THE EFFECT OF ARTIFICIAL LIVER PLASMADIAFILTRATION COMBINED WITH ENTECAVIR ON SHORT-TERM CURATIVE EFFECT, LIVER FUNCTION, AND HBV-DNA NEGATIVE CONVERSION RATE IN THE TREATMENT OF CHRONIC SUBACUTE LIVER FAILURE

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ABSTRACT

Objective: *To explore the effects of artificial liver plasma diafiltration (PDF) combined with entecavir in the treatment of patients with chronic and subacute liver failure on short-term efficacy, liver function, and hepatitis B virus deoxyribonucleic acid (HBV-DNA) conversion rates.*

Methods: *A total of 86 patients with chronic and subacute liver failure who were treated in our hospital from January 2019 to March 2020 were randomly selected and divided into a study group and control group with 43 patients each. Patients in the control group were treated with artificial liver PDF, and patients in the study group were treated with artificial liver PDF combined with entecavir. The clinical efficacy of treatment in the 2 groups was compared. The end-stage liver disease model score (MELD) and alanine aminotransferase (ALT), total bilirubin (TBIL), and aspartate transferase (AST) levels were measured before and after treatment in the 2 groups. Additionally, changes in the HBV-DNA negative conversion rate were measured at 4 weeks, 8 weeks, and 12 weeks after treatment in both groups, and the occurrence of adverse reactions was recorded.*

Results: *The total treatment efficacy rates in the study group and the control group were 95.35% and 79.07%, respectively, with the rate being significantly higher in the study group than in the control group (P<.05). Compared with before treatment, the MELD score and TBIL, ALT, and AST levels were significantly reduced after treatment in both groups, and the values in the study group were significantly lower than in the control group (P<.05). At 4 weeks, 8 weeks, and 12 weeks after treatment, the HBV-DNA negative conversion rate of the study group was significantly higher than that of the control group (P<.05 or P<.01). The incidence of adverse reactions in the study group and the control group was 6.98% and 25.58%, respectively, with the incidence in the study group being significantly lower than in the control group (P<.05).*

Conclusion: *Artificial liver PDF combined with entecavir for the treatment of chronic subacute liver failure can significantly improve clinical efficacy, promote HBV-DNA negative conversion, improve liver function, and reduce the occurrence of adverse reactions. Thus, this approach is worthy of clinical application and promotion.*

Keywords: *Artificial liver PDF, entecavir, chronic subacute liver failure, short-term efficacy, liver function, HBV-DNA negative conversion rate.*

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Introduction

Liver failure is severe liver damage caused by numerous factors that can result in serious barriers to or even decompensation in liver functions such as synthesis, detoxification, excretion, and biotransformation. There are several clinical manifestations of liver failure, including jaundice, coagulopathy, ascites, and hepatic encephalopathy. Liver failure is a common serious clinical syndrome with a high mortality rate(1). The pathogenesis of liver failure is relatively complicated and currently unclear. It is generally believed that liver failure may result from the interaction of virus, host, and environment. In particular, the immune pathological damage induced by viruses plays an important role in the pathogenesis of liver failure(2). In my country, chronic viral hepatitis B is an important cause

of chronic and subacute liver failure, accounting for 80% of all cases of liver failure. The mortality rate of patients can be as high as 65% to 80%, and the condition has a serious impact on the life and health of patients[3]. At present, there is no specific treatment for chronic viral hepatitis B infection that causes chronic and subacute liver failure, and comprehensive medical treatment is still the main strategy[4]. Artificial liver support systems include mechanical, physicochemical, or biological reaction devices outside the body. For patients with advanced liver disease having poor liver cell regeneration, an artificial liver can effectively improve symptoms. It wins precious time for patients with liver transplantation and plays a role as a bridge[5].

Artificial livers comprise non-biological artificial livers, biological artificial livers, and hybrid artificial livers. The plasma diafiltration (PDF) approach is one of many approaches among non-biological artificial livers and is an important intervention for the treatment of chronic and subacute liver failure[5].

With the widespread application of nucleic acid-based antiviral drugs, an effective treatment method is provided for chronic and subacute liver failure. Entecavir is a new type of antiviral drug with a strong antiviral effect and rapid onset of action that can cause serological or virological conversion in a short period of time, with a low resistance rate and mutation rate[6]. In this study, artificial liver PDF was combined with entecavir to treat chronic subacute liver failure to explore its short-term curative effect and impact on liver function and the negative conversion rate of hepatitis B virus DNA (HBV-DNA) in patients with chronic and subacute liver failure.

Materials and methods

General information

A random selection of 86 patients with chronic and subacute liver failure who were treated in our hospital from January 2019 to March 2020 was included in the study. Patients were randomly divided into a study group and control group based on the random number table method, with 43 patients in each group.

The inclusion criteria were as follows:

• All research subjects met the relevant diagnostic criteria for liver failure(7);

• Hepatitis B surface antigen (HBsAg) and HBV-DNA tests were positive, and hepatitis C virus (HCV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and other serum markers were all negative;

• This study was approved by the hospital ethics committee and compliant with the principles of medical ethics;

• The patients and their family members gave informed consent and signed an informed consent form.

Exclusion criteria:

• Patients with hyperthyroidism;

• Not using interferon, immunomodulators, or nucleoside antiviral drugs in the 6 months before participating in the study;

• Pregnant or lactating patients;

• Patients with severe kidney disease;

• Patients with a long history of exposure to liver toxicity.

Methods

Both groups of patients were prescribed bed rest to reduce energy consumption and liver burden. The patients were given a light diet to reduce protein intake and active supplementation of albumin and plasma to correct hypoalbuminemia and supplement coagulation factors, as well as other basic treatments. Liver and kidney function were regularly reviewed and electrolyte imbalances were corrected in a timely manner.

Patients in the control group were given artificial liver PDF treatment. Before treatment, a deep venous catheter was placed in the femoral vein to establish blood circulation. The Evacure3A 20 membrane separator was used. The dialysis components included 10.5 L 0.9% normal saline, 0.105 L 50% glucose injection, and 0.63 L 5% sodium bicarbonate injection, making a total volume of 11.135 L. The total duration of dialysis was 6 hours, the blood flow rate was 100–150 mL/min, the plasma ultrafiltration rate was 267 mL/h, the dialysate flow rate was 2000 mL/h, and the blood vessel replacement volume was 1600 mL. Patients in the study group were treated with artificial liver PDF combined with entecavir (China-US Shanghai Squibb Pharmaceutical Co., Ltd., production batch number: 20172237, specification: 0.5 mg*7 tablets) at 0.5 mg once a day.

Observation indexes

4 mL of fasting blood was drawn from the median cubital vein of all subjects before and after the treatment and left to stand. A low-temperature high-speed centrifuge was used to centrifuge the

samples at a speed of 3000 rpm and collect the supernatant, which was then stored for inspection in an ultra-low temperature refrigerator at –80 oC.

Patient characteristics

The basic characteristics of the 2 groups of patients, including age, gender, course of disease, body mass index (BMI), Child-Pugh classification of liver function, and baseline HBV-DNA value were evaluated.

Clinical efficacy

The clinical efficacy of the intervention in the 2 groups of patients was evaluated as being invalid, effective, or significantly effective. Cases where fatigue, jaundice, and other clinical symptoms did not improve significantly, the liver function index improved by less than 50%, and the HBV-DNA test result showed a positive conversion rate were considered invalid. Cases where fatigue, jaundice, and other clinical symptoms were significantly relieved, liver function indicators improved by more than 50%, and the HBV-DNA test result showed a negative conversion rate were considered effective. Cases showing complete recovery from fatigue, jaundice, and other clinical symptoms, complete recovery of liver function indicators, and a negative HBV-DNA conversion rate were regarded as significantly effective. Total efficacy rate = (significantly effective + effective) ÷ n × 100%.

Liver function test

An automated biochemistry analyzer was used to detect changes in the model score of end-stage liver disease (MELD) as well as the alanine aminotransferase (ALT), total bilirubin (TBIL), and aspartate transferase (AST) levels of the two groups before and after treatment.

Determination of HBV-DNA negative conversion rate

The PCR method was used to determine changes in the HBV-DNA negative conversion rate in the 2 groups at 4, 8, and 12 weeks after treatment.

Adverse reactions

The occurrence of adverse reactions in the 2 groups was recorded.

Statistical analyses

The SPSS 22.0 software package was used for statistical analysis. The chi-square test was used for data on gender, HBV-DNA conversion rate, and adverse reactions. Measurement data such as age and liver function indicators were compared using the independent sample t-test, and data from before and after treatment were compared using the paired sample t-test. A P value of <.05 was considered statistically significant.

Results

Comparison of patient characteristics

There were no statistically significant differences between the 2 groups of patients with regard to age, gender, Child-Pugh classification of liver function, and baseline HBV-DNA value (P>.05). The results are shown in Table 1.

Group	Research (n = 43)	Control (n = 43)	$\chi^{2/t}$ value	P value
Age (years)	51.79±9.66	52.35±9.24	0.275	0.784
Gender				
Male	27 (62.79%)	28 (65.12%)	0.050	0.822
Female	16 (37.21%)	15 (34.88%)		
Disease duration (years)	5.27±3.24	5.77±3.69	0.668	0.506
BMI (kg/m^2)	23.87±1.57	23.28±1.62	1.715	0.090
Child-Pugh classification of liver function				
A	16 (37.21%)	15 (34.88%)	0.053	0.974
B	24 (55.81%)	25 (58.14%)		
C	3 (6.98%)	3 (6.98%)		
Baseline HBV-DNA value (log^3 copies/mL)	3.27±0.54	3.32±0.59	0.410	0.683

Table 1: Comparison of patient characteristics.

Comparison of clinical efficacy

The total efficacy rates of the study group and the control group were 95.35% and 79.07%, respectively, and the rate in the study group was significantly higher than that in the control group (P<.05). The results are shown in Table 2.

Group	n	Significantly effective	Effective	Invalid	Total effective
Study	43	25 (58.14%)	16 (37.21%)	2 (4.65%)	41 (95.35%)
Control	43	18 (41.86%)	16 (37.21%)	9 (20.93%)	34 (79.07%)
χ^2					5.108
P					0.024

Table 2: Comparison of clinical efficacy between the two groups.

Measurement of liver function indexes

Compared with before treatment, the MELD score and TBIL, ALT, and AST levels of the 2 groups were significantly reduced after treatment, and the values in the study group were significantly lower than those in the control group (P<0.05). The results are shown in Table 3.

Group	n	Time	MELD (Scores)	TBIL (μmol/L)	ALT (U/L)	AST (U/L)
Study	43	Before treatment	26.47±6.78	33.57±11.26	88.47±21.27	85.78±16.68
		After treatment	9.77±3.41	23.38±7.68	33.46±10.23	33.42±8.77
Control	43	Before treatment	25.42±6.68	34.48±12.04	86.65±19.35	83.38±16.54
		After treatment	14.43±5.29	29.39±10.54	71.22±15.39	61.28±13.36

Table 3: Determination of liver function indexes (mean ± SD).

Changes in HBV-DNA negative conversion rate

At 4 weeks, 8 weeks, and 12 weeks after treatment, the HBV-DNA negative conversion rate of the study group was significantly higher than that of the control group (P<.05 or P<.01). The results are shown in Table 4.

Group	n	4 weeks after treatment	8 weeks after treatment	12 weeks after treatment
Study	43	28 (65.12%)	32 (74.42%)	38 (88.37%)
Control	43	18 (41.86%)	23 (53.49%)	27 (62.79%)
χ^2		4.674	4.086	7.623
P		0.031	0.043	0.006

Table 4: Examples of changes in HBV-DNA negative conversion rate.

Comparison of adverse reactions

The observed adverse reactions mainly included gastrointestinal bleeding, hepatic encephalopathy, ascites, and hepatorenal syndrome. The incidence of adverse reactions in the study group and the control group was 6.98% and 25.58%, respectively, with the incidence being significantly lower in the study group than the control group (P<.05). The results are shown in Table 5.

Group	n	Gastrointestinal bleeding	Hepatic encephalopathy	Ascites	Hepatorenal syndrome	Total
Study	43	1 (2.33%)	0 (0.00%)	2 (4.66%)	0 (0.00%)	3 (6.98%)
Control	43	3 (6.98%)	2 (4.66%)	5 (11.63%)	1 (2.33%)	11 (25.58%)
χ^2						5.460
P						0.019

Table 5: The ratio of adverse reactions in the two groups.

Discussion

Liver failure refers to severe liver damage caused by multiple factors and is the end-stage manifestation of liver disease, with a very high mortality rate. Based on the pathological characteristics of the liver and the speed of disease development, liver failure can be divided into 4 categories: acute liver failure, subacute liver failure, chronic subacute liver failure, and chronic liver failure. Among them, chronic and subacute liver failure are the main clinical manifestations of liver decompensation in a short period of time based on chronic liver disease. The course of liver failure is rapid, the mortality rate is high, and it is difficult to implement a complete, systematic, and standardized treatment plan in clinical practice[8]. Therefore, it is important to continuously explore its pathogenesis, pathological manifestations, and treatment methods to reduce patient mortality.

Due to severe liver necrosis in patients with liver failure, clinical treatment alone for the cause of the disease is not effective and it takes time for antiviral therapy to take effect. Studies have reported that artificial liver PDF combined with entecavir has obvious clinical benefits in the treatment of liver failure[9]. Artificial liver treatment is divided into three types: non-biological, biological, and mixed. At present, non-biological artificial livers are widely used in clinical practice, with approaches including plasma exchange (PE), hemofiltration (HF), hemodialysis (HD), and PDF. PDF is an integration of PE, HF, and HD. It can retain more clotting factors, reduce the loss of albumin, significantly reduce the amount of plasma exchange, and save blood resources[10]. Entecavir is the main drug for etiological treatment and is an analog of epoxy-hydroxycarbodeoxyguanosine. It targets the HBV-DNA polymerase and reverse transcriptase, inhibiting the initiation of replication and extension of viral DNA and thereby inhibiting the replication of HBV-DNA, reducing liver inflammation, and promoting the recovery of liver function[11]. The results of this study found that artificial liver PDF combined with entecavir has a significant clinical effect in the treatment of chronic subacute liver failure and can significantly reduce the occurrence of adverse reactions.

The liver is the body's main metabolic organ and has a biotransformative effect. It can completely decompose drugs, poisons, and some metabolites in the body or excrete them in their original form. ALT is

an intracellular functional enzyme mainly present in the liver. Studies have found that when the liver cell membrane is ruptured and the liver undergoes severe necrosis or destruction, AST and ALT are released into the blood, increasing serum AST and ALT levels significantly. AST and ALT levels can thus be used as important indicators of liver function[12]. Most of the TBIL is derived from hemoglobin produced after the destruction of senescent red blood cells, including direct bilirubin and indirect bilirubin. It is an effective marker for diagnosing liver disease and biliary obstruction. MELD is a scientific and objective continuous scoring system that has been used widely in liver transplantation, the prognosis of end-stage liver disease, and the evaluation of artificial livers in the treatment of liver failure[13]. The results of this study found that artificial liver PDF combined with entecavir can significantly improve the liver function of patients with chronic and subacute liver failure. Chronic HBV infection in some cases will induce rapid deterioration and development of liver failure. This phenomenon may be closely related to HBV reactivation, viral mutation, and immune status. HBV-DNA is the deoxyribonucleic acid of HBV. As the genome and replication template of HBV, it is considered the most direct and sensitive etiological basis for the replication and infection of HBV[14]. The results of this study found that the combination of artificial liver PDF and entecavir in the treatment of chronic subacute liver failure can significantly promote HBV-DNA negative conversion rates. This may be because the artificial liver PDF and entecavir can stop the elongation of the HBV-DNA chain, thereby inhibiting the replication of HBV[15].

In conclusion, artificial liver PDF combined with entecavir in the treatment of chronic subacute liver failure can significantly improve clinical intervention efficacy, promote HBV-DNA negative conversion, improve liver function, and reduce the occurrence of adverse reactions. Thus, it is worthy of clinical application and promotion.

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