CHB-infected patients (ALT <80 U/l) may be in the HBV immune-tolerant phase (7). According to local therapeutic guidelines of prevention and treatment of

CHB, patients exhibiting mild ALT elevation (40-80 IU/l) should receive antiviral therapy subsequent to confirmation of hepatic fibrosis status via biopsy or non-invasive examinations (8-10). For patients whose ALT level fluctuates, but never normalizes, the degree of liver inflammation and fibrosis were more serious, and the occurrence rate of cirrhosis and hepatocellular carcinoma may be higher (11). In clinical practice, antiviral treatment cannot be administered to CHB patients with low ALT levels due to lack of timely histological diagnosis; this may cause silent progression of the disease and result in severe sequelae.

Bicyclol is a liver-protective substance administered to patients with various types of liver disease. Its mechanism of action may be closely associated with free radical-scavenging properties, protection against lipid peroxidation, protection of hepatic cell membranes and mitochondrial function (12), and inhibition of inflammatory cytokines (13). It was demonstrated in experimental and clinical studies that Bicyclol decreased serum transaminase levels and resulted in improvements as observed by pathology (14-16). Although various studies have examined the clinical efficacy of Bicyclol in virus hepatitis patients, none, to the best of our knowledge, have investigated the effectiveness and safety of Bicyclol in a clinical setting.

The current study selected hospitalization data of CHB patients exhibiting mild ALT elevation from a hospital information system (HIS) database of 18 third-grade class A hospitals in China. The ALT normalization rate served as the evidence of successful treatment, and the curative effect of Bicyclol tablets on patients with HBV accompanied by mild ALT elevation was discussed in order to propose practical clinical applications.

Patients and methods

Data sources and standardization. Hospitalization data of patients included in the present study was obtained from a HIS database (compiled by the Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Science, Beijing, China) using data from 18 third-grade class A hospitals in China. Informed consent was not considered necessary due to the retrospective nature of the study. Research was performed subsequent to discussion and approval by the Ethics Committee of the Institute of Basic Research in Clinical Medicine, China academy of Chinese Medical Sciences. The HIS database was standardized prior to data extraction and data analysis, with the standardization process involving exclusion of redundant data in patients' general information, discordant data and advice from doctors that was deemed irrelevant. Dosages were standardized, as were physiochemical indexes. Following data integration, data meeting the following criteria were included in the current study.

Treatment analysis data inclusion criteria. Exposed group: Patients with HBV that were taking Bicyclol tablets were selected from the viral hepatitis database; the ALT examination was conducted 7 days prior to Bicyclol administration; the result revealed a mild abnormality in ALT level (40-80 U/l); ALT examination was conducted within 7 days of drug withdrawal; and medication consumption had been for >15 and <30 days. Non-exposed group: Patients with HBV that were not taking Bicyclol tablets were selected from the viral hepatitis database; duration of hospitalization was >15 days and <30 days; ≥2 ALT examinations had been conducted, with the first result revealing that there was mild abnormality (40-80 U/l).

Safety data inclusion criteria. Exposed group: Patients taking Bicyclol tablets were selected from the viral hepatitis database; creatinine/hemoglobin/leucocyte level measurements had been conducted 7 days prior to Bicyclol administration and within 7 days of Bicyclol withdrawal; and patients with an initially abnormal result were excluded. Non-exposed group: Patients not taking Bicyclol tablets were selected from the viral hepatitis database; duration of hospitalization was <30 days; ≥2 creatinine/hemoglobin/leucocyte level examinations had been conducted; and patients with an initially abnormal result were excluded. A 1:1 match of every index was made between the members of the exposed and non-exposed groups according to gender, age and state of illness on admission.

Data extraction and data analysis. All standardized data was extracted from the HIS database in strict accordance with the inclusion criteria; the data extraction and analysis process is presented in Fig. 1.

Definition of a treatment effect. The criteria for judging the curative effect indexes were as follows: The ALT examination result for patients of the exposed group was measured as close to the time of Bicyclol withdrawal as possible and no later than 7 days subsequently. For the patients in the non-exposed group, the last ALT detection value during hospitalization was used. When the final ALT detection value was ≤40 U/l, it was defined as normalization, when the final ALT detection value was >40 U/l, it was defined as not normalized.

Statistical analysis. Between-group differences with continuous variables were analyzed using the independent-samples T test or non-parametric test. Between-group differences in categorical data and single factor analysis of between-group ALT normalization rates were analyzed using χ^2-test (Pearson's method). In addition, multifactorial analysis of between-group ALT normalization rates was conducted using unconditional logistic regression. Variables such as the age of patients, gender, baseline ALT levels, initial illness severity, hospitalization conditions, hospitalization duration, drug combination (with/without reduced glutathione; GSH) and treatment regimen were converted to dichotomous variables, and modeled for Wald analysis. Subgroup analysis was performed using a single factor logistic regression model, and the ALT normalization rate was taken as a dependent variable and the groups as independent variables; the differences in ALT normalization rates were compared between the two groups. Statistical tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was performed using SQL Sever 2008 (Microsoft, Inc., Redmond, WA, USA) and SPSS 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Assessment of curative effect

General information of enrolled patients. There were 82 CHB patients taking Bicyclol tablets in the exposed group, which

Table I. Comparison of patient information between the two groups.

Variables	Exposed group (n=82)	Non-exposed group (n=82)	P-value
Age (years, means ± SD)	47.38±16.79	47.82±16.85	0.690
Gender			
Male	63	63	1.000
Female	19	19	
Baseline ALT (U/l, means ± SD)	58.80±11.06	55.60±10.30	0.062
State of illness on admission			
Common	62	62	1.000
Urgent	20	20	
Pattern of hospitalization			
Outpatient	72	67	0.277
Emergency patient	10	15	
Hospitalization days (means ± SD)	20.93±4.47	21.32±4.01	0.399
Drug combination			
Combination with GSH	30	37	0.266
Non-combination with GSH	52	45	

ALT, alanine aminotransferase; GSH, reduced glutathione; SD, standard deviation.

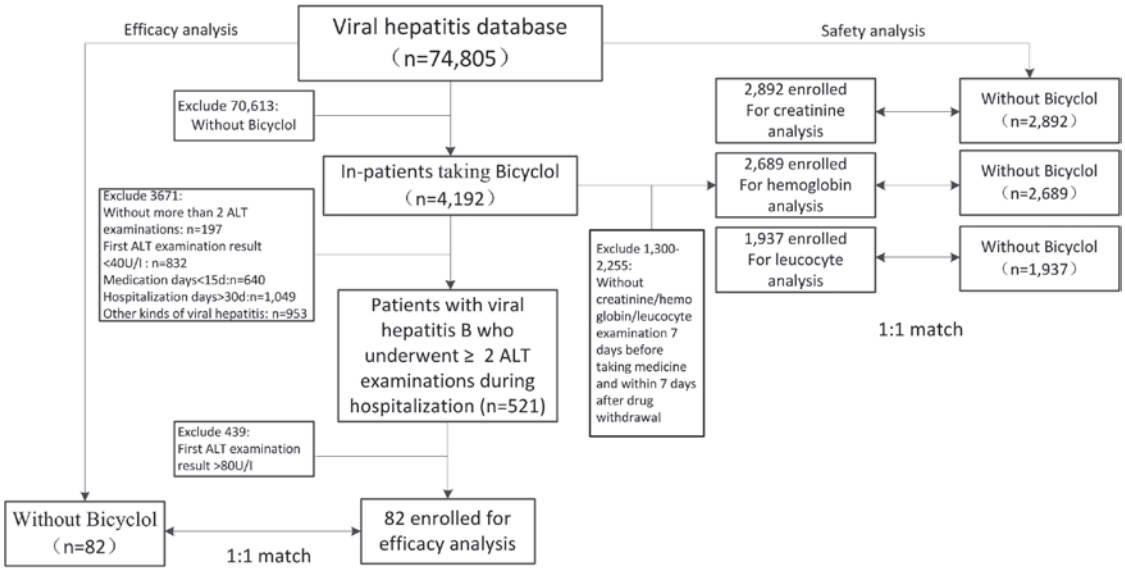

Figure 1. Data extraction and analysis flowchart.

met the inclusion criteria, and 82 CHB patients not taking Bicyclol tablets in the non-exposed group. The patients in the two groups were selected from the viral hepatitis database according to gender, age and state of illness on admission with a 1:1 match between groups. Differences between general information, such as age, gender, and baseline ALT levels of patients in the two groups were not identified as being statistically significant (P>0.05), therefore the experimental results of the two groups are comparable (Table I).

Single factor analysis of ALT normalization rates. No serious deterioration of liver function occurred in either of the two groups, and the ALT normalization rates of the exposed and non-exposed groups were 65.85 and 50.00%, respectively. Between-group differences were identified as being statistically significant (χ^2=4.228; P=0.040; Table II).

Multifactorial analysis of ALT normalization rates. After revising patient age, gender, baseline ALT levels, illness

Table II. Comparison of ALT normalization rates between the two groups.

Variables	Cases of outcome/total cases (%)		Pearson's χ^2	P-value
	Exposed group	Non-exposed group		
Without ALT normalization	28/82 (34.15)	41/82 (50.00)	4.228	0.040
With ALT normalization	54/82 (65.85)	41/82 (50.00)		

ALT, alanine aminotransferase.

Table III. Multfactorial analysis of ALT normalization rates.

Subgroup	Wald χ^2	P-value	Adjusted OR (95% CI)
Group (exposed vs. non-exposed)	5.049	0.025	2.156 (1.103-4.215)
Age (≥45 vs. <45)	0.320	0.571	1.226 (0.606-2.479)
Gender (male vs. female)	0.195	0.659	0.837 (0.380-1.842)
Baseline ALT levels (≥60 U/l vs. <60 U/l)	0.664	0.415	0.756 (0.385-1.482)
State of illness on admission (common vs. urgent)	0.035	0.852	0.924 (0.402-2.124)
Pattern of hospitalization (outpatients vs. emergency patients)	1.604	0.205	0.524 (0.193-1.424)
Hospitalization days (≥20 vs. <20)	2.983	0.084	1.804 (0.923-3.526)
Combination with GSH (yes vs. no)	2.377	0.123	0.593 (0.305-1.152)

ALT, alanine aminotransferase; GSH, reduced glutathione; OR, odds ratio; CI, confidence interval.

severity on admission, patterns of hospitalization, duration of hospitalization and drug combination (with/without GSH) using a multifactorial model, the results revealed that the differing group type was the independent influencing factor (P=0.025) that influenced ALT normalization. The patients in the exposed group possessed higher ALT normalization rates [odds ratio (OR)=2.156; 95% confidence interval (CI), 1.103-4.215] compared with the non-exposed group (Table III).

Subgroup analysis of ALT normalization rates. Subgroup analysis was performed for two levels of each of the above-mentioned variables (Table IV). For male patients or those whose baseline ALT levels were <60 U/l, consumption of Bicyclol tablets resulted in increased ALT normalization rates when compared with non-exposed group, and the difference was statistically significant (P<0.01). The ALT normalization rates of the two groups were not identified to be statistically significant when compared with the rest of the subgroup analysis.

Safety analysis. As shown in Table V, the safety data sets reveal that the occurrence rates of abnormal creatinine, hemoglobin and leucocyte levels in the exposed group were lower than those in the non-exposed group, and the difference was statistically significant (P<0.05). The findings indicate that Bicyclol tablets possess a good safety profile.

Discussion

CHB is a global health problem affecting millions of people worldwide. The clinical spectrum is wide, ranging from a subclinical inactive carrier state, to progressive chronic hepatitis, cirrhosis, decompensation and HCC (4). According to Chinese Guidelines for Prevention and Treatment of Chronic Hepatitis B (8), when ALT levels are between 1 x upper limit of normal (ULN) and 2 x ULN, liver biopsy or non-invasive examinations (such as transient elastography) should be performed in order to evaluate the state of liver fibrosis and establish whether antiviral treatment is required. In China, numerous patients were unable to undergo relevant examinations due to

Table IV. Comparison of ALT normalization rates in subgroup analysis.

Subgroup	Cases of ALT normalization/total (%)		Pearson's χ^2	P-value	OR (95% CI)
	Exposed group	Non-exposed group			
Age (years)					
≥45	38/57 (66.66)	29/56 (51.79)	2.569	0.109	1.862 (0.871-3.983)
<45	16/25 (64.00)	12/26 (46.15)	1.621	0.203	2.074 (0.675-6.377)
Gender					
Male	43/63 (68.25)	28/63 (44.44)	7.106	0.008	2.687 (1.299-5.559)
Female	11/19 (57.89)	13/19 (68.42)	0.450	0.502	0.635 (0.168-2.396)
Baseline ALT levels (U/l)					
≥60	22/41 (53.66)	15/27 (55.55)	0.024	0.878	0.926 (0.349-2.945)
<60	32/41 (78.05)	26/55 (47.27)	8.816	0.003	3.966 (1.597-9.847)
State of illness on admission					
Common	39/62 (62.90)	30/62 (48.39)	2.627	0.105	1.809 (0.883-3.703)
Urgent	15/20 (75.00)	11/20 (55.00)	1.720	0.190	2.455 (0.642-9.391)
Pattern of hospitalization					
Outpatients	45/72 (62.50)	33/67 (49.25)	2.457	0.117	1.717 (0.873-3.376)
Emergency patients	9/10 (90.00)	8/15 (53.33)	3.088	0.079	7.875 (0.788-78.671)
Hospitalization days					
≥20	32/46 (69.57)	29/50 (58.00)	1.374	0.241	1.655 (0.713-3.844)
<20	22/36 (61.11)	12/32 (37.50)	3.705	0.054	2.619 (0.983-6.981)
Combination with GSH					
Yes	18/30 (60.00)	16/37 (43.24)	1.843	0.175	1.969 (0.740-5.235)
No	36/52 (69.23)	25/45 (55.56)	1.916	0.166	1.800 (0.783-4.137)

ALT, alanine aminotransferase; GSH, reduced glutathione; OR, odds ratio; CI, confidence interval.

Table V. Occurrence rates (%) of creatinine/hemoglobin/leucocyte level abnormalities between the two groups.

Observation indexes	Exposed group % (n/N)	Non-exposed group % (n/N)	Pearson's χ^2	P-value
Creatinine	5.74 (166/2892)	7.92 (229/2892)	10.7846	0.0010
Hemoglobin	24.62 (662/2689)	28.93 (778/2689)	12.7614	0.0004
Leucocyte	34.9 (674/1931)	38.22 (738/1931)	4.5727	0.0325

A 1:1 match of every safety observation index was made between the exposed and non-exposed groups according to gender, age and state of illness. n, number of occurrences; N, total number of cases.

financial constraints, low prevalence of noninvasive equipment or resistance to invasive liver biopsy. A study conducted in Taiwan revealed that the cumulative occurrence rate of HCC at 3, 5 and 10 years (2.3, 5.3 and 13.4%, respectively) in patients with a continuously low (15-44 U/l) ALT level were lower than those of patients with ALT abnormalities (3.7, 8.5 and 21.0%, respectively) (17). Thus, CHB patients with mild ALT elevation should be observed in clinical practice and the elevated ALT levels should be controlled to within a normal range.

Health care administrative policy and financial support greatly accelerated the adoption of electronic health records (EHRs) in China. According to a 2012 national survey in China, ~50% of 1,004 responding hospitals had adopted at least the basic forms of EHR and practice management systems often referred to as HIS (18). Retrospective studies based on HIS data guarantee objectivity and veracity, identify potential patterns from within large quantities of data, and provide a reference point and ideas for prospective studies and clinical practice. All data in the current study was extracted from the HIS database, which contains diagnostic and treatment information for ~3 million patients from 39 large third-grade class A hospitals capable of more advanced levels of diagnosis and treatment. Detailed information, including disease diagnosis, laboratory exams, treatment regimens, and disease outcome

information is also compiled. There is an obvious advantage in veracity of data, large sample sizes, multidimensional analysis, multiple assessment indices and from obtaining information regarding diagnosis and treatment.

The single factor analysis result revealed that the ALT normalization rate of the exposed group was significantly higher than that of the non-exposed group (P<0.05). After adjusting for individual patient variables, the ALT normalization OR (95% CI) of the exposed group was 2.156 (1.103-4.215) compared with that of the non-exposed group. Subgroup analysis indicated that when gender or baseline ALT levels were taken as stratification factors, differences in ALT normalization rates between the two groups were statistically significant (P<0.05). This indicates that males or patients with baseline ALT levels that are <60 U/l are the dominant population, and the administration of Bicyclol results in improved curative effects. Furthermore, safety data analysis revealed that kidney and the occurrence rates of blood abnormalities in patients in the exposed group were lower than those of the non-exposed group (P<0.05), which demonstrates that Bicyclol possesses a good safety profile.

Bicyclol may improve injured liver cell function and alleviate pathological injuries of the liver. Pharmacological studies show that Bicyclol may inhibit the expression and activity of key inflammatory regulatory factors, such as nuclear transcription factor-κB, tumor necrosis factor-α, interleukin-1β, transforming growth factor-β1 and inducible nitric oxide (NO) synthase. In addition, Bicyclol may inhibit inflammatory injury, oxidative damage and abnormal apoptosis of hepatocytes caused by generation of reactive oxygen species and NO generation (19-22), thereby improving the structure and function of the hepatocyte and mitochondrial membranes (23,24). Previous clinical studies indicate that orally administered Bicyclol possesses a good safety profile and is advantageous in the setting of CHB-induced ALT elevation (14,25).

In conclusion, the present study demonstrated that Bicyclol tablets improved the ALT normalization rate of viral CHB patients exhibiting mild ALT elevation. However, there were certain limitations of the present study due to its inherent retrospective nature, and the number of cases and observation indices were, therefore, comparatively small. Large sample, randomized, controlled studies are required to provide more powerful, evidence-based treatment strategies for use in clinical practice concerning Bicyclol administration in the setting of HBV.

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