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Hepatocyte growth promoting factor combined with antiviral drug in the treatment of chronic hepatitis B and its effect on liver function, viral replication and fibrosis index.

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Abstract

Objective: To investigate the clinical efficacy of hepatocyte growth promoting factor (PHGF) combined with antiviral drug in the treatment of Chronic Hepatitis B (CHB) and its effect on viral replication and fibrosis index.

Methods: 120 cases of CHB patients in our hospital from January 2014 to August 2016 were randomly divided into treatment group and control group, 60 cases in each group. The control group was treated with entecavir and the treatment group was treated with entecavir plus PHGF. The liver function and liver fibrosis index changes before and after treatment in patients of the two groups were compared, and the negative rate of HBV-DNA was analysed after treatment.

Results: Before treatment, the serum levels of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Total Bilirubin (TBIL) of the two groups showed no significant difference (P>0.05). The serum levels of ALT, AST and TBIL of the two groups decreased significantly after treatment, and the treatment group were significantly lower than that of the control group (P<0.05). After the treatment of 24 and 48 w, the HBV-DNA negative conversion rate of the treatment group were significantly higher than that of the control group (P<0.05). Before treatment, the serum levels of Hyaluronic Acid (HA), type IV collagen (IV-C), type III procollagen (PIIIP) and layer fibronectin (LN) in the patients of two groups showed no significant difference (P>0.05). The serum levels of HA, IV-C, PIIIP and LN of the two groups decreased significantly after treatment, and the treatment group were significantly lower than that of the control group (P<0.05). The adverse reaction rate of the two groups had no significant difference (P>0.05).

Conclusion: PHGF combined with antiviral drug treatment of CHB could significantly enhance the antiviral effect and inhibit the progress of liver fibrosis with better clinical efficacy and less adverse reactions for clinical promotion.

Keywords: Hepatocyte growth promoting factor, Entecavir, Chronic hepatitis B, Viral replication, Liver fibrosis.

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Introduction

Chronic Hepatitis B (CHB) was usually defined as the persistence of HBsAg for more than six months or HBsAg positivity combined with clinical manifestations, which is a chronic infectious disease caused by Hepatitis B Virus (HBV), along with hepatocellular necrosis, degeneration and liver fibrosis in later stage [1,2]. Despite advances in the clinical treatment and life science, CHB is still a major epidemiological problem worldwide, an estimated two billion people was infected with hepatitis B, and the infectious rates of HBV are highest in China and other areas and countries of Asia [3]. At present, because there was no specially efficient drug for CHB, antiviral drugs are commonly used for treatment. However, CHB is a disease which results from the complicated interactions between personal genetic susceptibility and environmental factors, different CHB patients showed different antiviral therapy effect due to viral resistance, poor patient compliance and host's immune status [4]. Hepatocyte growth promoting factors (PHGF) are extracted from the liver of fresh suckling pig, which can stimulate the synthesis of DNA of hepatocytes, promote the regeneration of hepatocytes, synthesize albumin, regulate the immunity of hepatocytes function and repair damaged liver cells [5,6]. However, the details of mechanism and adverse events of PHGF are not yet completely clear, which need further exploration [7,8]. In this study, 60 patients with CHB were treated with PHGF combined with antiviral drugs to observe the clinical efficacy and the effect on viral replication and fibrosis.

Materials and Methods

General information

120 patients with CHB who were treated in hospital from January 2014 to August 2016 were randomly divided into treatment group and control group, each group of 60 cases. Treatment group: 36 males and 24 females, aged 29 to 54 y, mean age is 41.1 ± 10.5 y, duration of disease: 7 to 22 y, average duration is 11.2 ± 4.6 y, including 26 mild cases, 23 moderate cases, 11 severe cases, totally 21 patients with mild or moderate comorbidity (including hypertension, diabetes, chronic bronchitis, etc.). Control group: 34 males and 26 females aged 31 to 56 y, mean age is 41.8 ± 10.7 y, duration of disease is 6 to 24 y, average duration is 11.0 ± 4.4 y, including 25 mild cases, 26 moderate cases, 9 severe cases, totally 25 patients with mild or moderate comorbidity (including hypertension, diabetes, chronic bronchitis, etc.). There were no statistically significant differences between the two groups (P>0.05).

Inclusion and exclusion criteria

The diagnostic criteria for all patients were in accordance with the relevant standard in the Guidelines for Prevention and Treatment of Chronic Hepatitis B (2010 edition): positive HBsAg and HBeAg, HBV DNA quantitative ≥ 10^5 copies/ml; negative HBeAg, HBV DNA quantitative ≥ 10^4 copies/ml; serum alanine aminotransferase (ALT) ≥ 2 to 5 times of normal value; at least two abnormalities in serum Hyaluronic Acid (HA), layer Fibronectin (LN), type IV collagen (IV-C) or type III procollagen (PIIIP) [9]. Patients with other viral hepatitis, diabetes, liver cancer, hyperthyroidism or autoimmune diseases were excluded.

Treatment methods

Both groups were treated with conventional hepatoprotective and symptomatic therapy. On the basis of this, the control group was given oral administration of entecavir (Shanghai Bristol-Myers Squibb Pharmaceutical Co., Ltd., batch number: AAJ9769) 0.5 mg once a day; the treatment group was treated with entecavir plus intravenous infusion of promoting hepatocyte growth factor (Guangdong Yipinhong Pharmaceutical Co., Ltd., batch number: 15070704) 120 mg once a day for 3 consecutive months. Both groups were treated for 48 w.

Observational index

All patients were examined blood, liver and kidney function, blood electrolytes and liver fibrosis indicators before and after treatment. The serum HBV-DNA level of the two groups was detected by Gene-Light 9800 real-time fluorescence quantitative-analysis (PCR, ABI Vii 7 Dx). Automatic biochemical analyzer (Siemens ADVIA 2400) was used to detect the liver function indexes, including Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Total Bilirubin (TBIL). After treatment for 24 and 48 w, negative conversion rate of HBV-DNA was measured between the two groups. Automatic chemiluminescence analyzer (Autolumo A2000) was applied to detect the liver fibrosis indexes of the two groups, including HA, IV-C, PIIIP and LN. Adverse reactions of patients during the treatment were observed such as dizziness, nausea, vomiting and rash.

Statistical processing

SPSS 19.0 was used to deal with statistical data. The data were described as mean ± standard deviation ($\bar{x} \pm s$). The t test was used to compare the two groups and the count data were compared by χ^2 test. P<0.05 was defined as a significant difference.

Results

Comparison of serum liver function in two groups

There were no significant differences in serum ALT, AST and TBIL levels between the two groups before treatment (P>0.05). The levels of ALT, AST and TBIL in the two groups were significantly lower than those in the control group after treatment (P<0.05, Table 1).

Table 1. *Comparison of serum liver function in two groups ($\bar{x} \pm s$).*

Index	Treatment group (n=60)		Control group (n=60)	
	Before	After	Before	After
ALT(U/L)	214.4 ± 28.3	42.5 ± 11.8[ab]	212.8 ± 27.8	76.7 ± 13.0[a]
AST (U/L)	155.2 ± 22.1	43.6 ± 24.6[ab]	157.4 ± 23.4	66.5 ± 12.8[a]
TBIL (μmol/L)	37.8 ± 9.5	14.8 ± 4.8[ab]	37.4 ± 8.8	19.2 ± 5.6[a]

Comparison of negative conversion rate of HBV-DNA between the two groups

The negative conversion rate of HBV-DNA in the treatment group was significantly higher than that in the control group at 24 and 48 w (P<0.05, Table 2).

Table 2. *Comparison of negative conversion rate of HBV-DNA between the two groups (n, %).*

Groups	Cases	24 w	48 w
Treatment group	60	39 (65.0)	50 (83.3)
Control group	60	26 (43.3)	32 (53.3)
χ^2		5.67	12.48
P		0.017	0.000

Comparison of liver fibrosis in two groups

There was no significant difference in serum HA, IV-C, PIIIP and LN between the two groups before treatment (P>0.05). The levels of serum HA, IV-C, PIIIP and LN were significantly decreased after treatment (P<0.05), and the treatment group

was statistically lower than the control group (P<0.05, Table 3).

Table 3. *Comparison of liver fibrosis in two groups ($\bar{x}$ ± s, μg/L).*

Index	Treatment group (n=60)		Control group (n=60)	
	Before	After	Before	After
HA	183.2 ± 43.2	124.8 ± 20.6[ab]	184.4 ± 40.8	165.1 ± 22.0[a]
IV-C	340.4 ± 72.8	186.8 ± 30.6[ab]	342.3 ± 71.2	241.5 ± 36.0[a]
PIIIP	264.4 ± 51.0	114.9 ± 21.5[ab]	265.7 ± 54.2	138.6 ± 18.4[a]
LN	246.6 ± 17.5	131.8 ± 25.1[ab]	242.4 ± 17.5	184.8 ± 27.6[a]

Note: [a]Compared with the data before treatment, P<0.05; [b]Compared with control group, P<0.05.

Comparison of adverse reactions between the two groups

There were no serious adverse reactions during the treatment period. In the treatment group, there had 3 cases of nausea and vomiting, 1 case of dizziness and headache, and 1 case of rash. The incidence of adverse reactions was 8.3% (5/60). In the control group, there had 2 cases of nausea and vomiting, and 2 cases of dizziness and headache. The incidence of adverse reactions was 6.7% (4/60). There was no significant difference in the incidence of adverse events between the two groups (χ^2=0.120, P=0.729).

Discussion

According to the World Health Organization (WHO), the number of people infected with HBV in the world was about 2 billion, of which about 32 million were chronic HBV infected patients. About 100 million patients died of HBV infection caused by liver failure, liver cirrhosis, hepatocellular carcinoma and other diseases each year [10,11]. HBV DNA can be integrated into the host liver cell genome, make liver cells of the host be in long-term infection through a unique reverse transcription cycle replication [12]. The host's immune response could be activated, so that the liver was free from pathological damage. Moreover, microcirculation function confusion occurred, which results in liver cell ischemia and hypoxia, and finally leads to secondary damage to liver cells and liver fibrosis [13,14]. Chronic hepatitis B treatment guidelines clearly pointed out that the short-term goal of HBV treatment was as follows: viral replication inhibition, liver cell damage reduction, HBsAg disappearance, HBV-DNA negative shift and normal ALT [15,16]; While long-term goal of treatment was as follows: liver damage progress delay, reduction in cirrhosis, liver cancer and a variety of complications, effective improvement in patients' life quality and the prolonged survival time.

Entecavir is a kind of cyclopentanoic acid guanosine analog and a new type of nucleotide reverse transcriptase inhibitor could effectively inhibit the HBV-DNA polymerase, viral DNA replication and DNA chain extension, playing an important role in antiviral [17,18]. However, wide clinical application of antiviral drugs made increased drug-resistance, so that the treatment of hepatitis B has been seriously affected [19,20]. Studies have shown that compared with a single medication, the clinical efficacy of combination therapy was significantly improved in the patient's liver fibrosis index. Hepatocyte growth hormone was a hepatocyte growth stimulating factor, since animal models and various experiments have proved that it could protect and promote hepatocyte repair and regeneration [21]. In addition, the drug could also regulate the body's immune function, bring down bilirubin and HA content, as well as resist liver fibrosis, thus effectively improve the liver microcirculation and reduce further damage [22].

Compared with entecavir alone therapy, the combination of PHGF and entecavir in the treatment of CHB showed that improvement of patients' liver function and notable shift of negative HBV-DNA, as well as the patient's liver fibrosis index. Zhou et al. found that PHGF could promote collagen degradation by stimulating collagenase activity [23]. To inhibit pulmonary fibrosis, over expression of transforming growth factor-β1 (TGF-β1) mRNA, deposition of extracellular matrix and synthesis of collagen were all restrained by PHGF. The results also showed that no statistically significant difference was observed in the incidence of adverse events in both groups (P>0.05). The results suggested that PHGF combined with entecavir therapy had a better safety profile in the treatment of CHB.

The serological markers of HA, IV-C, PIIIP and LN can reflect the degree of hepatic ECM metabolism [24]. The results showed that the serum levels of HA, IV-C, PIIIP and LN after treatment in the treatment group were significantly lower than those in the control group, which suggested that PHGF combined with entecavir can reverse the liver fibrosis. The study showed that PHGF can regulate the organic immune function, decrease the levels of bilirubin and HA, inhibit the liver fibrosis, effectively improve the liver microcirculation and reduce the further liver injury [22]. PHGF is a variant for human body, the literatures showed that PHGF can cause severe allergic responses such as abdominal pain, allergic shock, acute laryngeal edema and perioral herpes [25]. In this study, there were 3 cases of nausea and vomiting, 1 case of headache and dizziness and 1 case of erythra in the treatment group, 2 cases of nausea and vomiting and 2 cases of headache and dizziness in the control group. The patients in the two groups had no serious adverse reactions. There was no significant difference in the occurrence of adverse events between the two groups (P>0.05), which suggested that PHGF combined with entecavir is safer for the treatment of CHB.

In summary, PHGF-assisted antiviral treatment of CHB could significantly enhance the clinical efficacy of anti-virus, inhibit the progress of liver fibrosis. The therapy had good clinical efficacy and less adverse reactions, which is worthwhile for further clinical spreading.

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