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• BRIEF REPORTS •

Effects of hemoperfusion adsorption and/or plasma exchange in treatment of severe viral hepatitis: A comparative study

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Abstract

AIM: Non-bioartificial liver has been applied to clinic for quite a long time, but the reported efficacy has been very different. The aim of this study was to compare the efficacy and safety of hemoperfusion adsorption, plasma exchange and plasma exchange plus hemoperfusion adsorption in treatment of severe viral hepatitis.

METHODS: Seventy-five patients with severe viral hepatitis were treated with hemoperfusion adsorption therapy (24 cases), plasma exchange therapy (17 cases) and plasma exchange plus hemoperfusion adsorption therapy (34 cases). The data of liver function, renal function, blood routine test, prothrombin time (PT) and prothrombin activity (PTa) pre- and post-therapy were analyzed.

RESULTS: Clinical symptoms of patients improved after treatment. The levels of aminotransferase, total bilirubin, direct bilirubin decreased significantly after 3 therapies ($P<0.05$ or $P<0.01$). PT, the level of total serum protein decreased significantly and PTa increased significantly after plasma exchange therapy and plasma exchange plus hemoperfusion adsorption therapy ($P<0.05$ or $P<0.01$). The side effects were few and mild in all patients.

CONCLUSION: Three therapies were effective in the treatment of severe viral hepatitis. Plasma exchange therapy and plasma exchange plus hemoperfusion adsorption therapy are better than hemoperfusion adsorption therapy.

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INTRODUCTION

The treatment of severe viral hepatitis is always intractable in clinic. The previous non-bioartificial liver has widely been applied to clinic treatment[1-16], but its reported efficacy is various. In order to make an objective evaluation and comparison of the effects of non-bioartificial liver in the treatment of severe viral hepatitis, we chose three therapies of hemoperfusion adsorption, plasma exchange and plasma exchange plus hemoperfusion adsorption and compared their efficacy and safety.

MATERIALS AND METHODS

Materials

Sixty-four males and 11 females aged from 23 to 66 (41.3 on average) years with severe viral hepatitis were hospitalized in our section from January 1998 to February 2002. The diagnosis of 75 patients meeting the criteria for severe viral hepatitis established in National Viral Hepatitis Symposium[17], was all severe chronic hepatitis. The conditions of 75 patients were 4 at the early stage, 31 at the middle stage, 40 at the late stage of liver failure. Among them, there were 56 with simple hepatitis B virus (HBV) infection, 8 with HBV combined with hepatitis D virus (HDV) infection, 3 with HBV combined with hepatitis A virus (HAV) infection, 1 with HBV combined with hepatitis E virus (HEV) infection, 2 with hepatitis C virus (HCV) infection and 5 with all hepatitis virus markers negative. Before treatment, 41 had occurred hepatoencephalopathy, 9 hepatorenal syndrome, 20 spontaneous peritonitis, 5 septic shock and 3 gastrointestinal hemorrhage. Seventy-five patients were divided into 3 groups, respectively receiving hemoperfusion adsorption therapy (24 cases), plasma exchange therapy (17 cases) and plasma exchange plus hemoperfusion adsorption therapy (34 cases). There was no significant difference between three groups in clinical classification, pathogen, complications and clinical data of liver function, renal function, blood routine tests, PT, PTa ($P>0.05$).

Methods

Hemoperfusion adsorption therapy In the computer-controlled system of Type HSZ2000 artificial liver device, we chose the program of hemoperfusion adsorption therapy. The blood was pumped out of the body with the flow velocity of 60-80 mL/min and into a new type of activated charcoal column for adsorption and then backed into the body with 100 mL saline through deferens. Meanwhile, the same quantity of protamine was infused to neutralize heparin so that coagulation time (CT) could become normalized. Each patient received hemoperfusion adsorption for 1 to 4 times and all patients received 52 times in total, averaging 2.2 times per person.

Plasma exchange therapy In the computer-controlled system of Type HSZ2000 artificial liver device, we chose the program of plasma exchange therapy. The blood was pumped out of the body with the flow velocity of 60-80 mL/min and into a plasma exchange filter to discard the plasma and then mixed up with fresh frozen plasma (FFP) with flow velocity of 30-50 mL/min to be reperfused back into the body with 50 mL 200 g/L albumin solution and 100 mL saline through deferens. The balance of output and input should be controlled closely. Meanwhile, the same quantity of protamine was infused to neutralize heparin so that coagulation time (CT) could get normalized. Each patient received plasma exchange for 1 to 4 times and all patients received 36 times in total, averaging 2.1 times per person.

Plasma exchange plus hemoperfusion adsorption therapy In the computer-controlled system of Type HSZ2000 artificial liver

device, we chose the program of plasma exchange plus hemoperfusion adsorption therapy. The blood was pumped out of the body with the flow velocity of 60-80 mL/min and into a plasma exchange filter to discard the plasma and then through activated charcoal column for adsorption and then mixed up with fresh frozen plasma (FFP) with flow velocity of 30-50 mL/min to be reperfused back into the body with 50 mL 200 g/L albumin solution and 100 mL saline through deferens. The balance of output and input should be controlled closely. Meanwhile, the same quantity of protamine was infused to neutralize heparin so that coagulation time (CT) could get normalized. Each patient received plasma exchange plus hemoperfusion adsorption from 1 to 4 times and all patients received 65 times in total, averaging 1.91 times per person. This process could last for one and a half to three hours and the exchanged plasma volume was up to 2 500-3 000 mL.

Experimental tests The blood samples were collected before and after each treatment to check the liver function, renal function, PT and for blood routine test.

Clinical therapeutic efficacy The standard to evaluate the clinical curative effect refers to the references[18,19].

Statistical analysis

All data were shown as mean±SD. *t* test was used to compare the data before and after treatment.

RESULTS

The effect of hemoperfusion adsorption therapy

Liver function improved significantly after treatment (Table 1). The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB) and direct bilirubin (DB) were decreased significantly ($P<0.05$ or 0.01). Total serum protein (TSP) level was decreased but not significantly ($P>0.05$). Coagulation function improved after treatment. Prothrombin time decreased from 24.4 s to 21.31 s ($t=1.268$, $P>0.1$) and prothrombin activity was increased from 28.61% to 33.14% ($t=1.216$, $P>0.1$), but no significant difference was presented on statistical analysis.

Table 1 Comparison of liver function between pre- and post-therapy of hemoperfusion adsorption

	Pre-therapy	Post-therapy	*t*	*P*
ALT (IU/L)	80.3±52.9	40.4±15.2	2.628	<0.01
AST (IU/L)	123.6±57.8	79.9±42.6	2.249	<0.05
TB (μmol/L)	619.0±193.9	403.3±132.7	3.376	<0.01
DB (μmol/L)	345.1±125.4	233.6±94.9	2.622	<0.01
TSP (g/L)	63.9±8.8	57.9±8.7	1.359	>0.05

ALT: alanine aminotransferase, AST: aspartate aminotransferase, TB: total bilirubin, DB: direct bilirubin, TSP: total serum proteins.

The effect of plasma exchange therapy

Liver function improved greatly after treatment (Table 2). The levels of ALT, AST, TB, DB and TSP were decreased and significant difference was presented ($P<0.05$ or 0.01). Coagulation function improved greatly after plasma exchange. Prothrombin time decreased from 29.46 s to 23.74 s ($t=1.713$, $P<0.05$) and prothrombin activity was increased from 23.73% to 32.15% ($t=2.338$, $P<0.05$). Both showed significant differences on statistical analysis.

The effect of plasma exchange plus hemoperfusion adsorption therapy

Liver function improved immensely after treatment (Table 3). The levels of ALT, AST, TB, DB and TSP were decreased and significant difference was presented ($P<0.05$ or 0.01). Coagulation function improved greatly. Prothrombin time decreased from 28.0 s to 22.9 s ($P<0.05$) and prothrombin activity was increased from 25.8% to 30.9% ($P<0.05$). Both showed significant differences on statistical analysis.

Table 2 Comparison of liver function pre- and post-therapy of plasma exchange

	Pre-therapy	Post-therapy	*t*	*P*
ALT (IU/L)	122.8±115.5	70.8±86.8	2.040	<0.05
AST (IU/L)	147.7±106.6	95.3±81.6	2.214	<0.05
TB (μmol/L)	488.3±189.9	300.6±135.9	4.596	<0.01
DB (μmol/L)	244.4±100.0	153.7±73.6	4.152	<0.01
TSP (g/L)	65.1±9.2	57.7±9.8	3.168	<0.01

Table 3 Comparison of liver function pre- and post-therapy of plasma exchange plus hemoperfusion adsorption

	Pre-therapy	Post-therapy	*t*	*P*
ALT (IU/L)	109.45±102.06	61.52±74.19	2.594	<0.02
AST (IU/L)	140.16±94.71	90.59±72.32	2.844	<0.01
TB (μmol/L)	528.75±200.57	332.16±142.91	5.459	<0.01
DB (μmol/L)	275.37±118.01	178.00±88.68	4.523	<0.01
TSP (g/L)	64.70±9.0	57.70±9.5	3.312	<0.01

The data of renal function and blood routine test pre- and post-therapy

Renal electrolytes showed no obvious changes and the levels of urea nitrogen and creatinine were shown no significant difference pre- and post-therapy ($P>0.01$ or 0.05).

There was no significant difference in the levels of white blood cells (WBC), red blood cells (RBC), hemoglobin (Hgb) and platelet (PLT) pre- and post-therapy ($P>0.01$ or 0.05).

Side effects

In the group with hemoperfusion adsorption therapy, 2 patients had side effects twice, skin itch and rash once, pyrogen reaction once. In the group with plasma exchange therapy, 3 patients experienced side effects 3 times, skin itch and rash once, hemolytic reaction once and transfusion reaction once. In the group with plasma exchange plus hemoperfusion adsorption therapy, 10 patients had side effects thirteen times, skin itch and rash once, numbed face and 4 limbs 4 times, blood pressure fluctuation once and hypothermia once, hemolytic reaction once, transfusion reaction once, pyrogen reaction once. All side effects were relieved after treatment and had no influence on the whole therapeutic process.

DISCUSSION

It has been proven that hemoperfusion adsorption plays a role in removal of bilirubin and intermediate molecular substances. Previously owing to the poor technique of activated charcoal filter, there were obvious side effects in application of hemoperfusion adsorption therapy. Especially some severe side effects such as serious hemorrhage following platelet destruction and hemolysis following erythrocyte destruction once made the clinical application and basic research of artificial liver support system home and abroad go to a standstill for a long period of time. In the past few years, because the advance of technique of activated charcoal filter and the particles of charcoal became smaller and their surface was processed, the chance of platelet destruction and erythrocyte destruction was

much less when the blood flowed through activated charcoal filter, biocompatibility of activated charcoal improved[20]. Therefore, the therapy of hemoperfusion adsorption has again been applied to clinic to treat the liver failure patients[21-23]. That 24 patients had an improvement in clinical symptoms temporarily and in liver function indicates hemoperfusion adsorption therapy has a temporary supportive effect on liver failure caused by severe viral hepatitis.

The mechanism of severe viral hepatitis is the cooperation of immunopathological lesion caused by hepatitis virus and the secondary lesion of liver cells that results from the great deal of cytokine such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL1-β), interleukin-10(IL10) released by intrahepatic and extrahepatic mononuclear macrophages due to the enteroendotoxemia following the impairment of hepatic barrier function. In this process, the secondary lesion plays an important role[24-28]. Cytokine can induce hepatocyte apoptosis[29]. Cytokine and endotoxin removal can relieve hepatic lesion, reduce leucocyte emigration and platelet aggregation and maintain the intracellular stablization so as to delay or reverse the disease progress and improve the prognosis.

Hemoperfusion adsorption therapy can eliminate endotoxin and cytokine nonspecifically and play an important role in supporting treatment of liver failure[30].

Plasma exchange separated and discarded plasma of liver failure patients to remove the toxic substances (especially those binding with proteins) and compensated with normal fresh frozen plasma to supplement some essential substances such as coagulation factors, albumin, immunoglobin so as to ameliorate the microenvironment of liver and accelerate the liver regeneration and the liver function recovery[31,32]. The therapeutic effects of 17 acute liver failure patients who received plasma exchange therapy were similar to those reported abroad[32,33], but quite different from those reported home[22]. This may be related to the severity of the patients in our series who are all in the intermediate or late stages of liver failure caused by severe chronic hepatitis[18,19] and in addition, the times of plasma exchange should be taken into consideration. Though the prognosis of patients receiving plasma exchange therapy did not live up to our expectation, the clinical symptoms of patients after treatment showed temporary relief and liver function and coagulation function improved obviously. So plasma exchange therapy has temporary supportive effects on liver failure caused by severe viral hepatitis.

Plasma exchange plus hemoperfusion adsorption therapy is a combination of plasma exchange and hemoperfusion adsorption, so it is more beneficial to the liver microenvironmental amelioration and liver regeneration and recovery of liver function. The therapeutic effects of 34 patients receiving plasma exchange plus hemoperfusion adsorption therapy showed coincidence with those receiving plasma exchange plus hemoperfusion adsorption therapy abroad[33,34]. That the patients' clinical symptoms after treatment showed temporary relief and liver function and coagulation function improved obviously indicates this therapy has temporary supportive effects on liver failure caused by severe viral hepatitis.

In comparison among three groups pre- and post-therapy, the coagulation function amelioration and plasma protein decrease by plasma exchange therapy and plasma exchange plus hemoperfusion adsorption therapy were more obvious than those by hemoperfusion adsorption therapy.

The main advantages of hemoperfusion adsorption therapy are low cost and less protein loss. Theoretically, plasma exchange therapy is a relatively complete liver substitutive therapy and its effects have been proven, but a large supply of plasma, high cost, and easy infection of blood-transmitted diseases fail them and plasma exchange deprives patients of hepatocyte growth substances. Consequently it may do harm to liver regeneration and long-term therapeutic effects. The concentrations of plasma proteins will decrease if plasma is not compensated enough after a great loss.

Through the liver failure rat model which received total blood exchange, Eguchi[35] found that the hepatocyte regeneration was suppressed. In the fresh frozen plasma for exchange, there are a great deal of citrates which can increase the incidence of side effects after infused into the body and can do harm to hepatocyte energy metabolism and hepatocyte regeneration. How to advance various therapies and combine them with bioartificial liver support system in order to get good effects and reduce the side effects await further study[36-41].

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