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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 (SPB) 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

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 cefoperazone 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 (OBG, 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 10×10^9 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.

Table 1. Comparison of general data between the two groups [n (%)]/($\bar{x}$ ± s)

General data		Observation group (n=49)	Control group (n=49)	t/X^2	*P*
Gender (cases)	Male	32 (65.31)	30 (61.22)	0.158	0.952
	Female	17 (34.69)	19 (38.78)		
Age (years)		61.25±1.25	61.08±1.19	0.117	1.058
Course of disease (years)		8.15±1.08	8.23±1.12	0.638	0.996
Child-Pugh grading of hepatic function (cases)					
Grade A		10 (20.41)	11 (22.45)	0.015	0.963
Grade B		25 (51.02)	23 (46.94)		
Grade C		14 (28.57)	15 (30.61)		

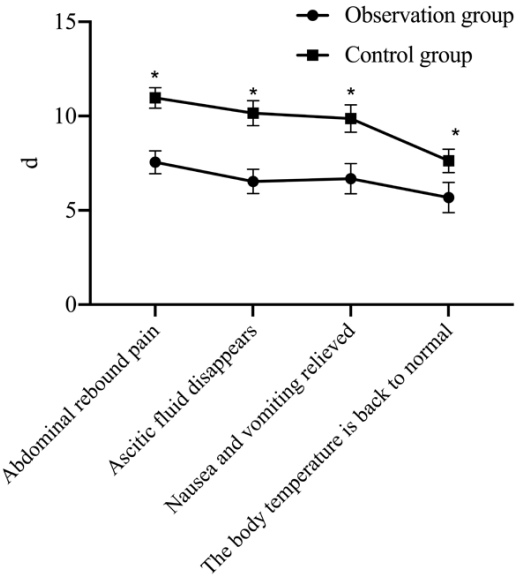

Figure 1. Comparison of time of symptomatic improvement between the two groups. The disappearance time of abdominal rebound tenderness, tenderness and ascites, the duration of nausea and vomiting responses, and body temperature recovery time in the observation group were shorter than those of the control group ($P < 0.05$). * indicates a comparison with the control group, $P < 0.05$.

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. 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**).

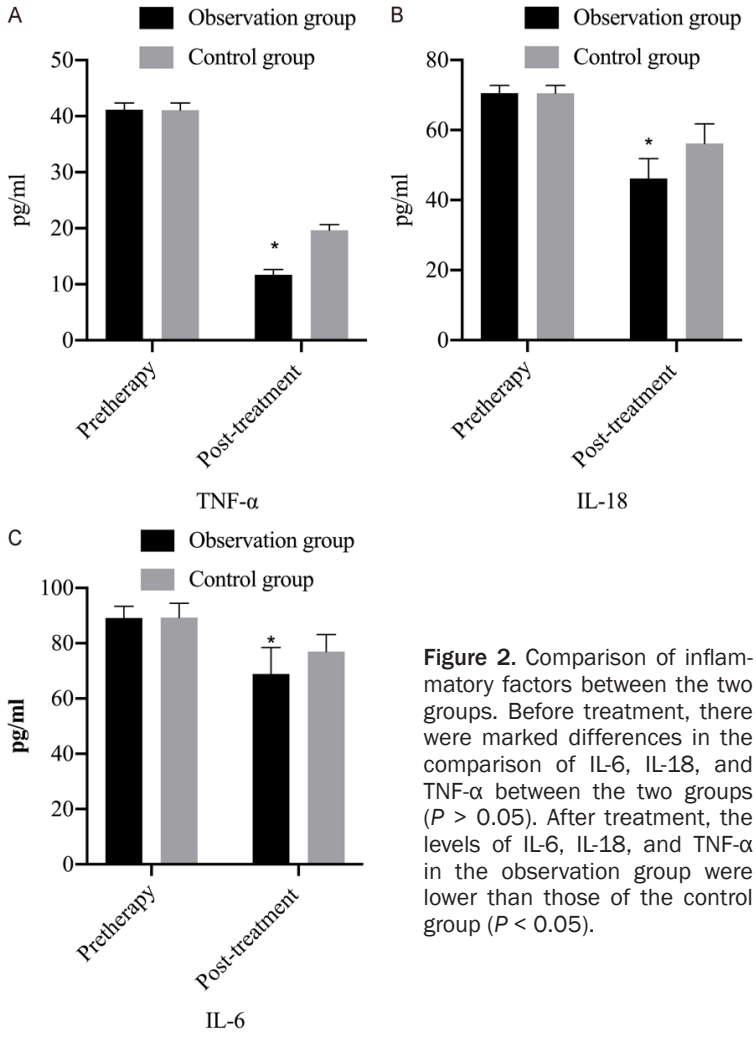

Figure 2. Comparison of inflammatory factors between the two groups. Before treatment, there were marked differences in the comparison of IL-6, IL-18, and TNF-α between the two groups ($P > 0.05$). After treatment, the levels of IL-6, IL-18, and TNF-α in the observation group were lower than those of the control group ($P < 0.05$).

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) pg/ml, (52.23±2.15) pg/ml, 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) μmol/L, (52.12±5.12) IU/L, and (52.12±3.25) IU/L] were lower than those in the CON [(268.96±8.13) μmol/L, (66.96±8.12) IU/L, 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-

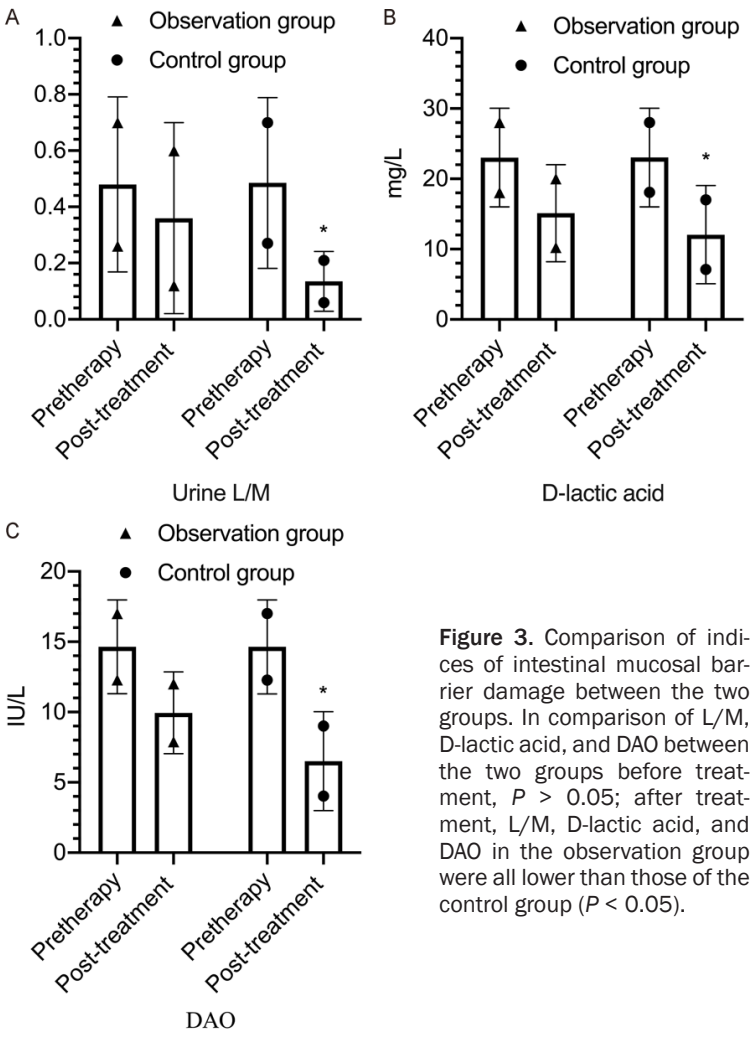

Figure 3. Comparison of indices of intestinal mucosal barrier damage between the two groups. In comparison of L/M, D-lactic acid, and DAO between the two groups before treatment, $P > 0.05$; after treatment, L/M, D-lactic acid, and DAO in the observation group were all lower than those of the control group ($P < 0.05$).

ducing SBP [12, 13]. 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-

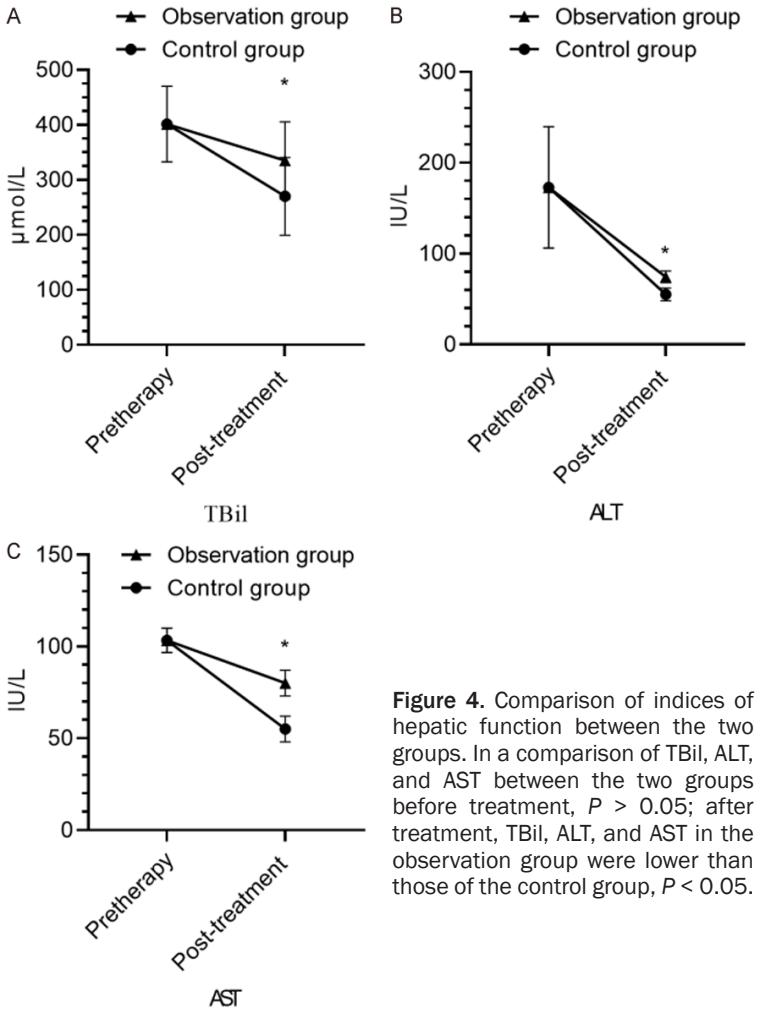

Figure 4. Comparison of indices of hepatic function between the two groups. In a comparison of TBil, ALT, and AST between the two groups before treatment, $P > 0.05$; after treatment, TBil, ALT, and AST in the observation group were lower than those of the control group, $P < 0.05$.

tors, and indices of intestinal mucosal barrier damage and hepatic function ($P < 0.05$), suggesting that Xuebijing injection combined with CSSS was conducive to improving the inflammatory responses of the body, intestinal tract barrier function and hepatic function, exhibiting a satisfactory efficacy in the treatment HBLC complicated by SBP. This is because CSSS, a compound preparation composed of sulbactam and cefoperazone, can not only enhance the stability of β-lactamase, but also improve the antibacterial activity [24]. Although CSSS can effectively kill pathogenic bacteria, its effect needs to be enhanced. Xuebijing injection is a traditional Chinese medicine preparation, and its effective compositions include Radix Angelicae Sinensis, Rhizoma Ligustici, Flos Carthami, and Radix Salviae Miltiorrhizae. It can clear heat and resolve toxin, dredge collaterals and vessels and quicken the blood. 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

None.

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References

[1] Pondé RA. Acute hepatitis B virus infection or acute exacerbation of chronic hepatitis B infection: the differential serological diagnosis. Eur J Clin Microbiol Infect Dis 2016; 35: 29-40.

[2] Nguyen MH, Lim J, Liou I, Ozbay AB, Fraysse J, Meyer N, Dusheiko G and Gordon S. SAT-132-higher and rising prevalence and incidence of renal impairment and chronic kidney disease in chronic hepatitis B patients compared to matched non-chronic hepatitis B controls in the United States: results of a real-world analysis. J Hepatol 2017; 66: S677-S678.

[3] Hansi N, Troke P, Gill U, Agarwal K, Aldersley M, Al-Shamma S, Brown A, Cobbold J, Collins P, Fowell A, Gelson W, Holt A, McPherson S, Phillips M, Prince M, Richardson P, Ryder S, Singhal S, Stone B and Kennedy P. PTH-107 chronic hepatitis B management The UK: a national survey of current practice following nice guidance. Gut 2016; 65 Suppl 1: A271.2-A272.

[4] Kim JH, Jeon YD, Jung IY, Ahn MY, Ahn HW, Ahn JY, Ku NS, Han SH, Choi JY, Ahn SH, Song YG, Han KH and Kim JM. Predictive factors of spontaneous bacterial peritonitis caused by gram-positive bacteria in patients with cirrhosis. Medicine (Baltimore) 2016; 95: e3489.

[5] Asil M and Dertli R. Serum soluble TWEAK levels are decreased in treatment naive noncirrhotic chronic hepatitis B patients. Medicine (Baltimore) 2016; 95: e4763.

[6] Abd-Elsalam S, Sharaf-Eldin M, Soliman S, Elfert A, Badawi R and Ahmad YK. Efficacy and safety of sofosbuvir plus ribavirin for treatment of cirrhotic patients with genotype 4 hepatitis C virus in real-life clinical practice. Arch Virol 2018; 163: 51-56.

[7] Tsai CC, Huang PK, Liu HK, Su YT, Yang MC and Yeh ML. Pediatric types I and VI choledochal cysts complicated with acute pancreatitis and spontaneous perforation: a case report and literature review. Medicine (Baltimore) 2017; 96: e8306.

[8] Ahmed O, Rodrigues D, Brahmania M and Patel K. Su1570 - low incidence of spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhosis undergoing paracentesis: a systematic review and meta-analysis. Gastroenterology 2018; 154: S-1181.

[9] Madsen BS, Nielsen KF, Fialla AD and Krag A. Keep the sick from harm in spontaneous bacterial peritonitis: dose of beta blockers matters. J Hepatol 2016; 64: 1455-1456.

[10] Merchante N, Aldámiz-Echevarría T, García-Álvarez M, Rivero-Juárez A, Macías J, Miralles P, Jiménez-Sousa MA, Mancebo M, Pérez-Latorre L, Pineda-Tenor D, Berenguer J, Resino S and Pineda JA. Bacterial translocation and clinical progression of HCV-related cirrhosis in HIV-infected patients. J Viral Hepat 2018; 25: 180-186.

[11] Fernandes SR, Santos P, Fatela N, Baldaia C, Tato Marinho R, Proença H, Ramalho F and Velosa J. Ascitic calprotectin is a novel and accurate marker for spontaneous bacterial peritonitis. J Clin Lab Anal 2016; 30: 1139-1145.

[12] Gouya H, Grabar S, Vignaux O, Saade A, Pol S, Legmann P and Sogni P. Portal hypertension in patients with cirrhosis: indirect assessment of hepatic venous pressure gradient by measuring azygos flow with 2D-cine phase-contrast magnetic resonance imaging. Eur Radiol 2016; 26: 1981-1990.

[13] Huynh DK, Toscano L, Phan VA, Ow TW, Schoeman M and Nguyen NQ. Ultrathin disposable gastroscope for screening and surveillance of gastroesophageal varices in patients with liver cirrhosis: a prospective comparative study. Gastrointest Endosc 2017; 85: 1212-1217.

[14] Volynets V, Louis S, Pretz D, Lang L, Ostaff MJ, Wehkamp J and Bischoff SC. Intestinal barrier function and the gut microbiome are differentially affected in mice fed a western-style diet or drinking water supplemented with fructose. J Nutr 2017; 147: 770-780.

[15] Bakke M, Nahrgang J and Ingebrigtsen K. Comparative absorption and tissue distribution of 14C-benzo(a)pyrene and 14C-phenanthrene in the polar cod (Boreogadus saida) following oral administration. Polar Biol 2015; 39: 1165-1173.

[16] Warners MJ, Vlieg-Boerstra BJ, Verheij J, van Hamersveld PHP, van Rhijn BD, Van Ampting MTJ, Harthoorn LF, de Jonge WJ, Smout AJPM and Bredenoord AJ. Esophageal and small intestinal mucosal integrity in eosinophilic esophagitis and response to an elemental diet. Am J Gastroenterol 2017; 112: 1061-1071.

[17] Abebayehu D, Spence AJ, Qayum AA, Taruselli MT, McLeod JJ, Caslin HL, Chumanevich AP, Kolawole EM, Paranjape A, Baker B, Ndaw VS, Barnstein BO, Oskeritzian CA, Sell SA and Ryan JJ. Lactic acid suppresses IL-33-mediated mast cell inflammatory responses via hypoxia-inducible factor-1α-dependent miR-155 suppression. J Immunol 2016; 197: 2909-2917.

[18] Sayyaf Dezfuli B, Castaldelli G and Giari L. Histopathological and ultrastructural assessment of two mugilid species infected with myxozoans and helminths. J Fish Dis 2018; 41: 299-307.

[19] Massironi S, Ulivieri FM, Marchelli D and Basilisco G. Reduced bone mineral density in chronic intestinal idiopathic pseudo-obstruction. Am J Gastroenterol 2008; 103: 1579-1581.

[20] Arumalla N, Zafar S, Rosario H, Abdi B, Taki Z, Denton C, Abraham D, Stratton R, Mazumder N, Etomi O, Mohamed A and Xing F. OP0048 IL-31 is an inflammatory pro-fibrotic factor elevated in a subset of scleroderma patients with severe pruritus. Ann Rheum Dis 2016; 75 Suppl 2: 72.3-72.

[21] Ribeiro AB, de Barcellos-Filho PC, Franci CR, Menescal-de-Oliveira L and Saia RS. Pro-inflammatory cytokines, IL-1β and TNF-α, produce persistent compromise in tonic immobility defensive behaviour in endotoxemia guinea-pigs. Acta Physiol (Oxf) 2016; 218: 123-135.

[22] Filip AA, Grenda A, Popek S, Koczkodaj D, Michalak-Wojnowska M, Budzyński M, Wąsik-Szczepanek E, Zmorzyński S, Karczmarczyk A and Giannopoulos K. Expression of circulating miRNAs associated with lymphocyte differentiation and activation in CLL-another piece in the puzzle. Ann Hematol 2017; 96: 33-50.

[23] Zamora C, Cantó E, Nieto JC, Bardina J, Diaz-Torné C, Moya P, Magallares B, Ortiz MA, Julià G, Juarez C, Llobet JM and Vidal S. Binding of platelets to lymphocytes: a potential anti-inflammatory therapy in rheumatoid arthritis. J Immunol 2017; 198: 3099-3108.

[24] Weiss K, Simon A, Graf N, Schöpe J, Oertel J and Linsler S. Clinical practice audit concerning antimicrobial prophylaxis in paediatric neurosurgery: results from a German paediatric oncology unit. Childs Nerv Syst 2017; 33: 159-169.

[25] Eroglu A and Sari A. O-2 evaluation of local injection of platelet rich plasma and corticosteroids in the treatment of lateral epicondylitis: a retrospective study. Br J Sports Med 2016; 50 Suppl 1: A1.2-A2.

[26] Tange M, Yoshida M, Nakai Y and Uchida T. The role of an impurity in ceftriaxone sodium preparation for injection in determining compatibility with calcium-containing solutions. Chem Pharm Bull (Tokyo) 2016; 64: 207-214.