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• BRIEF REPORTS •

Effects of *zhaoyangwan* on chronic hepatitis B and posthepatic cirrhosis

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Abstract

AIM: To study the therapeutic effects of *zhaoyangwan* (ZYW) on chronic hepatitis B and hepatic cirrhosis and the anti-virus, anti-fibrosis and immunoregulatory mechanisms of ZYW.

METHODS: Fifty cases of chronic hepatitis B and posthepatic cirrhosis with positive serum HBsAg, HBeAg, anti-Hbc and HBV-DNA were divided randomly and single-blindly into the treatment group (treated with ZYW) and the control group (treated with interferon). After 3 month treatment, the effects of the treatment group and the control group were evaluated.

RESULTS: The serum ALT normalization was 83.3%(30/36) in the treatment group and 85.7%(12/14) in the control group, with no significant difference (χ^2=0.043, P>0.05). After the course, the negative expression rates of the serum HBV-DNA and HBeAg were 44.4%(16/36) and 50%(18/36) in the treatment group, and 50%(7/14) and 50%(7/14) in the control group, respectively, with no significant difference (χ^2=0.125, χ^2=0.00, both P>0.05). Negative HBsAg and positive HBsAb appeared in 4 cases of the treatment group and 1 case of the control group. Serum anti-HBc turned negative in 6 cases of the treatment group and 1 case of the control group, respectively. After the ZYW treatment, serum CD_3^+, CD_4^+, CD_8^+, CD_4^+/CD_8^+ and NK cell activation were significantly increased. Only serum CD_3^+ and NK cell activation were significantly increased in the control group with a significant difference between the two groups. The serum C_4, C_{1q}, C_3, B and C_9 were significantly increased in the treatment group. In the control group only the serum C_4 was increased. The concentration of serum interferon had no change after treatment with ZYW, while it was significantly increased in the control group after treatment with interferon. The ultrastructure of the liver restored, which helped effectively to reduce the degeneration and necrosis of hepatic cells, infiltration of inflammatory cells and hepatic cirrhosis.

CONCLUSION: ZYW is a pure Chinese herbal medicine. It can exert potent therapeutic effects on chronic hepatitis B and posthepatic cirrhosis. ZYW has similar therapeutic effects to those of interferon. It is cheap and easily administered with no obvious side-effects. It can be widely used in clinical practice.

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INTRODUCTION

HBV is highly prevalent in China. HBsAg-positive rate is 8-10% among young adults, some of them may develop chronic hepatitis B (CHB), with poor liver function and positive HBeAg and HBV-DNA. Therefore, it is urgent to improve the immunity of CHB patients to make the virus unable to replicate so as to reduce the damage to the liver and to slow down the progress of CHB to fibrosis and cancer. Anti-virus treatment is the key point[1-7], and great attention has been paid to it. However, no specific therapy has been found. The use of interferon and lamivudine is clinically limited because they are expensive and the patients are easy to relapse[8-14]. An urgent issue of top priority is how to treat CHB and other virus infection with traditional Chinese medicine according to syndrome differentiation. Insufficienty of experience and the complexity of the drug ingredients result in the lack of objective parameters. This study used the proprietary Chinese medicine of *zhaoyangwan* (Morning Sun Pill) invented by Professor Jiang Tingdong. Interferon was used as controls. Fifty patients with hepatitis B were observed for the changes in liver function, cellular immunity function, NK cell activity, serum complement, serum marker of HBV, HBV-DNA, ultrastucture of the liver and serum interferon before and after treatment with ZYW to investigate the mechanisms of the anti-virus, anti-fibrosis activity in the liver and immuno- regulatory of traditional Chinese medicine and to provide theoretic basis for the treatment of chronic hepatic diseases with Chinese herbs.

MATERIALS AND METHODS

Materials

The 50 patients were all HBsAg, HBeAg, Anti-HBc and HBV-DNA positive. Thirty-four were males and 16 females, aged 15 to 57 years, with an average of 38.5 years. They were classified according to the diagnostic criteria devised on the Beijing Conference of Infectious and Parasitic Diseases in 1995. Thirty-eight cases were CHB, 22 cases were post-hepatitis active hepatocirrhosis(in compensation). They had no such chronic diseases as other types of hepatitis, diabetes or tuberculosis.

Methods

The 50 patients were divided into *zhaoyangwan* (ZYW) group and interferon group (control group). The 36 patients in ZYW group took orally 2 packs of ZYW a day, one in the morning and one in the evening, for 3 months. The 14 patients in the control group were administered intramuscularly with α-interferon made by Changchun Bio-product Institute, 3 mU once every other day for 3 months. Vitamins might be added to the patients in both groups, but no other anti-virus, immuno-

regulatory or liver enzyme reduction drugs were used during the treatment. One therapeutic course lasted for 3 months. Serum marker of HBV, T-cell subgroup, NK cell activity, contents of serum complement, and level of serum interferon were examined before and after the treatment, respectively. The liver function was examined once a week. Liver puncture and electrodiaphanoscopy were performed for some patients to observe the ultrastructure of the liver before and after the treatment.

Assay methods

HBVDNA was assayed with PCR, T-cell sub-group with direct method of bacterial ring, NK cell activity with MTT colorimetry, serum compliment with one-direction immunity diffusion, and serum interferon with ELISA, with reagent produced by Endogen of USA. The ultrastructure of the liver was observed under electrodiaphanoscope.

RESULTS

Changes of symptoms and signs before and after treatment

Changes of symptoms and signs in both groups before treatment (BT) and after treatment (AT) are compared in Table 1, which showed that the symptom disappearance rate (DR) of the treated group was similar to or higher than that of the control group, but the sign disappearance rate was lower, with no statistical significance.

Changes of liver function and serum markers before and after treatment

Serum glutamic-pyruvic transaminase (ALT) was evidently improved in both groups. The serum ALT returned to normal in 83.3% (30/36) of the treated group and 85.7% (12/14) of the control group. No significant difference was found between both groups. (χ^2=0.043, P>0.05). The negative conversion rate of HBVDNA and HBeAg in the treated group was 44.4% (16/36) and 50% (18/36), respectively, while in the control group, it was 50% (7/14) and 50% (7/14), respectively, with no significant difference (χ^2=0.123, χ^2=0.00, both P>0.05). HBsAg turned negative in 4 cases of the treated group and 1 case of the control group, and their HBsAb turned positive. Anti-HBc turned negative in 6 cases of the treated group and 2 cases of the control group.

Changes of T-cell sub-group and NK cell activity before and after the treatment

Serum $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and NK cell activity were significantly increased in the ZYW treated group (t=8.921-13.380, all P<0.001), while in the control group, only $CD3^+$ and NK cell activity were significantly increased (t=7.473, 10.101, P<0.001). The results of the two groups were significantly different after the treatment (t =6.812-14.108, all P <0.001), as shown in Table 2.

Changes of serum complement elements before and after treatment

The five serum complement elements, ie. C_4, C_{1q}, C_3, BF, and C_9, increased significantly compared with those before the treatment in the ZYW group (t=4.437-24.330, P<0.001), while in the control group, only C_4 increased (t=5.044, P<0.001). The results of the two groups were significantly different after the treatment (t=3.972-12.910, P<0.001), as shown in Table 3.

Changes of serum interferon concentration

The serum interferon concentration changed little in the ZYW group, while in the interferon group, it rose significantly. The results of the two groups were significantly different after treatment (t=2.723, P<0.001), as seen in Table 4.

Table 1 Improvement of symptoms and signs in both groups before and after treatment

Symptoms and signs	Treated group			Control group			χ^2	P
	BT	AT	DR(%)	BT	AT	DR(%)		
Fatigue	29	14	51.7	12	6	50	0.10	>0.05
Abdominal distension	31	9	71	13	5	61.5	0.375	>0.05
Nausea	12	7	41.7	8	6	25	0.586	>0.05
Anorexia	23	6	73.9	11	4	63.6	0.379	>0.05
Hepatic pain	17	10	41.2	7	5	28.6	0.336	>0.05
Sallow complexion	14	4	71.4	5	3	40	1.564	>0.05
Hepatomegaly	20	12	40	6	3	50	0.189	>0.05
Splenomegaly	9	7	22.2	4	3	25	0.012	>0.05
Percussion pain of liver	21	12	42.9	9	5	44.4	0.006	>0.05

Table 2 Changes of T-cell sub-group and NK cell activity before and after treatment (%)

		n	$CD3^+$	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$	NK
Treated group	BT	36	47.14±4.76	41.56±5.06	30.10±3.03	1.41±0.24	43.62±5.92
	AT	36	57.81±5.83	54.81±5.64[ab]	23.07±4.47[ab]	2.49±0.72[ab]	56.69±5.29[ab]
Control group	BT	14	39.93±5.00	28.38±3.40	23.38±3.40	1.40±0.18	40.36±5.90
	AT	14	52.28±7.18[b]	29.17±1.86	29.17±1.86	1.34±0.88	59.40±4.97[b]

[a]The treated group *vs* control group after treatment, P<0.001, [b]Results after treatment *vs* those before treatment for both groups, P<0.001.

Table 3 Changes of 5 serum complement elements before and after treatment (mg/L)

		n	C_4	C_{1q}	C_3	BF	C_9
Treated group	BT	36	339.68±35.40	245.09±47.11	842.13±62.51	220.91±32.84	746.28±62.79
	AT	36	529.48±42.49[b]	349.32±35.01[b]	1 114.05±218.22[b]	279.71±52.86[b]	819.31±103.17[b]
Control group	BT	14	331.84±42.63	240.08±25.32	838.54±44.32	219.56±25.08	715.06±77.58
	AT	14	427.57±112.18[ab]	238.35±23.59[a]	843.89±50.32[a]	225.08±26.85[a]	732.08±51.12[a]

[a]The treated group *vs* control group after treatment, P<0.001, [b]Results after treatment *vs* those before treatment for both groups, P<0.001.

Table 4 Changes of serum interferon concentration before and after treatment

	Case number	BT	AT	*t*	*P*
Treated group	13	156.25±17.62	155.93±19.76	0.046	>0.05
Control group	8	143.27±21.44	218.72±63.34	3.193	<0.05

After treatment, the serum interferon concentration of the two groups was significantly different (t=2.723, P<0.05).

Changes of hepatic ultrastructure

Degeneration, necrosis, cholestasis, fibrosis, and lysis of the organelles existed in different degrees in the liver cells before treatment, while after treatment, the necrotic cells of the liver resiled to a certain extent.

Side effects of ZYW

No evident side effects appeared in the ZYW group. Xerostomia and constipation appeared in one case and slight dizziness in another case, but they disappeared automatically with the continuous use of the pills. More side effects appeared in the interferon group, including influenza-like symptoms, symptoms of the digestive tract, sore and painful muscles. However,the patients continued taking their drugs after patient persuasion of the doctors.

DISCUSSION

Some studies indicated that ZYW had two-way immune modulation functions[15]. It could improve the function of Kupffer cells of the liver and the activity of natural killer (NK) cells. It also could induce interferon to produce antiviral activity and turn HBeAg negative. We investigated the effects of ZYW on chronic hepatitis by random single-blind ways. The effects of three-month short-term therapy were good and the over all effectiveness was 83.3%(30/36). Some main symptoms such as fatigue, abdominal distension, nausea, anorexia were improved or disappeared after the treatment. The effects of the treatment group were better than those of the control group and were statistically significantly different. In most patients, the color of facial skin turned from dark and gloomy to bright red, with their vigor improved, hepatosplenomegaly improved, percussive pain of the liver region disappeared and state of general health apparently improved. Liver function tests turned normal in half of the patients including 6 patients with slight jaundice which completely disappeared, and serum bilirubin turned normal after the three-month therapy. In the control group, the rate of ALT normalization was 85.7%(12/14) with no statistical significance compared with the treatment group (P>0.05). ZYW has some antiviral activity. After the treatment, the rates of negative conversion of HBVDNA and HBeAg were 44.4%(16/36) and 50%(18/36) in the treatment group. There was no statistical significance compared with the control group, in which the rates were 50%(7/14) and 50%(7/14). The HBsAg of four patients in the treatment group and one patient in the control group turned from positive to negative and their HBsAb turned positive. The HBcAb of six patients in the treatment group and two patients in the control group turned negative. Therefore, ZYW has high antiviral activity and the effectiveness is similar to that of interferon. Because the treatment was short-termed, we did not investigate the incidence of recurrence. If the course of treatment is lasted for six months, it would have better efficiency.

Hepatitis B virus infection is the primary cause of viral hepatitis. Persistent existence of hepatitis B virus in the body is the primary cause of chronic hepatitis B[16-19]. Hepatitis B virus infection leads to chronic hepatitis and persistent damage to the liver function. Low antiviral immunity of the body and abnormal immunity modulation are also the primary cause of chronicity[20-25]. Some studies have found that there are different degrees of low cellular immunity[26,27], which represent deficient T cell immunity and decreased activity of NK cells in patients with chronic hepatitis B and liver cirrhosis. NK cells of the liver are important to antiviral immunity and against tumor metastasis[28-31]. Kakimi *et al*[32] injected lactate(activator of NK-T cell) into HBV-transgenic mouse and found that interferon-γ in the liver of the mouse increased, reproduction of HBV stopped and OK-T cells decreased. They believed that activated OK-T cells could activate NK cells, release lots of cytokines and prevent virus from reproducing. It indicates that NK cell is important in the process of erasing HBV. The results of our study showed that there were different levels of modulation disturbance of cellular immunity, such as elevation of $CD3^+$, $CD4^+$, $CD8^+$ and decrease of $CD4^+/CD8^+$ and activity of NK cells in the patients of hepatitis B before ZYW treatment. After ZYW treatment, values of $CD3^+$, $CD4^+$,$CD8^+$ and $CD4^+/CD8^+$ and activity of NK cells improved differently, indicating that ZYW can improve cellular immunity, especially the total amount of T lymphocyte and function of NK cells. It remains to be further studied whether it can be used as an activator of NK cells.

Besides, low cellular immunity, the level of blood complement decreased differently in patients with chronic hepatitis B. HBV antigen is highly compatible with liver cells. The complex of HBV-antibody-complement can damage the liver cells by activating the typical route as common complexes, or by adhering to the liver cells as half-antigen through the typical route of antibody-complement[33]. Our study indicated that low serum complement was improved differently in patients with chronic hepatitis B after treatment with ZYW and interferon, especially in the ZYW treated group.

Interferon is a broad-spectrum antiviral protein and has some antiviral activity. It does not kill viruses directly but prevents viruses from replication by mediating RNA-dependent PKR or RHA-activated enzyme. Interferon can also improve phagocytosis of phagocytes and activity of T killer cells and NK cells[29,34-36]. Our study indicated that the activity of NK cells was only slightly elevated in some patients and had no change in patients treated with interferon, indicating that the immuno-modulating function of interferon is not evident. Besides, it is difficult for interferon to be widely used due to its high price and poor tolerance in practice. So other medications which can modulate and improve immunity are suggested to be used in conjunction with interferon, which is mainly used for antiviral treatment.

Liver fibrosis is a pathologic process in which abnormall hyperplasia of fibro-connective tissue develops after inflammatory necrosis has occurred in the liver. The liver can worsen the inflammatory necrosis by cytokines or microcirculation in the liver. The activity of lesions in the liver means the activity of liver fibrosis. Some authors[37] have suggested that drugs that can prevent or slow down liver fibrosis would cure most of chronic hepatosis. Thus, preventing or delaying liver fibrosis and treating viruses are two aspects of chronic hepatitis B therapy. Today drugs for anti-liver fibrosis are rare and the curative effect is not certain. Our study found that ultramicrocirulation in the liver and liver fibrosis were improved differently after ZYW treatment in patients with chronic hepatitis B and early-stage liver fibrosis. Since the case number was small, and it needs to be further studied.

Patina in ZYW is one of its characteristic ingredients that is different from other drugs in treating chronic hepatosis in practice. Modern medicine believes that copper is an important ingredient for blood-production in the body. Taking appropriate copper orally can improve retina cells and hemoglobin in the bone marrow and blood, and stimulate and repair the liver.

Copper combined with protein in the body produces copper-protein compounds which can restrain hepatitis viruses and induce the body to produce interferon. Our results indicated that the liver function and immunity index of the patients with chronic hepatitis B were differently improved after ZYW treatment and the rate of negative conversion of chronic hepatitis B markers was similar to that of interferon group. The level of serum interferon was elevated after ZYW treatment, but the difference was not statistically significant. Because our case number was small, this needs to be further investigated. We believe that ZYW has a good curative effect and fewer side-effects in treating chronic viral hepatitis. It is also cheap and can be easily taken. So it can be widely used in practice.

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