Effect of adjuvant reduced glutathione therapy on vasoactive molecules and oxidative stress in patients with cirrhosis-induced upper gastrointestinal hemorrhage

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OBJECTIVE: To study the effect of adjuvant reduced glutathione therapy on vasoactive molecules and oxidative stress in patients with cirrhosis-induced upper gastrointestinal hemorrhage.

METHODS: Patients diagnosed with cirrhosis-induced upper gastrointestinal hemorrhage in No. 215 Hospital of Shaanxi Nuclear Industry between June 2015 and March 2017 were selected as the research subjects, and random number table was used to divide them into the GSH group who accepted reduced glutathione combined with conventional therapy and the control group who accepted conventional therapy. Serum levels of liver function indexes, vasoactive molecules and oxidative stress reaction molecules in two groups of patients were detected before treatment and 3 d after treatment.

RESULTS: 3 d after treatment, serum ALT, AST, γ-GT, TBIL, PRA, AT-II, ALD, ox-LDL, AOPP and 8-OHdG levels of both groups of patients were significantly lower than those before treatment while SOD, GSH-Px and CAT levels were significantly high than those before treatment, and serum ALT, AST, γ-GT, TBIL, PRA, AT-II, ALD, MDA, ox-LDL, AOPP and 8-OHdG levels of GSH group were significantly lower than those of control group while SOD, GSH-Px and CAT levels were significantly higher than those of control group.

CONCLUSION: The adjuvant reduced glutathione therapy for cirrhosis-induced upper gastrointestinal hemorrhage can improve the liver function, regulate the secretion of vasoactive molecules and reduce the oxidative stress response.

1. Introduction

Viral hepatitis, non-alcoholic fatty liver disease, alcoholic liver disease and other liver disease can cause liver cell necrosis, hepatic lobular structure damage and hepatic interstitial fibrosis, and then gradually develop into liver cirrhosis. In the development of cirrhosis, portal hypertension and esophageal-gastric varices will occur, and the upper gastrointestinal hemorrhage can occur in severe cases[1]. The upper gastrointestinal hemorrhage caused by liver cirrhosis is critically ill and progresses rapidly, causes large amount of bleeding, and can aggravate cirrhosis ascites and increase the risk of hepatic encephalopathy without proper treatment. After gastrointestinal hemorrhage occurs, the hepatic tissue blood perfusion reduces, and the rehydration and hemostasis can further result in ischemia reperfusion and aggravate liver function injury[2]. Oxidative stress response activation is an important pathological change in hepatic ischemia reperfusion injury. Therefore, anti-oxidative drugs are more and more used in the treatment of upper gastrointestinal hemorrhage due to cirrhosis. Reduced glutathione is has antioxidant matter[3], and the effect of adjuvant reduced glutathione therapy on vasoactive molecules and oxidative stress in patients with cirrhosis-induced upper gastrointestinal hemorrhage was analyzed in the following study.
Changes in serum vasoactive molecules before and after treatment.

Table 2.

Before treatment and 3 d after treatment, and centrifuged to separate 3 mL of fasting venous blood was collected from the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
<th>γ-GT (U/L)</th>
<th>TBIL (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSH group</td>
<td>28</td>
<td>Before treatment</td>
<td>196.7±22.4</td>
<td>224.6±29.3</td>
<td>178.5±20.3</td>
<td>56.4±7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>115.4±14.7</td>
<td>130.5±17.5</td>
<td>99.5±10.8</td>
<td>36.2±5.5</td>
</tr>
<tr>
<td>Control group</td>
<td>28</td>
<td>Before treatment</td>
<td>199.1±23.2</td>
<td>227.1±28.6</td>
<td>179.2±19.6</td>
<td>57.2±8.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>153.5±18.5</td>
<td>172.5±20.4</td>
<td>135.2±16.7</td>
<td>46.8±6.4</td>
</tr>
</tbody>
</table>

*: compared with same group before treatment, P<0.05; #: comparison between GSH group and control group after treatment, P<0.05.

Table 2.

Changes in vasoactive molecules before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>PRA (ng/mL)</th>
<th>AT-II (pg/mL)</th>
<th>ALD (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSH group</td>
<td>28</td>
<td>Before treatment</td>
<td>3.84±0.52</td>
<td>5.69±0.77</td>
<td>386.6±45.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>2.15±0.29</td>
<td>3.31±0.48</td>
<td>259.6±33.5</td>
</tr>
<tr>
<td>Control group</td>
<td>28</td>
<td>Before treatment</td>
<td>3.91±0.49</td>
<td>5.74±0.79</td>
<td>389.1±47.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>2.88±0.34</td>
<td>4.29±0.59</td>
<td>321.4±33.9</td>
</tr>
</tbody>
</table>

*: compared with same group before treatment, P<0.05; #: comparison between GSH group and control group after treatment, P<0.05.

2. Case information

2.1 General case information

Patients diagnosed with cirrhosis-induced upper gastrointestinal hemorrhage in No. 215 Hospital of Shaanxi Nuclear Industry between June 2015 and March 2017 were selected as the research subjects, all patients were with a history of cirrhosis of the liver, admitted to hospital because of upper gastrointestinal hemorrhage this time, and diagnosed with upper gastrointestinal hemorrhage by endoscopy, and there were a total of 56 cases. Random number table was used to divide the 56 patients with upper gastrointestinal hemorrhage into two groups, each with 28 cases. GSH group received reduced glutathione combined with conventional therapy, 17 cases were male and 11 cases were female, they were 47-62 years old, 24 cases were with esophageal - gastric varices rupture hemorrhage, and 4 cases were with portal hypertension, 4 cases were with portal hypertensive gastropathy; control group received routine treatment, 18 cases were male and 10 cases were female, they were 45-64 years old, 23 cases were with esophageal - gastric varices rupture hemorrhage, and 5 cases were with portal hypertension, 4 cases were portal hypertensive gastropathy. There was no statistically significant difference in general information between the two groups (P>0.05).

2.2 Therapy

Both groups of patients received regular treatment for liver cirrhosis-induced upper gastrointestinal hemorrhage, specifically as follows: micropump injection of octreotide 0.5 μg/min + pituitrin 0.05 U/min for hemostasis, intravenous drip of pantoprazole to protect gastric mucosa as well as blood transfusion and Sengstaken-Blakemore tube oppression hemostasis if necessary. GSH group received reduced glutathione on the basis of routine treatment, and the method was as follows: 1.2 g reduced glutathione in 100 mL saline injection, intravenous drip, 1 time/d.

2.3 Serum index detecting

3 mL of fasting venous blood was collected from the two groups before treatment and 3 d after treatment, and centrifuged to separate serum, automatic biochemical analyzer was used to determine ALT, AST, γ-GT and TBIL levels, enzyme-linked immunosorbent kit was used to determine the contents of PRA, AT-II and ALD and radioimmununoprecipitation kit was used to determine the contents of MDA, ox-LDL, AOPP, 8-OHdG, SOD, GSH-Px and CAT.

2.4 Statistical methods

SPSS 21.0 software was used to input and analyze data, data comparison between two groups was by t test and P<0.05 indicated statistical significance in differences in test results.

3. Results

3.1 Serum liver function indexes ALT, AST, γ-GT and TBIL levels

Analysis of serum liver function indexes ALT, AST, γ-GT and TBIL between two groups of patients before treatment and 3 d after treatment was as follows: serum ALT, AST, γ-GT and TBIL levels were not significantly different between two groups of patients before treatment; 3 d after treatment, serum ALT, AST, γ-GT and TBIL levels of both groups of patients were significantly lower than those before treatment, and serum ALT, AST, γ-GT and TBIL levels of GSH group were significantly lower than those of control group.

3.2 Vasoactive molecules PRA, AT-II and ALD levels

Analysis of serum vasoactive molecules PRA (ng/mL), AT-II (pg/mL) and ALD (pg/mL) between two groups of patients before treatment and 3 d after treatment was as follows: serum PRA, AT-II and ALD levels were not significantly different between two groups of patients before treatment; 3 d after treatment, serum PRA, AT-II and ALD levels of both groups of patients were significantly lower than those before treatment, and serum PRA, AT-II and ALD levels of GSH group were significantly lower than those of control group.
Changes in serum antioxidant enzymes before and after treatment (U/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>SOD</th>
<th>GSH-Px</th>
<th>CAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSH group</td>
<td>28</td>
<td>Before treatment</td>
<td>9.83±1.06</td>
<td>48.4±6.7</td>
<td>221.3±28.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>5.78±0.68*</td>
<td>29.3±3.77*</td>
<td>138.9±16.5*</td>
</tr>
<tr>
<td>Control group</td>
<td>28</td>
<td>Before treatment</td>
<td>9.91±1.14</td>
<td>49.1±6.2</td>
<td>220.9±27.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>7.46±0.89</td>
<td>38.6±5.5*</td>
<td>179.4±20.5</td>
</tr>
</tbody>
</table>

*: compared with same group before treatment, P<0.05; #: comparison between GSH group and control group after treatment, P<0.05.

3.3 Serum oxidative stress reaction molecules MDA, ox-LDL, AOPP and 8-OHdG levels

Analysis of serum oxidative stress molecules MDA (μmol/L), ox-LDL (mmol/L), AOPP (μmol/L) and 8-OHdG (ng/mL) between two groups of patients before treatment and 3 d after treatment was as follows: before treatment, serum levels of above oxidative stress molecules were not significantly different between two groups of patients; 3 d after treatment, serum MDA, ox-LDL, AOPP and 8-OHdG levels of both groups of patients were significantly lower than those before treatment, and serum MDA, ox-LDL, AOPP and 8-OHdG levels of GSH group 3 d after treatment were significantly lower than those of control group.

3.4 Serum antioxidant enzymes SOD, GSH-Px and CAT levels

Analysis of serum antioxidant enzymes SOD, GSH-Px and CAT between two groups of patients before treatment and 3 d after treatment was as follows: before treatment, serum levels of antioxidant enzymes were not significantly different between two groups of patients; 3 d after treatment, serum SOD, GSH-Px and CAT levels of both groups of patients were significantly high than those before treatment, and serum SOD, GSH-Px and CAT levels of GSH group 3 d after treatment were significantly higher than those of control group.

4. Discussion

Upper gastrointestinal hemorrhage is a common complication of cirrhosis and progresses rapidly, which can aggravate cirrhosis with ascites and increase the risk of hepatic encephalopathy. The upper gastrointestinal hemorrhage can decrease the circulating blood volume of the whole body and affect the blood perfusion of the liver tissue, and the hepatic blood reperfusion can be obtained after rehydration, hemostasis and other treatment[4,5]. After upper gastrointestinal hemorrhage, the ischemia reperfusion process experienced by liver tissue can aggravate the liver damage and cause liver cell rupture, which will cause the ALT, AST and γ-GT in cells to be released into the blood circulation, also influence the bile acid metabolism and lead to the elevation of TBIL. Oxidative stress is an important pathological link in the ischemia-reperfusion process to cause tissue damage. Therefore, anti-oxidative drugs are widely used in the treatment of ischemia reperfusion injury. The reduced glutathione is a drug that has antioxidant effect and free radical-scavenging activity, and is the antioxidant drug with wide clinical application[6]. In order to define the value of reduced glutathione for the treatment of liver cirrhosis-induced upper gastrointestinal hemorrhage, the changes in serum liver function indexes before and after treatment were analyzed in the study, and the results showed that serum liver function index levels of both groups significantly decreased after treatment, and serum liver function index levels of GSH group after treatment were significantly lower than those of control group. This indicates that on the basis of routine therapy, the reduced glutathione therapy can alleviate the liver function injury in patients with cirrhosis-induced upper gastrointestinal hemorrhage.

The massive loss of circulating blood volume in patients with upper gastrointestinal hemorrhage caused by cirrhosis will increase the compensatory secretion of various vasoactive molecules[7]. Renin-angiotensin-aldosterone system (RAAS) is the important system in the body adjusting water sodium metabolism and vasomotor state, the secreted vasoactive molecules are involved in the regulation of vasomotor and water sodium metabolism[8,9]. The reduced circulating blood volume after upper gastrointestinal hemorrhage could stimulate the increased synthesis and secretion of PRA, it acts on angiotensinogen and makes it transformed into angiotensin I, and angiotensin I generates AT-II under the action of angiotensin converting enzyme[10]. On the one hand, AT-II can directly promote vasoconstriction and ensure circulating blood pressure, and on the other hand, it can increase the secretion of ALD, cause water sodium retention and increase circulating blood volume. In order to further clarify the value of reduced glutathione for the treatment of liver...
cirrhosis-induced upper gastrointestinal hemorrhage, the changes in serum levels of RAAS system vasoactive molecules before and after treatment were analyzed in the study, and results showed that serum RAAS molecule levels of both groups of patients significantly decreased after treatment, and serum RAAS molecule levels of GSH group after treatment were significantly lower than those of control group. This indicates that on the basis of routine therapy, the reduced glutathione therapy can inhibit the activation of RAAS system and reduce the synthesis and secretion of corresponding vasoactive molecules in patients with cirrhosis-induced upper gastrointestinal hemorrhage.

Oxidative stress response activation and massive oxygen free radical generation are the important pathological links of increased liver injury in patients with cirrhosis-induced upper gastrointestinal hemorrhage[11]. The lipid, protein and nucleic acids in the cells are all vulnerable to oxygen free radical attacks, which will cause the cell structure and function damage and also generate the corresponding oxidative stress products[12,13]. MDA and ox-LDL are the oxidative reaction products of lipid. AOPP and 8-OHdG are the oxidative reaction products of proteins and nucleic acids respectively[14,15]. In the study, the changes in the levels of above oxidative stress products before and after treatment were analyzed, and the results showed that the oxidation products of lipid, protein and nucleic acid in serum of both groups of patients significantly decreased after treatment, and the oxidation products of lipid, protein and nucleic acid in serum of GSH group after treatment were significantly lower than those of control group. This indicates that on the basis of routine therapy, the reduced glutathione therapy can relieve the oxidative stress response and reduce the generation of oxidative stress products in patients with cirrhosis-induced upper gastrointestinal hemorrhage. SOD, GSH-Px and CAT are catalytic enzymes with antioxidant activity. In the process of massive oxygen free radical generation, SOD, GSH-Px and CAT can be consumed in large quantities and reduce the antioxidant capacity. In the study, the changes in serum levels of above antioxidant enzymes before and after treatment were analyzed, and the results showed that the serum antioxidant enzyme levels of both groups of patients significantly increased after treatment, and serum antioxidant enzyme levels of GSH group after treatment were significantly higher than those of control group. This further confirms that on the basis of routine therapy, the reduced glutathione therapy can relieve the oxidative stress reaction, reduce the consumption of antioxidant enzymes and enhance the antioxidant capacity in patients with cirrhosis-induced upper gastrointestinal hemorrhage.

In the study, we mainly analyzed the application value of adjuvant reduced glutathione therapy for liver cirrhosis-induced upper gastrointestinal hemorrhage, and it can be preliminarily concluded from the analysis of the results that adjuvant reduced glutathione therapy could reduce the liver function injury and oxidative stress, and can regulate the secretion of vasoactive molecules in patients with liver cirrhosis-induced upper gastrointestinal hemorrhage.

References


