Curative effect and prognosis of endoscopic tissue glue + lauromacrogol therapy for patients with cirrhosis and variceal bleeding

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ABSTRACT

Objective: To study the curative effect and prognosis of endoscopic tissue glue + lauromacrogol therapy for patients with cirrhosis and variceal bleeding. Methods: Patients with cirrhosis and variceal bleeding who underwent endoscopic hemostasis in the First Hospital of Yulin between March 2015 and February 2018 were retrospectively studied and divided into the observation group who accepted endoscopic hemostasis by lauromacrogol - tissue glue - lauromacrogol solution and the control group who accepted endoscopic hemostasis by lipiodol - tissue glue - lipiodol solution according to the history data. After treatment, the hemostasis time was observed, and the differences in blood routine indicators, stress-related hormones, oxidation-related mediators and inflammation-related mediators were compared. Results: The mean hemostasis time of observation group was shorter than that of control group, hemoglobin and hematokrit after 24 h of treatment were higher than those of control group, and serum GAS, AT-II, NE, E, Cor, MDA, LPO, NO, iNOS, p38MAPK, NF-κB, TNF-α, IL-6 and IL-8 levels were lower than those of control group. Conclusion: Endoscopic tissue glue combined with lauromacrogol therapy is better than tissue glue combined with lipiodol therapy in hemostasis, and can also relieve the oxidative stress response and inflammatory response.

1. Introduction

Gastric and esophageal variceal bleeding is a serious complication of patients with cirrhosis, and the rupture of varicose veins can cause a large amount of hemorrhage in a short period of time, the disease is dangerous and the mortality rate is high[1-2]. At present, the gastrointestinal endoscopic hemostasis is the major means for clinical treatment of liver cirrhosis with variceal bleeding, lipiodol - tissue glue - lipiodol sandwich method is the most common injection scheme for endoscopic hemostasis, which stops the bleeding through finding the hemorrhagic spot and injecting lipiodol and tissue glue under endoscope. Butylecyanacrylate, stabilizer and polymerization inhibitor are the main components of tissue glue, which will undergo polymerization reaction under the action of anions in local blood and tissue fluid and block the local blood vessel to achieve immediate hemostasis with embolization. Although lipiodol - tissue glue - lipiodol sandwich method has the advantage of exact hemostatic effect, the local fibrosis effect of tissue glue is weak during treatment, the blockage on the bleeding vessels is not complete, and it easily causes secondary bleeding; the large use of lipiodol will increase the risk of distant embolism[3]. Lauromacrogol is a kind of vascular sclerosing agent, and its application in endoscopic sandwich method hemostasis instead of lipiodol can reduce the degree of local varices. It not only help stop bleeding, but also help prevent further hemorrhage[4]. In the following studies, we specifically analyzed the curative effect and prognosis of endoscopic tissue glue combined with lauromacrogol therapy for patients with cirrhosis and variceal bleeding.

2. Case information and research methods

2.1 General case information

Patients with cirrhosis and variceal bleeding who underwent endoscopic hemostasis in the First Hospital of Yulin between
March 2015 and February 2018 were selected and retrospectively studied, and all patients who had the history of liver cirrhosis were admitted to hospital for upper gastrointestinal variceal bleeding, and received endoscopic hemostasis. A total of 75 patients were included. After the medical history was reviewed and the endoscopic hemostasis solutions were referred, the patients were divided into observation group and control group. Observation group \((n=34)\) accepted endoscopic hemostasis by lauromacrogol - tissue glue - lauromacrogol solution, including 20 males and 14 females who were 56-71 years old and with the history of cirrhosis for 2-7 years; control group accepted endoscopic hemostasis by lipiodol - tissue glue - lipiodol solution, including 23 males and 18 females who were 54-72 years old and with the history of cirrhosis for 2-8 years. There was no significant difference in the general data between the two groups \((P>0.05)\).

### 2.2 Therapy

After admission, both groups of patients received routine fluid infusion, blood transfusion, acid suppression and so on, and accepted emergency endoscopic therapy after the vital signs were stable. Control group were treated with lipiodol - tissue glue - lipiodol for hemostasis. The bleeding site was confirmed under endoscope, then the needle was pre-filled with 2 mL of lipiodol. The needle was inserted into the bleeding site to inject 2.0 mL of lipiodol, then 1.0-3.0 mL of tissue glue was injected, and 2.0 mL of lipiodol was injected afterwards. Observation group were treated with lauromacrogol - tissue glue - lauromacrogol for hemostasis. The needle was pre-filled with 2 mL of lauromacrogol and inserted into the bleeding site to inject pre-filled pre-filled lauromacrogol, then 1.0-3.0 mL of tissue glue and 2.0 mL of lauromacrogol were again injected.

### 2.3 Hemostatic effect observation

After treatment, the hemostatic time of the two groups was observed, the blood routine test was performed after 24 h of treatment, and the hemoglobin and hematokrit were compared between the two groups.

### 2.4 Serum index detection

Twenty-four hours after treatment, cubital venous blood was collected from the two groups of patients and centrifuged to separate serum, and Elisa kit instructions were followed to determine the GAS, AT-II, NE, E, Cor, MDA, LPO, NO, iNOS, p38MAPK, NF-κB, TNF-α, IL-6 and IL-8 levels.

### 2.5 Statistical analysis

Software SPSS 19.0 was used for data input and t test analysis of the difference in measurement data. \(P<0.05\) indicated statistical significance in differences.

### 3. Results

#### 3.1 Hemostatic effects of the two groups of patients

The mean hemostasis time of observation group was \((11.9±1.5)\) h, the hemoglobin after 24 h of treatment was \((88.4±11.6)\) g/L and the hematokrit was \((46.12±6.2)\) L/L; the mean hemostasis time of control group was \((14.2±1.8)\) h, the hemoglobin after 24 h of treatment was \((81.6±9.4)\) g/L and the hematokrit was \((41.08±5.9)\) L/L. After t test analysis, the mean hemostasis time of observation group was shorter than that of control group, the hemoglobin and hematokrit after 24 h of treatment were higher than those of control group, and the differences were statistically significant \((P<0.05)\).

#### 3.2 Serum stress-related hormones in the two groups of patients

Comparison of serum stress-related hormones GAS (ng/L), AT-II (ng/L), NE (μg/L), E (μg/L) and Cor (μg/L) levels between the two groups of patients was as follows: serum GAS, AT-II, NE, E and Cor levels were significantly different between the two groups of patients 24 h after treatment \((P<0.05)\), and serum GAS, AT-II, NE, E and Cor levels of observation group were lower than those of control group.

#### 3.3 Serum oxidation-related mediators in the two groups of patients

Comparison of serum oxidation-related mediators MDA, LPO, NO and iNOS levels between the two groups of patients was as follows: serum MDA, LPO, NO and iNOS levels were significantly different between the two groups of patients 24 h after treatment \((P<0.05)\), and serum MDA, LPO, NO and iNOS levels of observation group were lower than those of control group.

### Table 1.

Comparison of serum stress-related hormones after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>GAS</th>
<th>AT-II</th>
<th>NE</th>
<th>E</th>
<th>Cor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>34</td>
<td>93.51±11.35</td>
<td>18.52±2.03</td>
<td>62.83±7.27</td>
<td>71.03±8.72</td>
<td>203.52±26.83</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>147.42±17.83</td>
<td>26.38±2.84</td>
<td>89.33±11.03</td>
<td>98.41±10.89</td>
<td>238.57±29.31</td>
</tr>
<tr>
<td>(t)</td>
<td></td>
<td>11.833</td>
<td>14.128</td>
<td>9.282</td>
<td>8.893</td>
<td>9.867</td>
</tr>
<tr>
<td>(P)</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
and serum MDA, LPO, NO and iNOS levels of observation group 24 h after treatment were lower than those of control group.

Table 2.
Comparison of serum inflammation-related mediators after treatment (μg/L).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>MDA</th>
<th>LPO</th>
<th>NO</th>
<th>iNOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>34</td>
<td>7.98±0.95</td>
<td>4.61±0.66</td>
<td>36.41±5.23</td>
<td>1.86±0.25</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>12.51±1.56</td>
<td>8.38±1.03</td>
<td>55.42±6.95</td>
<td>2.99±0.37</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>13.894</td>
<td>18.398</td>
<td>16.272</td>
<td>11.385</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

3.4 Serum inflammation-related mediators in the two groups of patients

Comparison of serum inflammation-related mediators p38MAPK (μg/L), NF-κB (μg/L), TNF-α (μg/L), IL-6 (ng/L) and IL-8 (ng/L) levels between the two groups of patients was as follows: serum p38MAPK, NF-κB, TNF-α, IL-6 and IL-8 levels were significantly different between the two groups of patients 24 h after treatment (P<0.05), and serum p38MAPK, NF-κB, TNF-α, IL-6 and IL-8 levels of observation group 24 h after treatment were lower than those of control group.

4. Discussion

Endoscopic hemostasis is an important method for clinical treatment of upper gastrointestinal variceal bleeding after liver cirrhosis, the traditional endoscopic hemostatic scheme is lipiodol + tissue glue + lipiodol sandwich method, and the use of lipiodol can avoid tissue glue from obstructing the needle, and guarantee the exact hemostatic effect. However, there are some deficiencies in the hemostatic method. Firstly, tissue glue has weak fibrosis effect on the local bleeding area, and cannot cause the complete occlusion of the bleeding blood vessels, which affects the hemostatic effect and increases the risk of rebleeding; secondly, the lipiodol that enters into the blood circulation from the bleeding site will increase the risk of distant embolism, such as pulmonary embolism and cerebral embolism[5,6]. Lauromacrogol is a type of vascular sclerosing agent used in the treatment of varices, and the combination of lauromacrogol and tissue glue in the process of varices bleeding can exert tissue hardening effect in local area, which not only relieves the degree of varices, but also reduces the blood loss[7,8]. In the study, in order to define the efficacy of tissue glue combined with lauromacrogol treatment, the hemostasis time and the blood routine-related indexes after treatment were analyzed, and the result showed that the mean hemostasis time of observation group was shorter than that of control group, and the hemoglobin and hematokrit after 24 h of treatment were higher than those of control group. This indicates that the hemostatic effect of tissue glue combined with lauromacrogol is better than that of tissue glue combined with lipiodol, with shorter hemostasis time and less loss of hemorrhibin.

The massive hemorrhage process of upper gastrointestinal tract is a strong stressor for the body, which will activate the stress response in the body and lead to the increased synthesis and release of various endocrine hormones. GAS is a kind of gastrointestinal hormone. The stimulation of upper gastrointestinal hemorrhage to gastric mucosa can directly increase the synthesis and release of GAS in parietal cells and G cells[9]. The rapid loss of blood volume after upper gastrointestinal hemorrhage will cause the activation of renin-angiotensin system, and the reduction of blood volume will enhance renin activity, then promote the angiotensinogen transformation to the AT-I and the AT-II, and finally ensure that the body is in the state of steady circulation under the pathological state of rapid blood volume loss through the vasoconstrictor activity of AT-II[10,11]. In addition, the endocrine function of adrenal gland is also significantly enhanced in the process of blood volume loss and stress response activation, and the NE and E synthesized by its medulla have strong cardiotonic and vasoconstrictor activity, and can maintain stable blood pressure under the conditions of blood volume loss; the Cor synthesized by the cortex mainly stabilizes the lysosomal membrane, and can guarantee the normal function of tissues and cells in the condition of rapid loss of blood volume[12]. After treatment, we analyzed the secretion of stress hormones in serum, and the results showed that serum GAS, AT-II, NE, E and Cor levels of observation group 24 h after treatment were lower than those of control group. This shows that in the treatment of cirrhosis with variceal bleeding, tissue glue combined with lauromacrogol is better than tissue glue combined with lipiodol in relieving the stress response.

Under the pathological condition of rapid blood volume loss, the blood perfusion significantly reduces in multiple tissues and organs, it will affect the electron transfer in the oxidation respiratory chain process, and also cause intracellular calcium overload. Also, the above two factors work together to further cause mass generation of strongly oxidizing reactive oxygen species. The reactive oxygen species generated in the local tissue will oxidize the lipids in cell
membrane and organelle membrane structure, which will one the one hand, cause cellular structure and function damage, and on the other hand, cause increased formation of oxidation products of MDA and LPO[13]. The oxidative stress activation in vivo caused by massive hemorrhage is not only dependent on the increase of ROS production, but also related to the mass production of gas molecule NO. iNOS is inducible NO synthase, and the activation of iNOS under ischemia state will increase the NO synthesis, and then aggravate the oxidative stress damage of local tissue through the cytotoxic effect and signal transduction of NO[14]. After treatment, we analyzed the generation of oxidation-related mediators in serum, and the results showed that serum MDA, LPO, NO and iNOS levels of observation group 24 h after treatment were lower than those of control group. It demonstrates that in the treatment of cirrhosis with variceal bleeding, tissue glue combined with lauromacrogol is better than tissue glue combined with lipiodol in relieving the oxidative stress.

Under the action of excessive stress reaction and oxidative stress, a variety of inflammatory cells in patients with digestive tract hemorrhage will be excessively activated, which will cause the increased secretion of inflammation-related mediators and the excessive activation of inflammatory reaction[15]. p38MAPK is the signal molecule that mediates inflammatory response in the condition of stress reaction and oxidative stress, it belongs to the MAPK family and can activate the NF-κB through the amplified downstream signal transmission, and the activated NF-κB transfers into the nucleus and starts the expression and secretion of TNF-α, IL-6, IL-8 and other cytokines. TNF-α is a pro-inflammatory cytokine that is massively secreted at the initial stage of inflammatory response activation. It is derived from activated mononuclear macrophages, and can cause the cascade activation of inflammatory response; IL-6 and IL-8 have multiple biological activities, which are secreted by lymphocytes, neutrophils and so on, and can mediate the adhesion and chemotaxis of inflammatory cells. Besides, it can amplify the inflammatory response. After treatment, we analyzed the generation of inflammation-related mediators in serum, and the results showed that serum p38MAPK, NF-κB, TNF-α, IL-6 and IL-8 levels of observation group 24 h after treatment were lower than those of control group. This shows that in the treatment of cirrhosis with variceal bleeding, tissue glue combined with lauromacrogol is better than tissue glue combined with lipiodol in relieving inflammatory response.

Based on the analysis of above curative effect and serum indicators, it can be concluded that endoscopic tissue glue combined with lauromacrogol in the treatment of cirrhosis with variceal bleeding has better hemostatic effect than tissue glue combined with lipiodol treatment, and can also relieve the stress response, oxidative stress and inflammatory response in the course of disease.

References


