Original Article

Influence of Xuebijing injection combined with cefoperazone sodium and sulbactam sodium in treating hepatitis B-induced liver cirrhosis complicated by spontaneous bacterial peritonitis: TNF-α, IL-18, IL-6, and hepatic function

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Abstract: Objective: To analyze the influences of Xuebijing injection combined with cefoperazone sodium and sulbactam sodium (CSSS) in the treatment of hepatitis B-induced liver cirrhosis (HBLC) complicated by spontaneous bacterial peritonitis (SBP) with respect to tumor necrosis factor-α (TNF-α), interleukin-18 (IL-18), interleukin-6 (IL-6), and hepatic function. Methods: A total of 98 patients with HBLC complicated by SBP admitted to our hospital were selected and divided into the control group (CON, n=49) and the observation group (OBG, n=49) in accordance with the therapeutic methods. The clinical data of the patients were retrospectively analyzed. The CON was treated with CSSS, while the OBG was treated with Xuebijing injection combined with CSSS. The time of symptomatic improvement and changes of serum inflammatory factors and indices of intestinal mucosal barrier damage and hepatic function were compared between the two groups before and after treatment. Results: The time of symptomatic improvement in the OBG was shorter than that in the CON (P < 0.05). After treatment, IL-6, IL-18, TNF-α, urinary L/M, D-lactic acid, DAO, total bilirubin, ALT, and AST in the OBG were lower than those in the CON (P < 0.05). Conclusion: Xuebijing injection combined with CSSS is conducive to improving the inflammatory responses of the body, intestinal tract barrier function, and hepatic function, showing satisfactory efficacy in the treatment of HBLC complicated by SBP.

Keywords: Hepatitis B, liver cirrhosis, spontaneous bacterial peritonitis, Xuebijing injection, cefoperazone sodium and sulbactam sodium, combined therapy, hepatic function, inflammatory factor

Introduction

Clinically, hepatitis B is a common chronic infectious disease, and is a serious public health concern, seriously threatening human life and health [1, 2]. If the intervention of hepatitis B is not performed in a timely manner, liver cirrhosis will occur as the disease progresses, leading to a markedly elevated mortality rate of patients [3]. Spontaneous bacterial peritonitis (SBP) is one of the common complications of decompensated liver cirrhosis, and patients with hepatitis B-induced liver cirrhosis (HBLC) complicated by SBP have extremely high mortality [4]. It is necessary to find an effective treatment method to improve the prognosis.

A study reveals that patients with HBLC are usually accompanied by varying degrees of inflammatory response and intestinal mucosal barrier damage. The increase of intestinal mucosal permeability leads to massive endotoxin, bacteria, and inflammatory factors entering the blood circulation through the intestinal mucosa, which not only induces SBP, but also further aggravates hepatocellular injury [5, 6]. Therefore, a new target for clinical treatment of HBLC complicated by SBP is that the release of inflammatory factors is blocked to protect the gastrointestinal tract mucosa. Previously, antibiotics were usually used to treat patients. Although antibiotics have satisfactory bactericidal effects and are beneficial to the control of
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In abdominal infection, it is difficult to obtain a satisfactory comprehensive therapeutic effect [7, 8]. In order to further improve the prognosis of patients with HBLC complicated by SBP, Xuebijing injection combined with cefoperoxazine sodium and sulbactam sodium (CSSS) was adopted in this study.

This study analyzed the influence of Xuebijing injection combined with CSSS in treating hepatitis B-induced liver cirrhosis complicated by SBP with regard to tumor necrosis factor-α (TNF-α), interleukin-18 (IL-18), interleukin-6 (IL-6), and hepatic function. The two groups were treated with CSSS alone and Xuebijing injection combined with CSSS, respectively, so as to provide more effective and safe methods for clinical treatment of HBLC complicated by SBP.

Materials and methods

General data

A total of 98 patients with HBLC complicated by SBP admitted to our hospital were selected and divided into the control group (CON, n=49) and the observation group (OG, n=49) in accordance with the therapeutic methods. The clinical data of the patients were retrospectively analyzed. The CON was treated with CSSS. The OBG was treated with Xuebijing injection combined with CSSS. In the CON, there were 30 males and 19 females aged 34-75 years. In the OBG, there were 32 males and 17 females aged 35-78 years. (1) Inclusion criteria: patients who signed an informed consent form voluntarily; those without contraindication to the study drugs; the white blood cell count of ascites was more than $10 \times 10^9$ L$^{-1}$; those with varying degrees of symptoms, such as abdominal rebound tenderness, tenderness and fever; Child-Pugh grading of hepatic function was between grades A and C. (2) Exclusion criteria: patients with administration of gastric prokinetic drugs and antibiotics within one week before enrollment; autoimmune diseases; alcoholic liver injury and drug-induced liver injury; traumatic peritonitis; perforated peptic ulcer; secondary peritonitis; neoplastic ascites. This study was approved by the Ethics Committee of Tianjin Nankai Hospital.

Methods

Patients in the CON were treated with conventional symptomatic treatment after admission, including vitamin supplementation, maintenance of water-electrolyte balance, diuresis, liver protection and nutritional support. Meanwhile, patients were treated with 100 ml of normal saline (manufacturer: China Otsuka Pharmaceutical Co., Ltd., approval number: SFDA approval number: H20043271, specification: 10 ml; 0.09 g) combined with 1.5 g of CSSS (approval number: SFDA approval number: H20063393, manufacturer: Anhui Xianfeng Pharmaceuticals Co., Ltd., specification: 2.0 g) by an intravenous drip twice a day for 2 weeks.

Patients in the OBG were additionally treated with Xuebijing injection based on the treatment in the CON. Patients were treated with 50 ml of Xuebijing injection combined with 100 ml of normal saline (manufacturer: Tianjin Chase Sun Pharmaceutical Co., Ltd., approval number: SFDA approval number: Z20040033, specifications: 10 ml × 5 pcs/box) via an intravenous drip twice a day for 2 weeks, and the duration for the drip was maintained within 30-40 min.

Observational indices

The time of symptomatic improvement, including the disappearance time of abdominal rebound tenderness, tenderness and ascites, the duration of nausea and vomiting responses, and body temperature recovery time, were compared between the two groups.

Serum inflammatory factors: before and after treatment, 2 ml of fasting venous blood was drawn in the two groups, respectively, and was centrifuged at a speed of 3000 r/min to separate serum for detection. IL-6, IL-18 and TNF-α were detected by the enzyme-linked immunosorbent assay (ELISA), and the kit was purchased from Hebei Changtian Pharmaceutical Co., Ltd.

Indices of intestinal mucosal barrier damage: the changes in urine fructose/mannitol (L/M), D-lactic acid and serum diamine oxidase (DAO) were compared between the two groups before and after treatment.

Indices of hepatic function: the changes in total bilirubin (TBil), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were compared between the two groups before and after treatment.
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Statistical analysis

SPSS22.0 was adopted for statistical analysis. Graphpad Prism 8.0 software was used for drawing statistical figures. The enumeration data were represented by [n (%)]. The comparison of enumeration data between groups was detected using \(X^2\) test. The measurement data were represented by mean standard ± deviation. The data conforming to normal distribution were detected by independent samples t test, and those not conforming to normal distribution were detected by Mann-Whitney U test. The comparison within groups was detected using the paired t test. \(P < 0.05\) indicated a significant difference.

Results

Comparison of general data between the two groups

The OBG included 32 males (65.31%) and 17 females (34.69%), aged 35-78 years, with a mean age of (61.25±1.25) years, while the CON included 30 males (61.22%) and 19 females (38.78%), aged 34-75 years, with a mean age of (61.08±1.19) years. The course of liver cirrhosis in the OBG was 3-15 years, with a mean course of (8.15±1.08) years, while that in the CON was 2-16 years, with a mean course of (8.23±1.12) years. The course of liver cirrhosis in the OBG was 3-15 years, with a mean course of (8.15±1.08) years, while that in the CON was 2-16 years, with a mean course of (8.23±1.12) years. In the OBG, there were 10, 25 and 14 patients with Child-Pugh grades A (20.41%), B (51.02%) and C (28.57%), respectively, while in the CON, there were 11, 23 and 15 patients with Child-Pugh grades A (22.45%), B (46.94%) and C (30.61%), respectively. There was no statistical significance in the comparison of general data (e.g., gender, mean age, mean course of disease, and Child-Pugh grading of hepatic function) between the two groups (\(P > 0.05\)) (Table 1).

Comparison of time of symptomatic improvement between the two groups

In the CON, the disappearance time of abdominal rebound tenderness, was (10.58±1.25) d, the disappearance time of ascites was (9.69±1.22) d, the duration of nausea and vomiting responses was (9.36±1.26) d, and body temperature recovery time was (7.19±0.88) d, whereas the time of above indices in the OBG was (7.12±0.28) d, (6.08±0.08) d, (6.12±0.23) d, and (5.12±0.28) d, respectively. The time of symptomatic improvement in the OBG was shorter than that in the CON (\(P < 0.05\)) (Figure 1).
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Comparison of serum inflammatory factors between the two groups

There was no difference in IL-6, IL-18 and TNF-α between the two groups before treatment ($P > 0.05$). Compared with those before treatment, the levels of IL-6, IL-18, and TNF-α were decreased in both groups after treatment ($P < 0.05$). The levels of IL-6, IL-18, and TNF-α in the OBG ($[62.12±2.18]$ pg/ml, $[42.15±1.28]$ pg/ml, and $[11.02±0.89]$ pg/ml) were much lower than those in the CON ($[72.56±4.26]$, $[52.23±2.15]$, and $[18.96±1.05]$ pg/ml) after treatment ($P < 0.05$) (Figure 2).

Comparison of indices of intestinal mucosal barrier damage between the two groups

There was no difference in urinary L/M, D-lactic acid, and DAO between the two groups before treatment ($P > 0.05$). Compared with those before treatment, the urinary L/M, D-lactic acid and DAO were decreased in both groups after treatment ($P < 0.05$). The urine L/M, D-lactic acid and DAO in the OBG ($[0.06±0.01]$, $[7.02±0.23]$, and $[4.05±0.52]$) were lower than those in the CON ($[0.12±0.02]$, $[9.68±0.52]$, and $[6.85±0.82]$) after treatment ($P < 0.05$) (Figure 3).

Comparison of indices of hepatic function between the two groups

There was no difference in TBil, ALT, and AST between the two groups before treatment ($P > 0.05$). Compared with those before treatment, TBil, ALT, and AST were decreased in both groups after treatment ($P < 0.05$). TBil, ALT, and AST in the OBG ($[220.03±5.12]$, $[52.12±5.12]$, and $[52.12±3.25]$ IU/L) were lower than those in the CON ($[268.96±8.13]$, $[66.96±8.12]$, and $[62.52±4.12]$ IU/L) after treatment ($P < 0.05$) (Figure 4).

Discussion

Spontaneous bacterial peritonitis (SBP) is a serious complication of hepatitis B-induced decompensated liver cirrhosis, with high morbidity, high mortality, and poor prognosis [9, 10]. HBLC complicated by SBP is not only closely related to impaired hepatic function, decreased immune function and long-term malnutrition, but also related to the release of many inflammatory factors and intestinal mucosal damage [7, 11].

The portal vein pressure is significantly increased in patients with liver cirrhosis, leading to edema and hyperemia of the gastrointestinal tract mucosa. In severe cases, it leads to ischemic necrosis of intestinal epithelial cells, intestinal mucosal barrier damage, and increased intestinal wall permeability, thereby in-
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Additionally, the massive endotoxin release induced by intestinal tract bacteria leads to intestinal mucosal barrier damage and translocation of intestinal flora, thereby inducing SBP. Currently, there are multiple indices (e.g., urine L/M, D-lactic acid, and DAO) used to assess intestinal mucosal permeability and barrier function [14, 15]. Currently, urine L/M is an indirect urine test index necessary to assess the intestinal mucosal barrier function and can be used to judge the intestinal mucosal permeability and promote the intestinal mucosal barrier function to be accurately reflected [16]. D-lactic acid, a product of glycolysis, is released by intestinal mucosal epithelial cells and intestinal bacteria. The serious damage of intestinal mucosal epithelial cells significantly promotes the release of D-lactic acid [17]. DAO is mainly distributed in intestinal mucosal cells and upper villous cells. The inflammatory injury and infection of intestinal mucosa lead to a large increase in the content of DAO [18].

Clinical studies show that inflammatory responses play a pivotal role in the occurrence and progression of HBLC complicated by SBP. The obvious imbalance of intestinal flora in patients with liver cirrhosis leads to a significant proliferation of gram negative bacilli and massive endotoxin release, thus promoting the activation of complement-mediated inflammatory responses [19]. In addition, the activation of massive monocytes and lymphocytes results in the release of a large number of inflammatory factors, which damage the intestinal mucosal epithelial cells and affect the intestinal mucosal barrier function, thereby inducing SBP. IL-6 is an important pro-inflammatory factor that activates B and T lymphocytes, induces natural killer cells, and plays a pivotal role in inflammatory injuries of intestinal mucosal epithelial cells and hepatic cells [20, 21]. TNF-α can induce the elevated expression of B and T lymphocytes, and promote the phagocytosis of monocytes. TNF-α is one of the inflammatory transmitters during the inflammatory responses in liver cirrhosis [22, 23]. IL-18 is mainly secreted by monocytes and NK cells, which leads to an increase in the inflammatory response cascade, and induces intestinal microcirculation disturbance, thus further aggravating patients’ conditions. Therefore, the key to the clinical treatment of HBLC complicated by SBP is to effectively protect the intestinal mucosal barrier function, reduce the incidence of bacterial translocation and endotoxin, block the inflammatory responses, and improve the hepatic function of patients.

In this study, the time of symptomatic improvement in the OBG was shorter than that in the CON. After treatment, the OBG was superior to the CON regarding the serum inflammatory fac-

Figure 3. Comparison of indices of intestinal mucosal barrier damage between the two groups. In comparison of L/M, D-lactic acid, and DAO between the two groups before treatment, $P > 0.05$; after treatment, L/M, D-lactic acid, and DAO in the observation group were all lower than those of the control group ($P < 0.05$).
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Modern pharmacologic study shows that Radix Salviae Miltiorrhizae can inhibit complement system and platelet activation, block inflammatory responses, and thus protect organ function. Radix Paeoniae Rubra and Flos Carthami can increase tissue blood flow, inhibit the release of inflammatory cytokines, reduce capillary permeability and promote the absorption of inflammatory transmitters [25, 26]. In a word, Xuebijing injection can inhibit the proliferation of bacteria and inflammatory responses, effectively regulate the immune function of the body, promote the scavenging of oxygen free radicals, and improve the microcirculation of important organs in the body.

In summary, Xuebijing injection combined with CSSS is conducive to improving the inflammatory responses of the body, intestinal tract barrier function and hepatic function, showing a satisfactory efficacy in the treatment of HBLC complicated by SBP.

However, the insufficient subjects enrolled in this study lead to the lack of representativeness in the results. Therefore, the future comprehensive studies with a longer duration and a larger sample size should be performed.

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Disclosure of conflict of interest

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