The effect of artificial liver DPMAES combined with Bu Gan Sheng Tang on the survival rate and mitochondrial function in chronic and acute liver failure

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Introduction. To explore the effects of artificial liver dual plasma molecular adsorption exchange system (DPMAES) combined with Bu Gan Sheng Tang on survival rate and mitochondrial function in patients with chronic acute liver failure (ACLF). Method: 68 patients with chronic acute liver failure from January 2022 to October 2023 were selected as the study subjects, and were divided into two groups using envelope method, with 34 cases in each group. The control group was treated with artificial liver DPMAES, while the observation group was treated with Bu Gan Sheng Tang in combination. Both groups had the same basic internal medicine treatment, completed 4 weeks of treatment, and underwent 3 months of outpatient follow-up. The liver function, coagulation function, mitochondrial function, inflammatory factors, survival rate, and adverse events were compared between the two groups. Result:After 8 weeks of intervention, ALT, AST and TBil in observation group were lower than those in control group (P<0.05). Both groups were associated with different degrees of coagulation dysfunction after treatment. After 8 weeks of intervention, INR and PT in observation group were higher than those in control group (P<0.05). FIB and D-D were lower than control group (P<0.05); After 8 weeks of intervention, mitochondrial function was improved in both groups, and the loss rate of mitochondrial membrane potential, IL-6 and TNF-α in observation group were lower than those in control group (P<0.05). There were no statistical differences in PCT and CRP levels between the two groups (P>0.05). There was no statistical difference in the incidence of adverse reactions between the two groups (P>0.05). The

3-month survival rate of observation group was higher than that of control group (P<0.05).Conclusion: The combination of artificial liver DPMAES and Bu Gan Sheng Tang has a significant effect on patients with chronic and acute liver failure. It can improve liver function and mitochondrial function, have a small impact on inflammatory factors in the body, and have high treatment safety. It can improve patient survival rate and is worthy of promotion and application.

[keyword]Artificial liver dual plasma molecular adsorption system; Bugan Shengsheng Tang; Chronic acute liver failure; Survival rate; Mitochondrial function; Inflammatory factors; renal function

Liver failure is due to many reasons to cause serious liver damage, resulting in the liver synthesis, detoxification and excretion dysfunction, such as some patients in decompensated state, the clinical manifestation of jaundice, blood coagulation dysfunction and hepatic encephalopathy, become our country residents of the important causes of death [1]. Li Kai et al. showed [2] that acute-on-chronic liver failure progresses rapidly and has a high mortality rate, so how to take appropriate intervention measures has become a research hotspot. Artificial liver molecular adsorption double plasma replacement system (DPMAES) is the use of plasma, plasma filtration apparatus for continuous separation and filtration into the specificity of plasma bilirubin adsorption BS330 and macroporous resin blood perfusion machine, can combined with proteins of bilirubin adsorption and inflammation medium, etc., at the same time plasma exchange, create the environment for the regeneration of liver cells [3]. As a common prescription in traditional Chinese medicine, Bugan Shengjiang Decoction is composed of silkworm, cicada, red peony root, rhubarb, wormwood, cinnamon twig, dried ginger, Schisandra and other drugs, which can play a role in soothing liver, regulating qi, reducing dampness and yellow [4]. However, there are few clinical studies on the effects of the above two intervention methods on mitochondrial function in patients with acute-on-chronic liver failure [5]. This study mainly discusses the application effect of artificial liver DPMAES combined with Bugan Shengjiang decoction in patients with acute-on-chronic liver failure, as

reported below.

1 MATERIALS AND METHODS

1.1 General Information

A total of 68 patients with acute-on-chronic liver failure from January 2022 to October 2023 were selected and divided into two groups by envelope method, with 34 cases in each group. There were 34 patients in the control group, 17 males and 17 females, aged (39-76) years, with an average age of (58.32±4.71) years. There were 15 cases of hepatitis B, 16 cases of hepatitis B combined with alcoholic hepatitis, and 3 cases of drug-induced hepatitis. There were 30 cases in the early stage of ACLF and 4 cases in the middle stage. There were 34 cases in the observation group, including 19 males and 15 females, aged (41-74) years, with an average age of (58.51±4.75) years. There were 23 cases of hepatitis B, 7 cases of hepatitis B combined with alcoholic liver disease, and 4 cases of drug-induced hepatitis. There were 28 cases in the early stage of ACLF and 6 cases in the middle stage. The study was approved by the hospital ethics committee, and the patients signed the consent form. There was no significant difference in general data between the two groups (P>0.05).

1.2 Inclusion and exclusion criteria

Inclusion criteria: (1) All cases were acute-on-chronic liver failure admitted to our hospital [6]; (2) The clinical manifestations were extreme fatigue, accompanied by gastrointestinal symptoms, and rapidly deepening jaundice; Stage: early stage, early stage and middle stage; (3) There were no contraindications to artificial liver DPMAES and Bugan Shengjiang decoction. Exclusion manifestations: (1) patients with other viral hepatitis and autoimmune liver disease; (2) hypersensitivity to blood products or drugs used in the treatment; (3) patients with malignant tumors during pregnancy or lactation or diagnosed.

1.3 Methods

The control group was treated with artificial liver DPMAES. Plasma separator, models: Bellco microplas MPS 05, bought in Italy, co., LTD., the one-time use plasma bilirubin adsorption BS330 and one-time blood perfusion, models: HA330 - type II,

purchase Yu Jian sails biological technology group co., LTD.; The blood flow rate was 100-160mL/min, the treatment time was 2-3h, and the amount of plasma adsorbed was about 5L. The hemoperfusion apparatus and bilirubin adsorption column were removed, plasma separation was continued, and 2500mL plasma was added to the patient. The treatment time was set for 1.5 hours each time. The interval and frequency of artificial liver treatment were determined according to the patient's tolerance and condition recovery.

The observation group was treated with Bugan Shengjiang decoction. The prescription consisted of: silkworm (30g), cicatonia cicatricae (10g), red peony root (60g), rhubarb (10g), Chenchen (30g), cinnamomum twig (9g), dried ginger (9g), Schisandrae chinensis (9g). The above drugs were given once a day, 200mL each time. For those with wet weight, Tianjihuang 15g and Poria 20g were added; For those with severe blood stasis, add 80g red peony root, 15g wine rhubarb; For those with spleen deficiency, American ginseng 10g Atractylodes 15g was added; The Yang deficiency group was decocted with cinnamomum spp. schisandrin and aconite (10g) for 30 minutes first, fried licorice (10g) and ginseng (10g) for 30 minutes first. Both groups completed 12 weeks treatment.

1.4 Indicators of observation

(1) Liver function; The levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil) and albumin (Alb) were measured by automatic biochemical analyzer before intervention and 12 weeks after intervention in the two groups [7]. (2) mitochondrial function and inflammatory factors. Flow cytometry was used to detect the loss rate of mitochondrial membrane potential in the two groups before intervention and 12 weeks after intervention. Five mL peripheral fasting blood was collected at different time points and centrifuged for 20 minutes at 3000 RPM. After serum separation, the 6-well plate was washed with PBS for 3 consecutive times, and JC-1 (5μg/mL) was added to the 6-well plate and the reaction was performed in the dark at room temperature for 30 minutes. A streaming sorter determination of mitochondrial membrane potential rate, records the red light (at 530

m, excitation light emission 600 nm red light detection) and green (with exciting light 485 nm, 535 nm light is emitted green light) fluorescence intensity, use the formula to calculate the mitochondrial membrane potential change; Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were detected by enzyme-linked immunosorbent assay [8]. The level of procalcitonin (PCT) was measured by electrochemiluminescence immunoassay analyzer. The level of C-reactive protein (CRP) was determined by immunoturbidimetry [9]. (3) Coagulation function. D-dimer (D-D), plasma fibrinogen (FIB), international normalized ratio (INR) and prothrombin time (PT) were measured by coagulation function analyzer before intervention and 12 weeks after intervention in the two groups. (4) Safety and survival rate. The incidences of headache, nausea and vomiting, acute lactic acidosis and bleeding were recorded. The two groups were followed up for 3 months after treatment, and the 2-month and 3-month survival rates were calculated.

1.5 Statistical Analysis

SPSS26.0 software was used to process the data. The enumeration data were analyzed by $\chi 2$ test, expressed by n (%), and the measurement data were analyzed by t test, expressed by（$\bar{x} \pm s$）, P<0.05 was statistically significant.

2 RESULTS

2.1 Comparison of liver function between the two groups

There was no statistically significant difference in Alb level between the two groups after 8 weeks of intervention (P>0.05). The two groups after intervention in 8 weeks liver function was improved; The levels of ALT, AST and TBil in the observation group were lower than those in the control group (P<0.05), as shown in Table 1.

Table 1 Comparison of liver function between the two groups（$\bar{x} \pm s$）

Groups	Point of time	Alb（g/L）	ALT（U/L）	AST（U/L）	TBil（μmmol/L）
Observation group (n=34)	Before intervention	32.19±3.41	434.79±46.63	423.26±45.49	275.63±32.51
	After 8 weeks of intervention	32.11±3.38#*	75.16±7.31#*	92.42±8.14#*	70.72±8.39#*
Control group (n=34)	Before intervention	32.21±3.43	437.81±46.68	424.31±45.62	276.14±32.26
	After 8 weeks of intervention	32.16±3.40	162.15±32.51	122.45±32.48	89.81±15.84

Compared with the control group, #P<0.05; Compared with before intervention, * P < 0.05

2.2 Coagulation function was compared between the two groups

Both groups were accompanied by different degrees of coagulation dysfunction after treatment. The INR and PT of the observation group were higher than those of the control group after 8 weeks of intervention (P<0.05). FIB and D-D were lower than those in the control group (P<0.05), as shown in Table 2.

Table 2 Comparison of coagulation function between the two groups（ $\bar{x} \pm s$ ）

Groups	Point of time	INR	PT（s）	FIB（g/L）	D-D（μg/L）
Observation group (n=34)	Before intervention	1.15±0.25	12.94±1.69	2.41±0.59	145.92±12.41
	After 8 weeks of intervention	0.94±0.31#*	12.53±1.43#*	3.45±0.74#*	302.59±23.25#*
Control group (n=34)	Before intervention	1.17±0.27	12.96±1.71	2.43±0.61	146.11±12.43
	After 8 weeks of intervention	0.77±0.16*	10.25±1.26*	3.87±0.88*	345.24±29.48*

Compared with the control group, #P<0.05; Compared with before intervention, * P < 0.05

2.3 The comparison of two groups of mitochondrial function and inflammatory factors

After 8 weeks of intervention, mitochondrial function was improved in the two

groups, and there was no significant change in inflammatory factors. The mitochondrial membrane potential loss rate, IL-6 and TNF-α in the observation group were lower than those in the control group (P<0.05). There was no significant difference in PCT and CRP levels between the two groups (P>0.05), as shown in Table 3.

Table 3 Comparison of mitochondrial function and inflammatory factors between the two groups

（$\bar{x} \pm s$）

Grouos	Point of time	Mitochondrial membrane potential loss rate (%)	IL-6 （pg/mL）	TNF-α （ng/mL）	PCT（μg/L）	CRP（mg/L）
Observation group (n=34)	Before intervention	41.74±4.31	35.73±4.39	53.25±3.73	1.98±0.32	16.43±3.51
	After 8 weeks of intervention	21.67±2.69#*	6.49±1.12#*	22.16±2.17#*	1.96±0.30	1.14±1.63
Control group (n=34)	Before intervention	41.76±4.34	35.75±4.41	53.31±3.75	2.00±0.35	16.45±3.54
	After 8 weeks of intervention	29.73±3.41*	14.26±2.69*	42.52±3.12*	1.95±0.29	16.62±2.17

Compared with the control group, #P<0.05; Compared with before intervention, * P < 0.05

2.4 The safety and survival rates were compared between the two groups

There was no significant difference in 6-month survival rate between the two groups (P>0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). The 12-month survival rate of the observation group was higher than that of the control group (P<0.05), as shown in Table 4.

Table 4 Comparison of safety and survival rates between the two groups [n（%）]

Grouos	Number of cases	Safety				Survival rate	
		Headache	Nausea and vomiting	Acute lactic acidosis	Incidence rate	6 months	12 months
Observation group	34	1（2.94）	2（5.88）	1（2.94）	4（11.76）	33（97.06）	29（85.29）
Control group	34	1（2.94）	1（2.94）	0（0.00）	2（5.88）	32（94.12）	23（67.65）
x^2	/	/	/	/	0.434	1.321	5.634
P	/	/	/	/	0.778	0.547	0.043

3 DISCUSSION

Hepatic failure is mainly caused by hepatitis b virus in China, on the basis of long hepatitis b hepatitis or liver cirrhosis, inside short time clinical syndrome, acute liver function to compensate some patients with extrahepatic organ involvement, with the onset of shortness, poor prognostic features, become the important cause of death in patients with liver disease (10 to 11). In this study, ALT, AST and TBil in the observation group were lower than those in the control group after 8 weeks of intervention (P<0.05). It can be seen from the results that DPMAES combined with Bugan Shengjiang decoction can improve the liver function of patients and help the

recovery of patients. Analysis of reasons: artificial liver DPMAES uses neutral macroporous adsorption resin and centrifugal exchange resin two adsorption columns to continuously complete the adsorption of plasma, and return it to the patient's body, and carry out a large number of plasma exchange at the same time. This treatment method can offer effective for slow and acute liver failure patients, continuous removal of plasma of macromolecular protein and endogenous toxic substances, help patients to remove the bilirubin level in the body [12]. Bugan Shengjiang decoction, as a commonly used decoction of traditional Chinese medicine, is mainly composed of silkworm, cicada decidua, red peony root, rhubarb, wormwood, cinnamon twig, dried ginger, Schisandra, etc. In the formulas, batryticated silkworm can play XiFeng antispasmodic and analgesic effect; functions of Cicatonia cicatonia can evacuate wind and heat, relieve spasmolysis and benefit pharynx. Radix paeoniae root has the functions of clearing heat and cooling blood, dispersing blood stasis and relieving pain. The rhubarb can play in attack product, cooling blood detoxification; Yinchen has the functions of relieving jaundice, clearing heat and dampness. Cinnamomum twig has the functions of warming meridians and diaphoresis and dissolving muscles. Dried ginger can play the role of rejuvenating the Yang, promoting the vein and warming the cold. Schisandra chinensis has beneficial effects on qi, body fluid and astringency [13]; All kinds of herbs play together, which has the effect of reducing dampness and yellow, lifting and lowering qi [14]. In this study, there was no significant difference in 6-month survival rate between the two groups ($P>0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). The 12-month survival rate of the observation group was higher than that of the control group ($P<0.05$). According to the results, the artificial liver DPMAES combined with Bugan Shengjiang decoction in the treatment of patients with acute-on-chronic liver failure is safe and can improve the survival rate of patients. Hsu Y C et al. [15] showed that the occurrence of acute-on-chronic liver failure is often accompanied by mitochondrial dysfunction and a cascade of inflammatory factors in the body, which can aggravate the development of the disease and increase

the difficulty of clinical treatment. In this study, the mitochondrial function of the two groups improved after 8 weeks of intervention, and there was no significant change in inflammatory factors. The mitochondrial membrane potential loss rate, IL-6 and TNF-α in the observation group were lower than those in the control group ($P<0.05$). There was no significant difference in PCT and CRP levels between the two groups ($P>0.05$). According to the results, artificial liver DPMAES combined with Bugan Shengjiang decoction can improve mitochondrial function in patients with acute-on-chronic liver failure, exert the advantages of different intervention methods, have little effect on inflammatory factors, and most patients can benefit from it.

Artificial liver DPMAES combined with Bugan Shengjiang decoction causes less trauma and mild inflammatory reaction, but has a greater impact on coagulation function. PT can reflect the status of exogenous coagulation pathway. FIB can reflect the fibrinolytic function of patients, and the above indexes can be used to measure the coagulation function of patients. In this study, both groups were accompanied by different degrees of coagulation dysfunction after treatment. The INR and PT of the observation group were higher than those of the control group after 8 weeks of intervention ($P<0.05$). FIB and D-D were lower than those in the control group ($P<0.05$). It can be seen from the results that DPMAES combined with Bugan Shengjiang decoction has little effect on coagulation function in patients with acute-on-chronic liver failure, which is helpful to improve the prognosis of patients.

Above all, artificial liver DPMAES joint tonifying liver lifting decoction for slow significantly in patients with acute liver failure effect, can improve patients with liver function and improve mitochondrial function, less effect on the body inflammation factors, and treatment of high security, can improve survival, is worthy of popularization and application.

REFERENCES

【1】 Guo Xiju, Wei Yunhua, Guo Weibo, et al. Study on the efficacy of three artificial liver therapies for acute-on-chronic liver failure and their effects on patients' inflammatory markers. Shaanxi Medical Journal, 2019, 48(9): 1167-1170.

【2】 Li Kai. Analysis of the effects of plasma exchange combined with double plasma molecular adsorption system on inflammatory levels and coagulation indicators in patients with acute-on-chronic liver failure. Modern Diagnosis and Treatment, 2021, 32(11): 1683-1685.

【3】 Beverley K, Reid W, Thomas F, et al. Health-Related Quality of Life: A Rapid Predictor of Hospitalization in Patients With Cirrhosis. The American Journal of Gastroenterology, 2021, 115(4): 575-583.

【4】 Ding Xiaojuan, Zou Xiaohua, Zhang Hongmei. Clinical observation of Ganlu Xiaodu Dan combined with Tuihuang Tang in the treatment of acute-on-chronic liver failure with damp-heat syndrome. Journal of Hunan University of Chinese Medicine, 2023, 43(6): 1049-1053.

【5】 Li Binhua, Xie Qing, Yan Xuehua. Research progress on the rules of traditional Chinese medicine in the treatment of hepatitis B virus-related liver failure. Shaanxi Journal of Traditional Chinese Medicine, 2022, 43(4): 538-540.

【6】 Zhao Wenxi, Li Li, Zhang Xiaoyou, et al. Efficacy of peritoneal dialysis in the treatment of liver failure and its effect on patients' inflammatory cytokines. Chinese Journal of Blood Purification, 2023, 22(6): 432-437.

【7】 Tandon P, Tomczak CR, Kruger C, et al. Impaired muscle oxygen extraction kinetics in cirrhosis: Muscle is a major contributor to impaired whole-body exercise capacity. Liver Transplantation: Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society, 2021, 28(2): 321-324.

【8】 Shu Faming, Huang Ying, Mao Dewen. Exploration and practice of reconstructing immune balance in HBV-related liver failure with the detoxification, blood stasis removal, and warming Yang method. Journal of Clinical Hepatology, 2023, 39(11): 2668-2673.

【9】 Li Chuyi, Wang Junke, Li Bin, et al. Evaluation of the effect of plasma exchange as an adjuvant therapy for acute-on-chronic liver failure. Journal of Hainan Medical University, 2022, 28(16): 1228-1231.

【10】 Zhang Jie, Zhao Chengyan, Zheng Rongjiong, et al. Comparison of the efficacy and safety of different anticoagulants in the treatment of liver failure with double bilirubin adsorption combined with plasma exchange. Journal of Xinjiang Medical University, 2022, 45(2): 150-154.

【11】 Beyer D, Hoff J, Sommerfeld O, et al. The liver in sepsis: molecular mechanism of liver failure and their potential for clinical translation. Molecular Medicine (Cambridge, Mass.), 2022, 28(1): 84.

【12】 Fu Shijing, Zheng Huicai. Clinical observation of the efficacy of acetylcysteine combined with plasma in the treatment of elderly liver failure. Journal of Hunan Normal University (Medical Edition), 2022, 19(4): 146-148.

【13】 Zhu Yuting, Zhang Liyuan, Du Yongguo, et al. Comparative study of the clinical efficacy of plasma exchange and double plasma molecular adsorption system in the treatment of acute liver failure and their effects on blood cell counts. Journal of Clinical and Experimental Medicine, 2022, 21(18): 1934-1937.

【14】 Zhou Lin, Zhou Xiaoling, Feng Lijuan. Clinical study of Jiawei Yinchen Shufu Tang combined with double plasma molecular adsorption system and plasma exchange in the treatment of acute-on-chronic liver failure. Shaanxi Journal of Traditional Chinese Medicine, 2023, 44(2): 170-173.

【15】 Hsu YC, Tseng CH, Su TH, et al. Pooling data to assess risks and benefits of discontinuing nucleos(t)ide analogs in patients with chronic hepatitis B: challenges and opportunities. Gut, 2022, 71(6): 1238-1240.

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