Effects of zhaoyangwan on chronic hepatitis B and posthepatic cirrhosis

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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 ($\chi^2=0.043$, $P>0.05$). 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 ($\chi^2=0.0125$, $P>0.05$). 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. The serum C4, C3, B, and C5 were significantly increased in the treatment group. The concentration of serum interferon interfered with 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.
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 electrodiiaphanoscopy 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 complement 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 electrodiiaphanoscope.

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. \( \chi^2=0.43, P<0.05 \). 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 \( \chi^2=0.123, \chi^2=0.00, \) 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\(_9\), C\(_{1q}\), C\(_{3}\), BF, and C\(_{4}\), increased significantly compared with those before the treatment in the interferon group, while in the treated group, it rose significantly. 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 | \( \chi^2 \) | \( P \) |
|-----------------------------|---------------|---------------|-------------|-------|
| Fatigue                     | 29 BT, 14 AT  | 12 BT, 6 AT   | 0.10        | >0.05 |
| Abdominal distension        | 31 BT, 9 AT   | 13 BT, 5 AT   | 0.375       | >0.05 |
| Nausea                      | 12 BT, 7 AT   | 8 BT, 6 AT    | 0.586       | >0.05 |
| Anorexia                    | 23 BT, 6 AT   | 11 BT, 4 AT   | 0.379       | >0.05 |
| Hepatic pain                | 17 BT, 10 AT  | 7 BT, 5 AT    | 0.336       | >0.05 |
| Sallow colliquium           | 14 BT, 4 AT   | 5 BT, 3 AT    | 1.564       | >0.05 |
| Hepatomegaly                | 9 BT, 7 AT    | 6 BT, 3 AT    | 0.189       | >0.05 |
| Splenomegaly                | 21 BT, 12 AT  | 4 BT, 3 AT    | 0.012       | >0.05 |
| Percussion pain of liver    | 21 BT, 12 AT  | 9 BT, 5 AT    | 0.006       | >0.05 |

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

| 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 |
|          | 36 52.28±7.18 | 427.57±112.18 | 238.35±23.59 | 59.40±4.97 |
| Control group BT | 14 331.84±42.63 | 240.08±25.32 | 838.54±44.32 | 219.56±25.08 | 715.06±77.58 |
|          | 14 339.68±35.40 | 279.71±52.86 | 819.31±103.17 | 40.36±5.90 |

\( a\)The treated group vs control group after treatment, \( P<0.001\).

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

| n     | C\(_9\) | C\(_{1q}\) | C\(_{3}\) | BF | C\(_8\) |
|-------|--------|--------|--------|----|--------|
| Treated group BT | 36 339.68±35.40 | 245.09±47.11 | 842.13±62.51 | 220.13±22.84 | 746.28±62.79 |
|          | 36 529.48±42.98 | 349.32±55.03 | 1144.05±188.22 | 279.71±52.86 | 819.31±53.17 |
| Control group BT | 14 331.84±42.63 | 240.08±25.32 | 838.54±44.32 | 219.56±25.08 | 715.06±77.58 |
|          | 14 427.57±112.18 | 238.35±23.59 | 843.89±60.32 | 220.89±66.85 | 732.08±51.12 |

\( b\)The treated group vs control group after treatment, \( P<0.001\).
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 resided 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, the color of facial skin turned from dark and gloomy to bright red, with their vigor improved, hepatosplenomegaly improved, the color of facial skin turned from dark and gloomy to bright red, with their vigor improved, hepatosplenomegaly improved, the color of facial skin turned from dark and gloomy to bright red, with their vigor improved, hepatosplenomegaly improved, the color of facial skin turned from dark and gloomy to bright red, with their vigor improved, hepatosplenomegaly improved.

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[29-31] have suggested that drugs that can prevent or slow down liver fibrosis would cure much of chronic hepatitis. 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 hepatitis 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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