Influence of antiviral drugs combined with antioxidant therapy on liver injury and fibrosis process in patients with chronic hepatitis B cirrhosis

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Objective: To study the influence of antiviral drugs combined with antioxidant therapy on liver injury and fibrosis process in patients with chronic hepatitis B cirrhosis. Methods: A total of 118 patients with chronic hepatitis B cirrhosis who were treated in Dongying Hospital for Infectious Diseases between May 2013 and February 2016 were retrospectively analyzed and divided into the control group (n = 60) who underwent routine antiviral therapy and the observation group (n = 58) who underwent antiviral drugs combined with antioxidant therapy. Serum levels of oxidative stress indexes, liver function indexes and liver fibrosis indexes were compared between two groups of patients before and after treatment. Results: Before treatment, there were no significant differences in serum oxidative stress indexes, liver function indexes and liver fibrosis indexes between two groups of patients. 3 months after treatment, serum oxidative stress index SOD level in observation group was higher than that in control group while AOPPs level was lower than that in control group; serum liver function indexes AST, ALT and TBIL levels in observation group were lower than those in control group while ALB level was higher than that in control group; serum liver fibrosis indexes HA, IV-C, PCIII and LN levels in observation group were lower than those in control group. Conclusion: Antiviral drugs combined with antioxidant therapy can significantly reduce oxidative stress injury in patients with chronic hepatitis B cirrhosis so as to protect the liver function and inhibit the liver fibrosis process.

1. Introduction

Liver cirrhosis is a serious chronic progressive liver disease, chronic hepatitis b cirrhosis is the most common in our country, liver decompensation and liver failure will gradually occur with the disease progression, and positive early intervening measures need to be taken[1,2]. Liver protection and antiviral therapy are both basic therapies for chronic hepatitis b cirrhosis, they inhibit HBV replication to reduce further damage of liver cells, but their overall efficacy are limited[3]. A growing number of studies have shown that oxidative stress is closely related to hepatic stellate cell activation and liver fibrosis, so antioxidant indexes become the important means for liver cirrhosis intervention[4]. In the study, on the basis of antiviral treatment, antioxidant treatment was used for patients with chronic hepatitis b cirrhosis in our hospital in order to clarify the optimizing effect of combination therapy on the disease, and it was specifically elaborated from three aspects of oxidative stress, liver function and liver fibrosis, now reported as follows.

2. Information and methods

2.1 Case information

A total of 118 patients with chronic hepatitis B cirrhosis who were treated in Dongying Hospital for Infectious Diseases between May 2013 and February 2016 were enrolled, and the patients signed
enrolled patients were retrospectively analyzed and divided into the control group \((n=60)\) who underwent routine antiviral therapy and the observation group \((n=58)\) who underwent antiviral drugs combined with antioxidant therapy. Control group included 32 male cases and 28 female cases, they were 43-71 years old, and the course of liver fibrosis was 1-5 years; observation group included 31 male cases and 27 female cases, they were 40-73 years old, and the course of liver fibrosis was 1-6 years. The differences between the two groups of patients were not statistically significant \((P>0.05)\), and the ethics committee members approved the study after discussion.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with liver cirrhosis by histopathological biopsy; (2) with history of chronic hepatitis b; (3) with estimated survival time 6 months; (4) cooperating with clinical treatment and laboratory examination. Exclusion criteria: (1) associated with hepatolithiasis, liver malignancy and other hepatic malignancies; (2) associated with systemic infectious diseases; (3) associated with diabetes, chronic kidney failure and other diseases that led to systemic oxidative stress.

2.3 Therapy

Two groups of patients received liver-protecting, cholagogue, anti-infection, antiviral and other conventional treatment, antiviral drug was lamivudine (Shandong Weifang Pharmaceutical Co., Ltd., approved by H20123047), 100 mg/d, taken orally, 1 time/d; observation group, based on conventional treatment, received antioxidant drug therapy, specifically as follows: reduced glutathione (Shandong Luye Pharmaceutical Co., Ltd., approved by H20041620) 1 200 mg in saline 100 mL, by intravenous drip, 1 time/d. Both groups were treated for 3 consecutive months.

2.4 Observation indexes

Before and after treatment, morning fasting cubital venous blood (2.0-3.0 mL) was extracted from two groups of patients, anti-coagulated and then centrifuged at low temperature to get supernatant and freeze it in -70 °C environment for testing. Specific detection indexes were as follows: (1) oxidative stress indicators: xanthine oxidase method was used to determine serum levels of superoxide dismutase (SOD), advanced oxidation protein products (AOPPs), and other oxidative stress indicators. (2) Liver function indexes: the fully automatic biochemical analyzer (Xiamen Haifei Biotechnology Co., Ltd., the article number P003) was used to determine serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), albumin (ALB) and other liver function indexes. (3) Liver fibrosis indexes: RIA method was used to detect serum levels of hyaluronic acid (HA), collagen type IV (IV-C), procollagen type III (PCIII), laminin (LN) and other fibrosis indexes. The radioimmunoassay kits were purchased from the US Roche company, and the article number was DMJ-2827, AFG-0817, MDJ-7482 and KAH-1632 respectively.

2.5 Statistical processing

Statistical software in the study was SPSS 20.0, and the data were recorded and calculated by the professionals. Oxidative stress indexes, liver function indexes, liver fibrosis indexes and other measurement data were in terms of \(\bar{x}\pm s\) and comparison between groups was by t test. \(P<0.05\) was the standard of statistical significance in differences.

3. Results

3.1 Serum oxidative stress indexes before and after treatment

Before treatment, serum SOD (U/mL) and AOPPs (μmol/L) levels were not significantly different between two groups of patients \((P>0.05)\). 3 months after treatment, serum SOD levels in observation group and control group were significantly higher than those before treatment while AOPPs levels were significantly lower than those before treatment \((P<0.05)\), and serum SOD level in observation group 3 months after treatment was significantly higher than that in control group while AOPPs level was significantly lower than that in control group \((P<0.05)\), shown in Table 1.

Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>SOD</th>
<th>AOPPs</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>56.83±7.19</td>
<td>73.28±8.12</td>
</tr>
<tr>
<td>Observation group</td>
<td>58</td>
<td>55.95±6.94</td>
<td>91.63±10.29</td>
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<tr>
<td>(T)</td>
<td></td>
<td>0.182</td>
<td>9.372</td>
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<tr>
<td>(P)</td>
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<td>&gt;0.05</td>
<td>&lt;0.05</td>
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</table>

Note: compared with same group before treatment, \(^{*}P<0.05\).
3.2 Serum liver function indexes before and after treatment

Before treatment, serum AST (U/L), ALT (U/L), TBIL (μmol/L) and ALB (g/L) levels were not significantly different between two groups of patients \( (P>0.05) \). 3 months after treatment, serum AST, ALT and TBIL levels in observation group were significantly lower than those before treatment \( (P<0.05) \), and serum AST, ALT and TBIL levels in observation group 3 months after treatment were significantly lower than those in control group while ALB level was significantly higher than that in control group \( (P<0.05) \), shown in Table 2.

3.3 Serum liver fibrosis indexes before and after treatment

Before treatment, serum HA (mg/L), IV-C (μg/L), PCIII (μg/L) and LN (μg/mL) levels were not significantly different between two groups of patients \( (P>0.05) \). 3 months after treatment, serum HA, IV-C, PCIII and LN levels in observation group were significantly lower than those before treatment \( (P<0.05) \), and serum HA, IV-C, PCIII and LN levels in observation group 3 months after treatment were significantly lower than those in control group \( (P<0.05) \), shown in Table 3.

4. Discussion

Cirrhosis of the liver is the severe chronic liver disease with high incidence and bad prognosis in our country, patients can be without any clinical discomfort because of the strong liver compensation function in early stage, portal hypertension, ascites and other severe performances can appear when liver function damage is increasing and beyond compensation, and liver failure and death may appear eventually\(^5\). Liver-protecting, cholangogue and antiviral therapy are the routine therapies for clinical liver cirrhosis, but their curative effect is limited for the treatment of patients with progressive disease, and some patients can still develop progressive liver function decline. Many studies have shown that the pathogenic processes of many liver injury factors are accompanied by oxidative stress, the long-term effects can lead to liver fibrosis and even cirrhosis, so the active antioxidant treatment is expected to open the new phase for liver cirrhosis treatment.

The role that oxidative stress plays in viral hepatitis and the related complications is neglected over a long period of time, the latest study confirms that serum levels of oxidation metabolites increase in hepatitis c patients, and they are mainly distributed in piecemeal necrosis area of liver cells and around the portal vein\(^7\). Reduced glutathione is an important metabolism-regulating substance, which is involved in REDOX process the body, and is combined with peroxides and free radicals under the action of glutathione transferase to achieve antioxidant and thiol-damaging effects\(^9\). Reduced glutathione can effectively reduce the systemic oxidative stress in patients with chronic hepatitis b cirrhosis, but its effect on liver function and liver fibrosis remains to be confirmed in the following study.

Patients with liver cirrhosis have different levels of hepatic necrosis, and severe cases may develop sharp liver function decline and even liver failure. There are continuous hepatitis b virus replication and attack to normal liver cells in patients with chronic hepatitis b cirrhosis, which directly cause the increase in...
AST and ALT contents; The metabolism and excretion of bile acids are weakened in patients with persistent liver disorders, causing increased levels of TBIL. Liver is the main organ that produces albumin, blood ALB content decreases generally in patients with severe liver dysfunction, and this is one of the important causes of ascites in patients with advanced disease\[13,14\]. In the study, liver function index contents were compared between two groups of patients, and it was found that serum AST, ALT and TBIL levels in observation group after treatment were lower than those in control group while ALB level was significantly higher than that in control group, showing that antioxidant treatment is helpful for the optimization of liver function in patients with chronic hepatitis b cirrhosis.

Oxygen free radical scavenging obstacles in the liver can cause peroxidation damage of liver cells, kupffer cells and neutrophils as well as the activation of hepatic stellate cells, and prompt extracellular matrix production, which is the central part of the liver fibrosis\[15,16\]. At the same time, oxygen free radicals can directly act on the liver cells, change their cell membrane and subcellular structure, lead to membrane permeability and fluidity loss, and accelerate liver fibrosis and liver lobule formation\[17\]. HA, IV-C, PCIII and LN are the liver fibrosis indexes commonly studied at present, and their levels directly reflect liver fiber synthesis and inflammation activity\[18\]. In the study, liver fibrosis process was compared between two groups of patients, and it was found that serum HA, IV-C, PCIII and LN levels in observation group were lower than those in control group, it shows that positive antioxidant treatment can effectively inhibit the liver fibrosis process in patients with chronic hepatitis b cirrhosis, and this is the main reason why the liver function is optimized in this paper.

To sum up, it is concluded that antiviral combined with antioxidant therapy for patients with chronic hepatitis b cirrhosis can effectively reduce the degree of systemic oxidative stress response, also effectively optimize the liver function levels and inhibit liver fibrosis process, it is a feasible therapy and it is worth popularization and application in clinical practice in the future.

References


