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Original Article

Effects of plasma exchange on serum NO and TGF-β_1 of severe hepatitis patients

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Abstract: Objective: To investigate the mechanism of plasma exchange in the treatment of severe hepatitis, by studying the changes of serum nitric oxide (NO) and transforming growth factor-β_1 (TGF-β_1) in patients with severe hepatitis before and after plasma exchange. Methods: Select 50 cases of normal control group, 35 cases of acute severe hepatitis group, 33 cases of chronic severe hepatitis, 23 cases of early severe hepatitis group, 20 cases of medium severe hepatitis group and 25 cases of late severe hepatitis group; among them, the plasma exchange group and control group were both of 34 cases. The level of serum TGE-β_1 was measured by enzyme-linked immunosorbent assay, serum NO level was detected by Griess. Compare levels of serum NO and TGF-β_1 between the groups, and carry out statistical analysis. Results: The levels of serum NO, TGF-β_1 of patients in each group were higher than that of normal control group ($P<0.05$), besides, the expressions of serum NO (151.5±44.65 ng/L)_and TGF-β_1 (176.7±45.24 ng/L) in late severe hepatitis patients were the highest in different stages of severe hepatitis groups. Levels of serum NO and TGF-β_1 in patients with severe hepatitis treated with plasma exchange were significantly decreased. Compared with those before treatment, the difference was statistically significant ($P<0.05$). As for the treatment group, the expression levels of serum NO and TGF-β_1 in the patients with effective treatment were significantly lower than that before treatment ($P<0.05$), and the levels of serum NO and TGF-β_1 in the patients with ineffective treatment were not significantly changed compared with those before treatment. Conclusion: The effects of plasma exchange on the expression of serum NO and TGF-β_1 were effective, besides, it significantly reduced the damage of inflammatory reaction to liver cells and improved the prognosis of patients with severe hepatitis. Hence, the detection of NO and TGF-β_1 indicators is helpful in evaluating the conditions as well as guiding treatment strategies.

Keywords: Severe hepatitis, plasma exchange, nitric oxide (NO), transforming growth factor-β_1

Introduction

Serve hepatitis is one of the most serious complications after hepatitis B virus (HBV) infection, which is characterized by the necrosis or apoptosis of a large number of liver cells, moreover, it can cause acute and chronic liver failure. It has serious conditions, quick development speed, poor prognosis and high mortality rate [1, 2]. It was reported that the pathogenesis of severe hepatitis was complicated which may closely related to the damage of immune system, pathogen invasion, etc. And Cytokine plays a vital role in the development of severe hepatitis. A variety of pathogenic microorganisms and endotoxin can stimulate the release of a large number of cellular factors of mononuclear macrophage, such as serum NO and β_1 (TGF-β_1), further aggravated the damage on liver cells [3, 4]. Other studies have indicated that TGF-β_1 was associated with the pathogenesis of chronic liver disease, and could inhibit the regeneration of liver cells [5, 6]. Therefore, TGF-β_1 may be the key to regulate the regeneration of liver cells in patients with severe hepatitis. NO is a kind of inorganic gas information molecule. It is widely distributed in immune inflammatory cells during the development of severe hepatitis. NO is oxidized in body fluid, forming nitrate, nitrate ion and superoxide anion. The reactive nitrogen intermediate has great cytotoxicity, and plays an important role in the pathogenesis of severe hepatitis. It results in poor efficacy of severe hepatitis after medi-

Table 1. Comparison of general data of patients between the two groups (mean ± standard deviation)

Group	Albumin (g/L)	Prothrombin activity (%)	GPT (U/L)	GOT (U/L)	TBil (μmol/L)	Complications (cases)
Treatment group	29.1±7.3	27.8±7.5	785.2±26.5	585.2±21.8	278.8±75.8	20
Control group	28.7±7.7	26.6±8.8	773.6±35.2	615.1±27.2	262.5±70.1	18

cal conservative treatment, with report that the mortality rate is as high as 60%-80% [7, 8]. In recent years, with the rapid development of artificial liver support system technology, plasma exchange has been gradually applied to treat severe hepatitis in clinic and has obtained exact effectiveness. However, its specific mechanism is still unclear. Some studies reported that plasma exchange could clear toxic metabolite, endotoxin and inflammatory cytokine in the body. At the same time, it could supply blood clotting factors to gain blood purification and promotion of liver cell regeneration [9, 10]. But the effects of plasma exchange on NO and TGF-β_1 are rarely reported. This study revealed the effects of NO and TGF-β_1 in the pathogenesis of severe hepatitis by detecting the levels of serum NO and TGF-β_1 before and after plasma exchange. It offered the experimental evidence to treat severe hepatitis in clinical practice.

Materials and methods

Clinical data

Select 68 cases of severe hepatitis patients who were received and cured from June, 2013 to June, 2016. The selected patients were all up to the diagnostic criteria of the prevention and treatment of viral hepatitis and this study was approved by the hospital Ethics Committee; there were 35 cases in acute severe hepatitis group, including 16 males and 19 females, whose age range was from 25.7 to 42.3 years old and the mean age was (35.7±2.8) years; there were 33 cases in chronic severe hepatitis group, including 15 males and 18 females, whose age range was from 23.2 to 39.7 years old and the mean age was (36.7±2.9) years; the patients in severe hepatitis were randomly divided into two groups: there were 34 cases in the plasma exchange treatment group, including 16 cases of male, 18 cases of female, whose mean age was (36.1±3.0) years old. There were 34 cases in the control group, including 15 cases of male, 19 cases of female, whose mean age was (36.4±3.1) years old.

There was no significantly statistical difference between the two groups in general clinical data such as age, sex, biochemical parameter and complications (ascites, hepatic encephalopathy, hepatorenal syndrome and hemorrhage) and it was comparable, see **Table 1**. The patients in the treatment group were given plasma exchange who were hospitalized within one week as well as given medical comprehensive treatments like protecting the liver, declining the enzyme, decreasing icterus, maintaining the balance of electrolyte, water and acid-base, replenishing energy and albumin, and anti-infection. The control group was only treated by medical comprehensive treatments after hospitalization. Patients with severe hepatitis were divided into early stage, middle stage and late stage according to their clinical manifestations, which were respectively 23 cases, 20 cases and 25 cases. There was no significantly statistical difference to patients among the different stages in the basic data and it was comparable; all the indexes of liver function were normal in the control group with 50 cases of health checkup patients (**Table 1**), including 24 cases of male and 26 cases of female, whose age range was from 26.8 to 38.7 years old and mean age was (35.9±3.5) years old.

Inclusion criteria and elimination criteria

Inclusion criteria: Liver failure caused by different kinds of reasons, in accordance with the diagnostic criteria of severe hepatitis; less than 30 s of thrombinogen time; in accordance with indication of plasma exchange and no contraindication; patients and their family members informed consent in this study. Exclusion criteria: Severe obstacles of cruor function; cardiovascular and cerebrovascular diseases; pregnancy or frail elderly patients.

Methods

Measurement of levels of serum NO and TGF-β_1: Patients' levels of serum NO and TGF-β_1 in

Table 2. Comparison of levels of serum NO and TGF-β_1 in each group

Group	Cases	NO (ng/L)	TGF-β_1 (ng/L)
Control group	50	75.5±18.20	90.74±28.32
Acute severe hepatitis group	35	87.8±17.65*	123.7±30.52*
Chronic severe hepatitis group	33	107.9±42.87*,#	144.5±35.41*,#

Note: Compared with the control group, *P<0.05; compared with the acute severe hepatitis group, #P<0.05.

each group were measured before and after plasma exchange. The operation methods were as follows: firstly, 5 ml of fasting venous blood was collected and stored at room temperature. The serum was then isolated by centrifugation at 3000 r/min and the sample was stored at-20°C for inspection. Secondly, the levels of serum TGF-β_1 were measured by ELISA (enzyme-linked immunosorbent assay) and the concentration was expressed in ng/L. The human TGF-β_1 ELISA kit was purchased from ADL Company (USA) and the operation was strictly in accord with the instructions. Thirdly, the levels of serum NO were measured by Griess and concentration was expressed in ng/L. The NO kit was purchased from the Shenzhen Jingmei Biotech Co. Ltd and the operation was strictly in accord with the instructions.

Plasma exchange treatment

WLXGX-888 exchange device, plasma separator and blood return tubes were provided by the Beijing Weili New Century Science & Tech. Deve. Co. Ltd. Patients were performed in the supine position after installing and connecting the exchange tubes correctly. Then the vital signs including blood pressure, heart rate and respiratory function were supervised when patients were undergoing the femoral vein catheterization. 5 mg of dexamethasone was injected for anti-allergic treatment before the plasma exchange and moderate amount (10%) of calcium gluconate would be injected to avoid complications when necessary.

Patients' Y-type double lumen catheters were connected correctly and the dosages of heparin were calculated according to the illness severity, the general dosage in the first time was ranged from 10 mg to 15 mg and then doses of 5 mg were needed at hourly intervals. The plasma bags were connected and then the exchange device was started, the parameters were set as follows: the blood flow rate ranged from 70 ml/min to 100 ml/min; the plasma separation rate ranged from 20 ml/min to 30 ml/min; the plasma exchange volume was 3000 ml/time. The protamine should be used to neutralize the heparin after the plasma exchange, achieving the recovery of patients' blood clotting function. The plasma exchange took 3 hours every time and patients should complete the plasma exchange for three times during the first two weeks.

Observation indicators

Patients' levels of serum NO and TGF-β_1 were measured before and after the treatment. The effectiveness of treatment was evaluated by the short-term effect of artificial liver support system. And clinical cure and improvement were identified as the effective treatment. Automatic discharge without significant effects or death was identified as the ineffective treatment.

Statistical methods

Data were analyzed by using SPSS17.0 statistical software. Measurement data were expressed by mean ± standard deviation ($\bar{X}\pm S$); comparison between two groups was analyzed by t test. One-way analysis of variance was applied to compare data among groups; Chi-square test was used for the comparison of rates. P<0.05 indicated statistically significant difference.

Results

Comparison of levels of serum NO and TGF-β_1 between each group

The levels of serum NO and TGF-β_1 in each group were higher than those in the control group, and the differences were statistically significant (P<0.05). Compared with the levels of serum NO and TGF-β_1 in the acute severe hepatitis group, those in the chronic severe hepatitis group showed a significant rise, which was statistically significant (P<0.05), as shown in **Table 2**.

Table 3. Comparison of levels serum of NO and TGF-β_1 of severe hepatitis patients at different stages (mean ± standard deviation)

Group	Cases	NO (ng/L)	TGF-β_1 (ng/L)
Normal control group	50	75.5±18.20	92.74±28.32
Early severe hepatitis group	23	126.7±38.42*	126.41±27.85*
Medium severe hepatitis group	20	132.4±40.69*,#	157.5±35.83*,#
Late severe hepatitis group	25	151.5±44.65*,#,Δ	176.7±45.24*,#,Δ

Note: Compared with the control group, *P<0.05; compared with the early severe hepatitis group, #P<0.05; compared with the medium severe hepatitis group, ΔP<0.05.

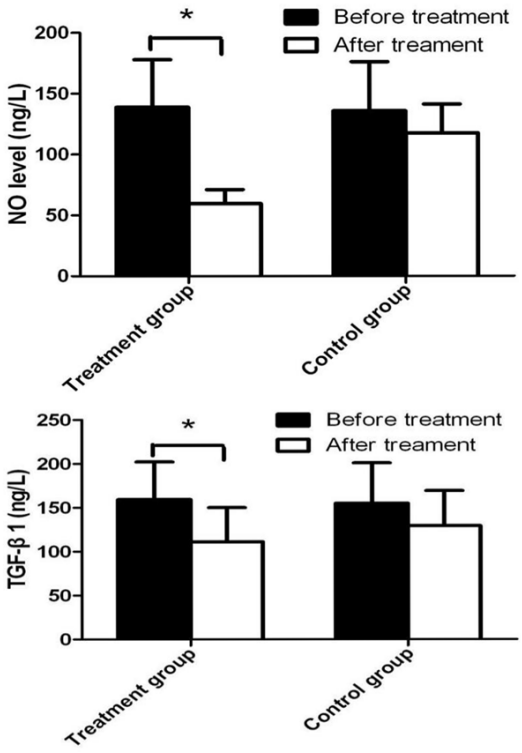

Figure 1. Comparison of serum levels of NO and TGF-β_1 of patients in two groups before and after treatment, *compared with before treatment, P<0.05.

Comparison of levels of serum NO and TGF-β_1 between each stage in the severe hepatitis group

The levels of serum NO and TGF-β_1 at early stage, middle stage and late stage in the severe hepatitis group were higher than those in the control group (P<0.05), and the levels of serum NO and TGF-β_1 at early stage, middle stage and late stage in the severe hepatitis group also showed statistically significant differences (P<0.05).

The expression levels of serum NO and TGF-β_1 increased with the progress of the severe hepatitis clinical stage expression, and the serum expression of NO (151.5±44.65 ng/L) and TGF-β_1 (176.7±45.24 ng/L) in the late severe hepatitis group were the highest. See **Table 3**.

Comparison of levels of serum NO and TGF-β_1 before and after treatment in the two groups of patients

The serum NO level of severe hepatitis patients in treatment group reduced from (137.7±37.7) ng/L before the treatment to (59.5±11.52) ng/L, and the expression of TGF-β_1 also reduced from (158.5 reduce) ng/L before the treatment to (111.2±38.82) ng/L. The differences were statistically significant; in addition, compared with that before treatment, the levels of serum NO and TGF-β_1 in the control group reduced after treatment, but the differences were not significant (P>0.05). See **Figure 1**.

The expressions of serum NO and TGF-β_1 in the treatment group when it was effective or ineffective

In the treatment group, the recent effective rate was 61.8% (21/34) when patients underwent plasma exchange and internal comprehensive treatment. Among them, the serum expressions of NO and TGF-β_1 in the ineffective group were significantly higher than that in the effective group and the differences were statistically significant (P<0.05). Compared before treatment, there was no significant change in the levels of serum NO and TGF-β_1 when the serum expression of NO and TGF-β_1 in the effective group significantly reduced, the differences were statistically significant (P<0.05). See **Figure 2**.

Discussion

There is high fatality rate in patients with severe hepatitis and the pathogenesis of severe hepatitis is very complex. In addition to the immune damage mechanism, inflammatory cytokines plays a key role in the development of severe inflammation. Casde reaction caused by the

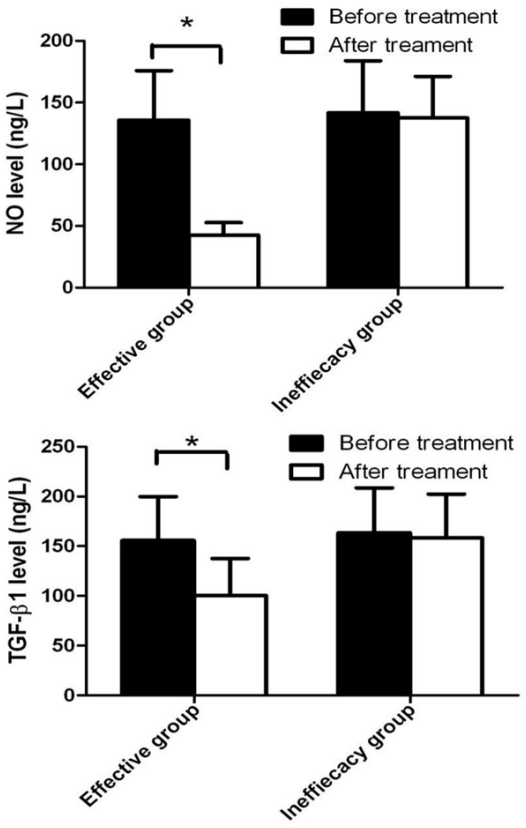

Figure 2. Comparison of serum levels of NO and TGF-β_1 of effective and ineffective patients in treatment group, *compared with before treatment, P<0.05.

cytokine networks is an important reason that leads to secondary liver injury [11]. Therefore, reducing the expression level of inflammatory factors is conducive to successfully rescue the patients with severe hepatitis. Plasma exchange is an artificial liver treatment therapy in the process of clinical treatments at present. Its' mechanism is to use the powerful regeneration of liver cells and reversible liver damages, through the principle of mechanical purification to help patients recover liver function [12].

NO, as inorganic gas information molecules, has extremely strong fat soluble, can penetrate the cell membrane and play a direct role in the process; when the severe hepatitis occurs and develops, NO which has an induced effect widely distributed in the immune inflammatory cells [13]. In the healthy body, the NO synthase expression level of immune inflammatory cell is extremely low; in the immune inflammation pathological state, endotoxin or immune factors will stimulate the inflammatory cells to produce a lot of NO synthase and mediate the high expression of NO through inflammatory cell. After oxidizing, NO derives acid radical which has stronger cytotoxicity, thereby damaging the liver cells in the incidence of severe hepatitis [14]. Excessive NO will cause great damage to liver cells by inhibiting the mitochondrial respiratory chain, inducing apoptosis of liver cells and producing reactive nitrogen intermediate [15].

TGF-β_1 produced by reactive hepatic stellate cells and hepatic stellate cells is a multifunctional cell growth regulation factor [16]. It was reported that TGF-β_1 played a role in the regulation of liver fibrosis and liver cells necrosis as well as had a close connection with the occurrence of liver cancer [17, 18]. Some animal studies displayed that the expression of TGF-β_1 significantly increased after hepatectomy and had positive correlation with inhibition degree of DNA synthesis [19, 20], demonstrating that TGF-β_1 could inhibit regeneration of liver cells and was bad for the prognosis of severe hepatitis [21, 22]. Some other studies showed that liver cells damage was the promoter factor of TGF-β_1 in hepatic stellate cells or hepatic stellate cells [23, 24]. In the study, compared with the control group, the level of serum NO and TGF-β_1 of patients in each severe hepatitis group had obviously increased with statistical difference (P<0.05). Also, the levels of serum NO and TGF-β_1 in early, medium and late severe hepatitis groups had significant increased, with statistical differences (P<0.05). It was found that the expression of serum NO and TGF-β_1 gradually increased with the staging progress of severe hepatitis and its expression level was the highest in the late severe hepatitis group. Other studies reported that the levels of serum NO and TGF-β_1 significantly increased under the circumstance of severe hepatitis patients' deterioration or death; whereas the levels of serum NO and TGF-β_1 could restore patients to the healthy body under the circumstance of severe hepatitis patients' healing or good prognosis [25, 26]. These results suggested that serum NO and TGF-β_1 could be regarded as biochemical parameters of severe hepatitis patients and their expression levels might had positive correlation with degree of severe hepatitis.

In the study, there were 34 cases in which the level of serum NO and TGF-β_1 of severe hepatitis patients decreased after plasma exchange. Compared to the pre-treatment level, there was significant difference ($P<0.05$). During the process of plasma exchange for severe hepatitis, we purified the blood by separating plasma and importing fresh plasma so as to help alleviate patient's condition. However, with the development of disease, the expression of inflammatory cytokines such as serum NO and TGF-β_1 gradually increased. Although plasma exchange could remove the inflammatory cytokines, there were lots of cytokines remained which did harm to liver cells with inflammatory cascade reaction. It might be an important factor to influence the recent effects of severe hepatitis. In the study, the effective rate of plasma exchange for severe hepatitis was 61.8%. In the invalid patients or exacerbation of patients, even if they underwent the plasma exchange, serum NO and TGF-β_1 still produced a lot or could not be effectively removed in the liver because of less residual liver tissue, little improved liver function, resulting in further damage of liver cells.

In conclusion, serum NO and TGF-β_1 could be regarded as biochemical parameters of severe hepatitis patients. Plasma exchange for severe hepatitis could significantly decreased the levels of serum NO and TGF-β_1. We could value the degree, effects and prognosis of severe hepatitis patients by evaluating and analyzing the levels of serum NO and TGF-β_1. In this study, there are still some limitations like the little sample sizes. It needs experiments which are multicenter, have randomized control groups and large sample sizes to further demonstrate. With the further research of the functions of serum NO and TGF-β_1, people can employ more ways to eliminate or inhibit the damage to human organs caused by the excessive expression of serum NO and TGF-β_1 so that the survival rates of the severe hepatitis patients could be further improved.

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Disclosure of conflict of interest

None.

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