Clinical study on treatment of chronic viral cholestatic hepatitis with Chishaodanpide decoction

Heping Zhao, Tianqing Hou, Dandan Shao

OBJECTIVE: To observe the therapeutic effect of Chishaodanpide decoction (CSDPD) on chronic viral cholestatic hepatitis.

METHODS: A total of 107 subjects with chronic viral cholestatic hepatitis were enrolled in our hospital from March 2007 to November 2012. Patients were randomly divided into treatment (54 cases) and control groups (53 cases). The control group was treated with potassium magnesium aspartate, diammonium glycyrrhizinate, glucurolactone, vitamin C, and lamivudine, once a day. The treatment group was treated with modified CSDPD, 100 mL a time, twice a day, in addition to the treatment given to the control group. The patients in both groups were treated for 8 weeks. The main symptoms and signs were recorded every day throughout the clinical trial. Before and after the trial, changes in liver function including total bilirubin (TBil), direct bilirubin (DBil), total bile acid (TBA), and the activities of alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (γ-GT), were all detected. Adverse reactions were also recorded.

RESULTS: There were no differences in gender, age, disease duration, symptoms, signs, or laboratory findings between the two groups (P>0.05). After an 8-week treatment, improvements in jaundice, weakness, poor appetite, abdominal distention, and skin itching were significantly better in the treatment group than in the control group (P<0.05). In the treatment group, 43 patients had a significant response to the treatment, seven patients had a response, and four patients had no response, with 21, 12, and 20 patients in the control group, respectively. The total effective rate was 92.6% in the treatment group and 62.3% in the control group, which was a significant difference (P<0.05). The levels of TBil, DBil, TBA, ALP, ALT, AST, and γ-GT in both groups were significantly lower after treatment, and were significantly different between the two groups (P<0.05). A few patients in the treatment group had mild adverse effects such as increased bowel movement frequency and mild stomach-ache. No other adverse reactions were observed in either group.

CONCLUSION: CSDPD has a satisfactory therapeutic effect on chronic viral cholestatic hepatitis.

INTRODUCTION

Cholestatic hepatitis, a liver disease that often results from chronic viral hepatitis, is mainly characterized by intrahepatic cholestasis, long durations of jaundice,
poor appetite, skin itching, clay-colored stools, and increased levels of total bilirubin (TBil), direct bilirubin (DBil), total bile acid (TBA), and activities of alkaline phosphatase (ALP) and γ-glutamyl transferase (γ-GT). Chronic cholestatic hepatitis can develop into fulminating hepatitis or cholestatic cirrhosis, which can increase patient mortality. Therefore, creating effective treatments for cholestatic hepatitis and slowing the progress of cirrhosis and its complications are problems that need to be solved. Protecting the liver, promoting bile flow, relieving jaundice, and resisting viral infection are the treatment strategies used in clinical practice for cholestatic hepatitis. However, conventional Western Medicine is not very efficacious, and treatments are expensive. For example, studies have shown that the first-line drug for cholestatic hepatitis, ursodeoxycholic acid, had no differences in the improvement of clinical symptoms, such as weakness and abdominal distention, compared to placebo.

Chronic viral cholestatic hepatitis, characterized under “jaundice” in Traditional Chinese Medicine (TCM), is caused by damp-heat attack, which leads to toxic heat spreading throughout the body. The stagnation of toxic heat in the blood leads to blood heat stroke and blood stasis, resulting in a gradual exacerbation of jaundice. Therefore, the pathogenic basis for cholestatic hepatitis is stagnated blood and heat, and the therapeutic principle of activating blood, clearing heat, and removing toxins is used for treatment. Reports indicate that TCMs that protect the liver and relieve jaundice are effective in treating chronic cholestatic hepatitis, and herbs such as Chishao (Radix Paeoniae Rubra) are commonly used to clear heat, remove toxins, and cool blood. He et al. used Chidantuihuang granules to treat acute and chronic viral cholestatic hepatitis with satisfactory curative effects.

In this study, modified Chishaodanpi decoction (CSDPD) was used to treat chronic viral cholestatic hepatitis compared with conventional therapy. The results could serve as a reference for the clinical treatment of chronic viral cholestatic hepatitis.

**MATERIALS AND METHODS**

**Recruitment of participants**
A total of 107 participants meeting the diagnostic criteria for viral hepatitis and cholestatic hepatitis. Patients with alcohol- or drug-induced cholestatic hepatitis, and cholestatic hepatitis resulting from extrahepatic biliary obstruction, were excluded from this trial. The 107 patients (74 subjects with hepatitis B and 33 with hepatitis C) were randomly divided into a treatment group (54 cases) and a control group (53 cases). This study was approved by the ethics committee of the 150th Hospital of PLA. All patients signed an informed consent form.

**Treatment**
The patients in both groups were conventionally treated with potassium magnesium aspartate (30 mL), di-ammonium glycyrrhizinate (30 mL), glucuronic acid (0.4 g), vitamin C (2.0 g), and lamivudine (100 mg, an antiviral drug), once a day. In addition, patients in the treatment group took modified CSDPD, 100 mL orally, twice a day in the morning and evening. The decoction consisted of Chishao (Radix Paeoniae Rubra) 60-120 g (over 180 g for severe cases), Yinchen (Herba Artemisiae Capillaris) 30 g, Zhihu (Fructus Gardeniae) 30 g, Dahuang (Radix Et Rhizoma Rhei Palmae) 10 g, Dan-shen (Radix Salviae Miltiorrhizae) 25 g, Mudanpi (Cortex Moutan Radici) 25 g, Dihuang (Radix Rehmanniae) 25 g, Zexie (Rhizoma Alismatis) 15 g, Danshen (Radix Codonopis) 15 g, Banxia (Rhizoma Pinelliae) 10 g, Fuling (Poria) 25 g, Baizhu (Rhizoma Atractylodis Macrocephalae) 25 g, Cheqianzi (Semen Plantaginis) 30 g, and prepared Gancao (Radix Glycyrrhizae) 6 g. For Yin jaundice, prepared Fuzi (Radix Aconiti Lateralis Prepara-tae), Ganjiang (Rhizoma Zingiberis), and Guizhi (Ramulus Cinnamomi) were added to warm the middle Jiao and disperse cold. For skin itching, Difuzi (Fructus Kochiae Scopariae), Jingjie (Herba Schizonepetae Tenuifoliae), Baixianpi (Cortex Dictamni Radici), and Fangfeng (Radix Saposhnikoviae) were added to dispel wind and relieve itching. The herbal decoction was prepared by the Pharmaceutical Factory of the 150th Hospital of Chinese People’s Liberation Army. Both groups were treated for 8 weeks.

**Indexes of observation**
Changes in jaundice, weaknesses, poor appetite, abdominal distention, skin itching, and adverse reactions were observed and recorded before and after treatment. The levels of TBil, DBil, TBA, and activities of ALP, ALT, AST, and -GT were determined before and after treatment.

**Criteria for evaluating curative effect**
A “significant effect” indicated relief of jaundice, weaknesses, poor appetite, abdominal distention, and skin itching, and normalization or more than 50% improvement in biochemical indexes of liver function. “Effective” indicated significant alleviation of jaundice, weaknesses, poor appetite, abdominal distention, and skin itching, and more than 25% and less than 50% improvement of biochemical indexes of liver function. “Ineffective” indicated no improvement, or exacerbation of symptoms. The total effective rate was considered as all patients experiencing a significant effect and patients experiencing effective treatment divided by the total number of patients.

**Statistical analysis**
The statistical software SPSS 13.0 (Chicago, IL, USA) was used for analysis of experimental data. Analysis of variance and covariance was used to determine whether
there were significant differences between the two groups. In descriptive analyses, continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range), and categorical variables as absolute figures and percentages. Comparison of the measurement data was analyzed by t-test, and count data were analyzed by χ² test. P-values less than 0.05 were considered statistically significant.

RESULTS

Patient information
Among the 54 patients in the treatment group were 35 males and 19 females, aged 23-67 years, (49±10) years on average, with a disease duration of 7-24 months, (15±6) months on average. Among the 53 patients in the control group were 32 males and 21 females, aged 24-69 years, (50±9) years on average, with a disease duration of 7-24 months, (15±7) months on average. There were no significant differences in gender, age, disease duration, symptoms, signs, or laboratory findings between the two groups (P>0.05, Tables 1-3).

Improvements in main symptoms and signs
After treatment, improvements in jaundice, weakness, poor appetite, abdominal distention, and skin itching were significantly better in the treatment group than those in the control group (P<0.05, Table 4).

Comparison of clinical effects
In the treatment group, there was a significant effect in 43 patients, effective treatment in seven patients, and ineffective treatment in four patients. In the control group, there was a significant effect in 21 patients, effective treatment in 12 patients, and ineffective treatment in 20 patients. The total effective rate was 92.6% in the treatment group and 62.3% in the control group, which is significantly different (P<0.05) (Table 5).

Changes in laboratory findings of liver function before and after treatment
After treatment, the liver function of both groups improved significantly (P<0.05). The liver function improvement was significantly greater in the treatment group than in the control group (P<0.05) (Table 6).

Adverse reactions
Patients in the control group had no obvious adverse reactions. Three patients in the treatment group had mild adverse reactions such as increased bowel movement frequency and mild stomachache in the first week of treatment. However, the patients could tolerate the adverse reaction. The mild adverse reactions gradually disappeared as treatment continued. All patients finished the treatment.

DISCUSSION
Chronic viral cholestatic hepatitis, which is mainly...
characterized by intrahepatic cholestasis, results from necrosis of hepatic cells, blockage of bile, and eventual obstruction of bile capillaries in the portal area. In patients with chronic viral cholestatic hepatitis, there are significant increases in serum bilirubin (mainly DBil) and activities of ALP and γ-GT. During cholestasis, it is difficult to treat jaundice with the usual treatments such as protecting the liver, promoting bile flow, and improving liver enzyme levels, and there is no specific treatment for the disease. Prolonged cholestasis can lead to cirrhosis and eventually liver and kidney failure.

Chronic viral cholestatic hepatitis, which is characterized as “jaundice” in TCM, is caused by excessive damp-heat, which leads to toxic heat spreading throughout the body. The stagnation of toxic heat in the blood forms blood stasis, which causes a gradual exacerbation of jaundice. Therefore, the pathogenic basis for the disease is stagnated blood and heat. The therapeutic principle of activating blood, clearing heat, removing toxins, and inducing purgation should be used to treat chronic viral cholestatic hepatitis.

In the CSDPD prescription, Chishao (Radix Paeoniae Rubra), Mudanpi (Radix Salviae Miltiorrhizae), and Dihuang (Radix Rehmanniae) can cool and activate the blood. Danshen (Radix Salviae), Banxia (Rhizoma Pinelliae), and Yinchen (Herba Artemisiae Capillaris) can invigorate the spleen and harmonize the stomach. Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Fuling) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach. Yinchen (Herba Artemisiae Capillaris), Zhizhi (Fructus Gardeniae), Fu Ling (Poria), Zexie (Rhizoma Alismatis), Cheqianzi (Semen Plantaginis), and Dahuang (Radix Et Rhizoma Rhei Pahmi) can clear heat and drain dampness to promote the elimination of damp-heat from the excrement and urine. Prepared Gancao (Radix Glycyrrhizae) can invigorate the spleen and harmonize the stomach.

Table 4: Comparison of improvement of signs and symptoms between the two groups [(n) %]

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Treatment</th>
<th>Weakness</th>
<th>Abdominal distention</th>
<th>Poor appetite</th>
<th>Skin itching</th>
<th>Jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>54</td>
<td>Before</td>
<td>51 (94.4)</td>
<td>35 (64.8)</td>
<td>41 (75.9)</td>
<td>34 (62.9)</td>
<td>54 (100.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>13 (24.1)</td>
<td>9 (16.7)</td>
<td>12 (22.2)</td>
<td>8 (14.8)</td>
<td>11 (20.3)</td>
</tr>
<tr>
<td>Control</td>
<td>53</td>
<td>Before</td>
<td>49 (92.4)</td>
<td>34 (64.1)</td>
<td>42 (79.2)</td>
<td>32 (60.4)</td>
<td>53 (100.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>24 (45.3)</td>
<td>21 (39.6)</td>
<td>25 (47.2)</td>
<td>19 (35.8)</td>
<td>23 (43.4)</td>
</tr>
</tbody>
</table>

Notes: control group was treated with conventional Western Medicine. Treatment group was treated with modified CSDPD and conventional Western Medicine. CSDPD: Chishaodanpi decoction. \( P<0.05 \), compared with the datum in the same group before treatment, \( P<0.05 \), compared with the datum in the control group.

Table 5: Comparison of efficacy between the two groups [(n) %]

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Significant effect</th>
<th>Effectiveness</th>
<th>Ineffectiveness</th>
<th>Total effective rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>54</td>
<td>43 (79.6)</td>
<td>7 (13.0)</td>
<td>4 (7.4)</td>
<td>92.6%</td>
</tr>
<tr>
<td>Control</td>
<td>53</td>
<td>21 (39.6)</td>
<td>12 (22.6)</td>
<td>20 (37.7)</td>
<td>62.3%</td>
</tr>
</tbody>
</table>

Notes: control group was treated with conventional Western Medicine. Treatment group was treated with modified CSDPD and conventional Western Medicine. CSDPD: Chishaodanpi decoction. \( P<0.05 \), compared with the datum in the control group.

Table 6: Comparison of liver function before and after treatment in the same group and after treatment between the two groups (\( \bar{x} \pm s \))

<table>
<thead>
<tr>
<th>Liver function</th>
<th>Treatment (n=54)</th>
<th>Control (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>TBA (μmol/L)</td>
<td>55.8±5.2</td>
<td>12.0±1.7*</td>
</tr>
<tr>
<td>TBil (μmol/L)</td>
<td>181.5±38.6</td>
<td>41.5±19.6*</td>
</tr>
<tr>
<td>DBil (μmol/L)</td>
<td>127.8±25.2</td>
<td>21.8±7.9*</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>300.8±21.2</td>
<td>69.2±10.8*</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>133.6±60.1</td>
<td>47.3±28.1*</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>349.8±53.4</td>
<td>66.7±31.6*</td>
</tr>
<tr>
<td>γ-GT (U/L)</td>
<td>406.5±90.4</td>
<td>57.5±41.1*</td>
</tr>
</tbody>
</table>

Notes: control group was treated with conventional Western Medicine. Treatment group was treated with modified CSDPD and conventional Western Medicine. TBA: total bilirubin; DBil: direct bilirubin; TBA: total bile acid; ALP: activities of alkaline phosphatase; γ-GT: γ-glutamyl transferase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CSDPD: Chishaodanpi decoction. Compared with the datum before treatment in the same group, \( P<0.05 \); compared with the datum after treatment in the control group, \( P<0.05 \).
Mudanpi (Cortex Moutan Radicis) at large dosages can significantly improve jaundice. Modern pharmacological studies indicate that total Paeonia glycosides, a main component of Chishao (Radix Paeoniae Rubra), can cool and activate blood, resolve stagnations, lower blood viscosity, relieve endotoxemia, remove jaundice, inhibit the production of plasma thromboxane, improve liver microcirculation, prevent liver fibrosis, and promote the repair and regeneration of injured liver cells. Therefore, Paeonia glycosides have an excellent therapeutic effect on cholestatic hepatitis. 21–27 Mudanpi (Cortex Moutan Radicis) is a bitter and pungent herb that is slightly cold in nature, and is mainly used to treat pathogenic heat attacking the blood, and blood stasis. The therapeutic action of Mudanpi (Cortex Moutan Radicis) is related to the heart, liver, and kidney meridians and it can clear heat from the blood, promote blood circulation, and remove blood stasis. Coumarin, an active ingredient of Yinchen (Herba Artemisiae Capillaris), can protect hepatic cell membranes, prevent hepatic necrosis, promote liver cell regeneration, improve liver microcirculation, inhibit glucuronidase activity, strengthen liver detoxifying activity, and dilate the bile duct. 28,29 6,7-Dimethylsulfoxirin, another active ingredient of Yinchen (Herba Artemisiae Capillaris) can normalize gallbladder function, resist lipid peroxidation, and prevent liver cell necrosis and hepatic steatosis, which promotes liver cell regeneration and protects the integrity of liver cell membranes. 30–32 Danshen (Radix Salviae Miltiorrhiza) can remove stasis and activate blood. The combination of Danshen (Radix Salviae Miltiorrhiza) and other herbs for cooling and activating blood has an excellent therapeutic effect on jaundice. Da-huang (Radix Rhei Radix Et Rhizoma), which is bitter in taste and cool in nature, can remove blood stasis, and is considered to be the main herb for cooling blood and treating jaundice. The combined use of Da-huang (Radix Rhei Radix Et Rhizoma) and other herbs for cooling blood is also an effective therapy for jaundice.33 Smooth defecation can block or reduce the enterohepatic circulation of bilirubin and accelerate the excretion of bilirubin. The combination of the herbs in CSDPD can eliminate damp-heat and resolve blood stasis to cure jaundice, and can complement effective Western drugs. The results from this trial indicate that the therapeutic effect of CSDPD combined with conventional Western Medicine on chronic viral cholestatic hepatitis is superior to that of conventional Western Medicine alone. The total effective rate of CSDPD combined with conventional Western Medicine is much higher than that of conventional Western Medicine. This therapy is safe and effective on chronic viral cholestatic hepatitis. However, there are also limitations to our study. Because of small samples and short observational time, studies with large samples and longer durations should be conducted. Moreover, a detailed study on the mechanism of CSDPD should be performed.

REFERENCES

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