



Effects of adjuvant therapy with anluohuaxian capsule on serum inflammatory factors, hepatic fibrosis indexes and immune function in patients with hepatitis B cirrhosis

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ABSTRACT

Objective: To investigate the effect of adjuvant therapy with anluohuaxian capsule on the treatment of hepatitis B cirrhosis, and its influence on serum inflammatory factors, liver fibrosis indexes and immune function. **Methods:** A total of 112 cases of hepatitis B cirrhosis patients were divided into the control group ($n=55$) and observation group ($n=57$) according to the random data table, patients in the two groups were given routine treatment, on this basis, the control group received the treatment of Adefovir Dipivoxil Tablets, and the observation group was treated with Adefovir Dipivoxil Tablets combined with Anluo Huaxian pill treatment, two groups were treated for 48 weeks. The levels of serum inflammatory factors, liver fibrosis indexes and immune function indexes of the two groups were compared before and after treatment. **Results:** Before treatment, There was no significant difference between the two groups of TNF- α , IL-6, hs-CRP, IVC, HA, PIIIP, LN, CD3⁺, CD4⁺, CD8⁺ and CD4⁺/CD8⁺ levels. After treatment, TNF- α , IL-6, hs-CRP, IVC, HA, PIIIP, LN, CD3⁺, CD4⁺, CD8⁺ and CD4⁺/CD8⁺ levels in the observation group and control group were significantly lower than those before treatment in the same group, and levels in the observation group after treatment were significantly lower than the control group; Compared with the group before treatment, the levels of CD3⁺, CD4⁺ and CD4⁺/CD8⁺ of two groups after treatment were significantly increased, and the observation group was significantly higher than the control group. **Conclusion:** Adjuvant therapy with anluohuaxian capsule on the treatment of hepatitis B cirrhosis, can effectively reduce the inflammatory stress reaction, reduce the level of serum liver fibrosis index and improve the immune function, and has important clinical value.

1. Introduction

Hepatitis B cirrhosis was a disseminated solid lesion of liver cell that resulted from one or multiple factors acted on liver repeatedly. Its clinical manifestation was liver function damage and portal hypertension. Patients in decompensated period always were with severe complication, such as hemorrhage of digestive tract, hepatic encephalopathy, spontaneous peritonitis, functional liver failure and primary liver cancer, which threatened health of patients seriously[1,2]. Adefovir Dipivoxil Tablets was new type nucleoside anti-hepatitis B virus (HBV) drug that could improve liver function and delay development of disease[3]. Anluohuaxian capsule was a

anti-fibrosis drug, related research pointed out that combination of Adefovir Dipivoxil Tablets and Anluohuaxian capsule was better and was able to prevent the process of liver fibrosis[4,5]. This research was aimed to explore effect of combined therapy on biochemical indexes of hepatitis B cirrhosis patients. Now reported as following:

2. Subjects and material

2.1. General data

A total of 112 cases of hepatitis B cirrhosis patients who were admitted in our hospital from March 2014 to May 2016 were selected as research subjects. All of patients were conformed to related diagnostic criteria in 'Diagnostic standard of Chinese

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hepatitis B cirrhosis prevention and cure[6]; HBV-DNA>2 000 IU / mL. Exclusion criteria: (1) patients were not non-HBV infection or other hepatitis; (2) self-immunity and drug-induced liver fibrosis; (3) with severe hepatic and renal dysfunction, hemopoietics system disease and primary liver cancer; (4) accepted anti-viral drug and anti-fibrosis drug in recent; (5) patients with mental disease and cannot coordinate for treatment; (6) as for research drug, patients were contraindication; (7) patients with bad compliance and cannot complete treatment according to course of treatment; (8) clinical data was incomplete after admission. All of patients were divided into the control group (n=55) and observation group (n=57) according to the random data table. In control group, 31 males, 24 females, aged from 36-74 years old; average course of disease was (2.51±0.47) years; In observation group, 34 males, 23 females, aged from 37-75 years old; average course of disease was (2.49±0.52) year. There was no difference in gender, age and average course of disease ($P>0.05$), it was comparable. Research content and process were conformed to standard of ethic committee and was approved. All patients and their family were informed and signed informed consent.

2.2. Treatment method

Patients of both groups were given conventional decrease enzyme, liver protection and cholagogue treatment. On this basis, control group was given Adefovir Dipivoxil Tablets (Daiding, Tianjing pharmaceutical institute Co, Ltd, approval number: H20050803, product standard 10 mg 7 s), took orally 1 time/d, 10 mg/time, before and after meal. Observation group was given Anluohuaxian capsule (Senlong, Senlong pharmaceutical Co. Ltd, approval number: Z20010098, product standard 6 g 10 bag), 2 times/d, 6 g/ time, treatment for 48 weeks in both groups.

2.3. Observation indexes

Extracted 3-5 mL of fasting periphery venous blood of patients before treatment and after 48 weeks of treatment, divided two parts for detection, one part, centrifuge for serum, stocked at -70 °C freezer for using. Observation indexes including inflammatory factor [tumor necrosis factor- α (TNF- α), hypersensitive C-reaction protein (hs-CRP) and interleukin-6 (IL-6)]; liver fibrosis indexes [laminin (LN), hyaluronic acid (HA), III precollagen peptide (PIIIP) and IV collagen (IV C)], ELISA was applied to detect TNF- α , IL-6, IVC, HA, PIIIP and LN, selected correspond kits that purchased from Shanghai Meilian biotechnology Co., Ltd, hs-CRP level was

detected by latex-enhanced immunoturbidimetric assay (Kits was provided by Shanghai Xinyu biotechnology Co., Ltd.). The other part was detected for immune function (CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺), equipment was American Beckman Coulter flow cytometry, operation was strict with kits introduction of equipment and kits.

2.4. Statistical analysis

Statistical Software SPSS 17.0 was used for all row data processing and analyzing, inflammatory factors, liver fibrosis indexes and immune function indexes level was conformed to normal distribution and represented by Mean \pm SD, t-test was applied to comparison of intra-group before and after treatment and inter-block, $P<0.05$ indicated the difference was statistical significant.

3. Results

3.1. Comparison of inflammatory factor of both groups

Before treatment, TNF- α , IL-6 and hs-CRP level in observation group and control group were close, the difference was not statistical significant ($P>0.05$). After treatment, TNF- α , IL-6 and hs-CRP level in control group were respectively (54.86±11.41) ng/L, (56.01±10.39) ng/L and (9.19±1.84) mg/L, which were lower than before treatment intragroup, the difference was significant statistical ($P<0.05$); TNF- α , IL-6 and hs-CRP level in observation group were respectively (39.97±9.74) ng/L, (35.85±12.19) ng/L and (5.72±1.63) mg/L, compared with before treatment of observation group, these levels were decreased significantly ($P<0.05$), moreover, after treatment TNF- α , IL-6 and hs-CRP level in observation group was obviously lower than control group ($P<0.05$). As shown in Table 1.

3.2 Comparison of serum liver fibrosis indexes of both groups

Before treatment, IVC, HA, PIIIP and LN level of both groups were closed ($P>0.05$). IVC, HA, PIIIP and LN level after treatment were (92.31±10.34) ng/mL, (207.28±53.42) ng/mL, (186.89±51.71) ng/mL and (116.29±32.94) ng/mL, these in observation group were (69.99±8.67) ng/mL, (151.24±29.68) ng/mL, (140.46±38.26) ng/mL and (96.25±23.92) ng/mL, which was lower than before treatment intragroup ($P<0.05$); moreover, after treatment IVC, HA, PIIIP and LN level in observation group was significantly lower than control group ($P<0.05$). As shown in Table 2.

Table 1.

Comparison of inflammatory factor of both groups.

Group	n	Treatment time	TNF- α (ng/L)	IL-6 (ng/L)	hs-CRP (mg/L)
Control group	55	Before treatment	86.35±14.01	87.53±13.66	12.43±2.56
		After treatment	54.86±11.41 [*]	56.01±10.39 [*]	9.19±1.84 [*]
Observation group	57	Before treatment	86.09±16.06	88.29±14.01	12.54±2.62
		After treatment	39.97±9.74 ^{*#}	35.85±12.19 ^{*#}	5.72±1.63 ^{*#}

Note: compared with before treatment intragroup, ^{*} $P<0.05$; Compared with control group after treatment, [#] $P<0.05$.

Table 2.

Comparison of liver fibrosis indexes of both groups before and after treatment.

Group	n	Treatment	IVC (ng/mL)	HA (ng/mL)	P[III]P (ng/mL)	LN (ng/mL)
Control group	55	Before treatment	141.93±17.25	326.83±81.45	329.91±71.22	158.32±43.77
		After treatment	92.31±10.34 [*]	207.28±53.42 [*]	186.89±51.71 [*]	116.29±32.94 [*]
Observation group	57	Before treatment	141.43±15.94	327.31±72.38	324.84±67.88	157.25±41.95
		After treatment	69.99±8.67 ^{*#}	151.24±29.68 ^{*#}	140.46±38.26 ^{*#}	96.25±23.92 ^{*#}

Note: compared with before treatment intragroup, ^{*}P<0.05; Compared with control group after treatment, [#]P<0.05.

Table 3.

Comparison of immune function of both groups.

Group	n	Treatment time	CD3 ⁺ (%)	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺
Control group	55	Before treatment	58.52±5.64	31.53±4.34	33.08±5.69	1.09±0.18
		After treatment	60.67±5.67 [*]	34.55±4.42 [*]	30.54±4.88 [*]	1.19±0.27 [*]
Observation group	57	Before treatment	58.24±5.62	31.68±4.05	33.17±4.92	1.09±0.26
		After treatment	65.74±4.92 ^{*#}	38.77±3.65 ^{*#}	25.29±3.28 ^{*#}	1.45±0.36 ^{*#}

Note: compared with before treatment intragroup, ^{*}P<0.05; Compared with control group after treatment, [#]P<0.05.

3.3 Comparison of immune function of both groups

T lymphocyte level in observation group and control group was not difference ($P>0.05$). After treatment, CD8⁺ level in observation group and control group were (25.29±3.28)% and (30.54±4.88)%, compared with intragroup before treatment, its level was significantly decreased ($P<0.05$), after treatment, the level in observation group was obviously lower than control group; CD3⁺, CD4⁺ and CD4⁺/CD8⁺ level in observation group were (65.74±4.92)%, (38.77±3.65)% and (1.45±0.36), which was dramatically higher than intra-group before treatment ($P<0.05$), moreover, significantly higher than control group, the difference was significant ($P<0.05$). As shown in Table 3.

4. Discussion

Hepatitis B cirrhosis in decompensate period was terminal stage of liver disease, there was more complications in this stage and the condition was extremely repeated, bad prognosis and higher mortality[7]. In our country, this disease was caused by HBV infection[8]. Related researches pointed out that HBV continuous replication and liver inflammatory factor infiltration were determinant factor of genesis and development of liver cirrhosis[9]. Therefore, inhibited HBV replication, reduced liver inflammatory stress reaction and improved liver function was key of treatment. At present, recognized antiviral drug mainly included interferon and nucleoside. Interferon was broad-spectrum antiviral and immunomodulator drug, due to adverse effect of drug was many, therefore, its indication and usage was limited and tolerance was bad, especially elderly patients was not suitable[10]. Therefore nucleoside antiviral drug was optimal choice of treatment for hepatitis B cirrhosis, including Adefovir Dipivoxil Tablets, lamivudine and entecavir. Research showed that Adefovir Dipivoxil Tablets had strong antiviral effect as for virus that was tolerant with lamivudine, low drug resistance rate, moreover compared with the other two

drugs, its price was low and suitable for clinical application[11]. In recent, pure western medicine could not obtain perfect effect, combined with traditional Chinese medicine could increase cure rate and promote liver function recovery, relieve process of liver fibrosis. Its efficacy was better than pure western medicine[12,13].

Chinese traditional medicine thought that hepatitis B cirrhosis was syndrome of blood stasis, stagnation of liver qi and spleen deficiency and liver dysfunction as main pathogenesis, treatment should be tonifying spleen benefiting stomach, helping liver pathogenesis[14]. Anluohuaxian capsule mainly composed by buffalo horn powder, radix curcumae, rehmannia, pseudo-ginseng, leech, bezoar, white atractylodes rhizome and stiff silkworm, the complete prescription could tonify spleen, nourish liver, promote blood circulation and remove blood stasis, regulate tissue repair and regeneration, modulate immune function, eliminate sedimentation of liver, improve blood microcirculation[15,16]. In addition, research showed that Anluohuaxian capsule could delayed liver fibrosis and improve liver function through inhibiting collagenous fibroplasia in tissue, promoting reabsorption[17]. This research was aimed to determine efficacy of adjuvant therapy with anluohuaxian capsule in patients with hepatitis B cirrhosis through analyzing serum inflammatory factor, liver fibrosis and immune function.

A lot of researches had demonstrated that inflammatory factors that mediated by inflammatory cytokines played critical roles in genesis and development of hepatitis B cirrhosis. TNF- α , IL-6 were pro-inflammatory factors that had coordinated effect, which could promote hepatitis development and genesis of liver fibrosis, its level was related to liver cell damage and liver fibrosis at some degree[18,19]. hs-CRP was a reaction protein in acute stage generated by liver cell, research pointed that its high expression of hs-CRP in cirrhosis patients, its level was positively significant relevant to liver inflammation degree and damage degree[20]. TNF- α , IL-6 and hs-CRP were important indexes that evaluated severe degree of cirrhosis, efficacy of treatment and prognosis[21]. This research found that both therapies could relieve inflammatory stress reaction of patients, moreover effect of combined Anluohuaxian capsule was better. This revealed that Adefovir Dipivoxil Tablets could inhibit

HBV replication, reduce genesis of inflammatory reaction, combined with Anluohuaxian capsule on this basis could further decrease inflammatory reaction, however, the detailed mechanism was still explored.

Liver fibrosis was certain stage that all liver diseases developed to cirrhosis. Serum liver fibrosis were common indexes that evaluated degree of cirrhosis. Researches had demonstrated that serum liver fibrosis indexes abnormally increased, abnormal coagulation after cirrhosis[22]. This research results found that after long time treatment serum liver fibrosis indexes in both groups significantly decreased, level decreased after Adefovir Dipivoxil Tablets treatment mainly due to inhibiting collagenous fiber composition and activation of sternzellen, however after combination of Anluohuaxian capsule serum liver fibrosis indexes further decreased, the reason might be related to coordinated anti-fibrosis effect between Adefovir Dipivoxil Tablets and Anluohuaxian capsule.

Liver was important participated organ of immune system, after cirrhosis cellular immune function was damaged, added portal hypertension and hypersplenism which could reduce immune function[23]. This research found that Adefovir Dipivoxil Tablets combined with Anluohuaxian capsule could effectively enhance CD3⁺, CD4⁺ and CD4⁺/CD8⁺ level, reduce CD8⁺ level, moreover regulated effect of combined treatment for immune function was better. This results were conformed to the report Adefovir Dipivoxil Tablets could improve immune function of chronic hepatitis B cirrhosis of Wang Rugang et al[24], further demonstrated that regulation effect on immune function of Adefovir Dipivoxil Tablets, combined with Anluohuaxian capsule on this basis, due to coordinated effect on immune function, further improve immune function of patients.

In conclusion, Adefovir Dipivoxil Tablets single treatment and combined with Anluohuaxian capsule for hepatitis B cirrhosis could effectively reduce serum inflammatory factors and liver fibrosis indexes, improve immune function of patients, moreover, the efficacy of combination treatment was better, with positive clinical significance.

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