Clinical efficacy of modified Ganlu Xiaodu Dan and kuhuangsan combined with interferon on the treatment of HFMD of damp-heat accumulation toxin syndrome and its effects on liver function, myocardial enzymes, inflammatory factors and immunoglobulin

Qing Chen*, Bin Zhong, Yan Li, Yang-Cheng Yan, Dong-Mei Tang, Ming-Ming Li, Ze-Hui Liao, Juan Pan, Yuan Tao, Lan Tang

Department of Pediatrics, Wuzhou Traditional Chinese Medicine Hospital, Wuzhou, Guangxi 543003

Objective: To observe the curative effect of Modified Ganlu Xiaodu Dan and Kuhuang San combined with interferon on the treatment of HFMD of damp-heat accumulation toxin syndrome and its effects on liver function, myocardial enzymes, inflammatory factors and immunoglobulin. 

Method: From June 2018 to November 2018, 74 children with damp-heat accumulation toxin syndrome who were diagnosed with hand, foot and mouth disease have been randomly divided into the observation group (38 cases) and the control group (36 cases). The control group is given conventional Western medicine symptomatic treatment, and sprayed on the oral cavity with IFN-α atomized inhalation or IFN-α2b spray. On the basis of the control group, the observation group is given Modified Ganlu Xiaodu Dan, and Kuhuangsan for washing body. 7 d is a course of treatment. The recurrence time of the two groups, the time of rash regression and the efficacy of the children have been observed. The changes of liver function, myocardialzymogram, inflammatory factors and immunoglobulin are compared before and after treatment. 

Results: The efficacy of the observation group was 92.1% higher than that of the control group (83.3%), and the difference was statistically significant. The time required for the body temperature of the observation group (2.64±0.57) d was lower than that of the control group (3.12±0.62) d, and the time required for the rash to resolve was (4.18±0.69) d, which was lower than that of the control group (5.25±0.73) d. Statistically significant. The levels of ALT, AST, CK-MB, IL-4 and IL-6 in the observation group were lower than those in the control group after treatment, the difference was statistically significant. The serum IgA and IgM levels in the observation group were higher than those in the control group after treatment.

Conclusion: Modified Ganlu Xiaodu Dan and Kuhuang San combined with interferon for the treatment of HFMD of damp-heat accumulation toxin syndrome have a sound curative effect and it can improve liver function, protect cardiomyocytes, reduce inflammatory factors, and regulate immune function for children.

1. Introduction

Hand foot and mouth disease (HFMD) is a common infectious disease in pediatrics. Currently, more than 20 kinds of enterovirus have been clinically found that can cause HFMD, among which coxsackievirus A16 (Cox A16) and enterovirus 71 (EV 71) are the most common ones[1]. HFMD mostly occurs in children under 5 years old, mainly transmitted through digestive tract, respiratory tract and interpersonal contact. Its obvious clinical symptoms include fever, oral pain, herpetic ulcer or oral mucosa, and maculopapules on hands, feet and buttocks, etc. In severe cases, meningitis, pulmonary edema, circulatory disorders and other life-threatening diseases may also occur[2]. At present, there is no specific drug for HFMD, but traditional Chinese medicine and the combination of traditional Chinese and western medicine has achieved good efficacy in the treatment of HFMD[3]. Therefore, in this study, Modified Ganlu Xiaodu Dan and Kuhuangsan combined with interferon of damp-heat accumulation toxin syndrome
have better curative effect combined with interferon have used to treat damp-heat-accumulated toxic hand foot and mouth disease, with the purpose to evaluate its efficacy and influence on liver function, myocardial enzyme spectrum, inflammatory factors, and immunoglobulin, which is reported below.

2. Clinical data and methods

2.1 General data

Accordingly, 74 children with hand foot and mouth disease (HFMD) with damp-heat accumulation poison from June 2018 to November 2018, who were diagnosed in pediatrics department of Wuzhou Hospital of Traditional Chinese Medicine, have been selected. Children have been divided into the observation group (38 cases) and the control group (36 cases) by the random number table method. The observation group consists of 17 male and 21 female children, whose average age were (3.78 ± 0.75) years old, and their average temperature were (38.4 ± 0.27) ℃, while in the control group, 17 male and female 19 children have been included. Their average age were (3.65 ± 0.67) years old, and the average temperature were (38.3-0.21) ℃. There is no statistically significant difference in gender, age, body temperature and other clinical data between the observation group and the control group ($P < 0.05$).

2.2 Diagnostic criteria

Western Medicine Diagnosis: the diagnosis of HFMD is based on The Diagnostic Criteria of The Diagnostic Guidelines for HFMD (2018 edition)[4]. Traditional Chinese Medicine Diagnosis: the diagnosis of dampness, heat and toxin accumulation of TCM syndromes is based on the The Diagnostic Criteria of The Diagnostic Guidelines for HFMD (2018 edition)[4]. The syndromes are mainly manifested as persistent fever; herpes in hands, feet, buttocks and mouth; weariness; pale red or red tongue, moss greasy; pulse number; red and purple fingerprints.

### Table 1.
Comparison of efficiency n(%) between the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Cured</th>
<th>Improved</th>
<th>Ineffective</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation Group</td>
<td>38</td>
<td>20</td>
<td>16</td>
<td>2</td>
<td>94.7%</td>
</tr>
<tr>
<td>Control Group</td>
<td>36</td>
<td>12</td>
<td>16</td>
<td>8</td>
<td>77.8%</td>
</tr>
</tbody>
</table>

*compared with the control group, $P < 0.05$.

### Table 2.
Comparison on the time required for the body temperature to return to normal and the time required for the body temperature to return to normal between the two groups ($d$).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>The Time required for the Body Temperature to Return to Normal</th>
<th>The Time required for the Body Temperature to Return to Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation Group</td>
<td>38</td>
<td>2.64±0.57</td>
<td>4.18±0.69</td>
</tr>
<tr>
<td>Control Group</td>
<td>36</td>
<td>3.12±0.62</td>
<td>5.25±0.73</td>
</tr>
</tbody>
</table>

*compared with the control group, $P < 0.01$. 

2.3 Inclusion and exclusion criteria

Inclusion Criteria: (1) Children diagnosed with damp-heat-accumulating toxic hand foot and mouth disease according to the diagnostic criteria of both traditional Chinese medicine and western medicine; (2) the typical symptoms of fever and/or rash do not appear for more than 48 h; (3) Children’s age should range from 1 to 14; (4) the guardians know, willing to be cooperative in this study and agrees to sign relevant informed consent paper. Exclusion criteria: (1) patients with an experience of allergy to traditional Chinese medicine; (2) merger with other serious diseases; (3) patients who have used other drugs to treat HFMD before this treatment; (4) the child and/or guardian who have mental illness.

2.4 Treatment

Both the control group and the observation group have been given conventional western medicine symptomatic treatment; at the same time, they were asked to have rest properly and bland diet. Children whose body temperature were 38.5 ℃ or less should be given physical cooling, and those with fever temperature were > 38.5 ℃ could be given antifebrile drug treatment. The control group has been given conventional symptomatic treatment by western medicine, and ifn-a atomized inhalation (ifn-a2b 200 000 - 400 000 IU/ (kg• times) or ifn-a1b 2-4 μ g/（kg• times）has been used for 7d every 12 h twice a day, depending on the condition of the children.) Or ifn-a2b spray (1 million IU/d, every 1-2 h/time, can be sprayed on oral lesions to cover lesions is appropriate, a treatment course of 7 d). The observation group has been coped with equally with control group; moreover, mannose disinfection Modified Ganlu Xiaodu Dan and Kuhuangsan powder (for washing) have been employed for treatment. The prescription of Modified Ganlu Xiaod includes: 15 g talcum powder, 10 g each for honeysuckle, forsythia forsythia, semen coix seed, patchowli, 8 g each for white root, scutellaria baicalensis, artemisia annua, fried burdock seeds, Perilla, 5 g each for herb and licorice. Decoction of all drugs is carried out in pure water, with 200-300 mL of water added to decoction to 100 mL, divided into two bags with 50 mL each. Let children of this group have clyster twice a day. The temperature of the drugs are kept around 38-40 ℃, which should be filled from one’s anus slowly and steadily. Generally speaking, the process is repeated at dawn.
Comparison of myocardial enzymes between the two groups (U/L).

### Table 4.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>CK before the Treatment</th>
<th>CK after the Treatment</th>
<th>CK-MB before the Treatment</th>
<th>CK-MB after the Treatment</th>
<th>LDH before the Treatment</th>
<th>LDH after the Treatment</th>
<th>α-HBD before the Treatment</th>
<th>α-HBD after the Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>38</td>
<td>23.91±4.35</td>
<td>27.32±3.69</td>
<td>14.54±3.69</td>
<td>23.91±4.35</td>
<td>268.36±35.14</td>
<td>263.95±32.24</td>
<td>213.85±21.38</td>
<td>212.59±23.25</td>
</tr>
<tr>
<td>Control</td>
<td>36</td>
<td>23.91±4.35</td>
<td>27.32±3.69</td>
<td>14.54±3.69</td>
<td>23.91±4.35</td>
<td>268.36±35.14</td>
<td>263.95±32.24</td>
<td>213.85±21.38</td>
<td>212.59±23.25</td>
</tr>
</tbody>
</table>

*P < 0.05 compared with the same group before treatment, and *P < 0.05 compared with the control group.

and 30-60 min before their bed rest or after cacion. It can reduce abdominal pressure and clean the intestinal tract, which is conducive to drug absorption, 10-30 mL for infants and 50 mL for seniors. Kuhuangsan prescription consists of: cypress, sophora sophora, honeysuckle vine, 100, ground skin, snakebed, three ya bitter, wild chrysanthemum with 15 g for each. It is grinded into powder, and soaked in boiling water when using, making the effective ingredients precipitate out in this process. The patient’s affected parts should be soaked in the drug liquid, 1 dose per day, 1 time per day, 10-15 min each time, 7 d as a course of treatment.

### 2.5 Observation index

The time of children’s temperature returning to normal, the time of rash regression and the efficacy of the prescription the two groups have been observed. Their liver and kidney function, myocardial enzyme spectrum, inflammatory factors and immunoglobulin have been recorded before and after the treatment. The evaluation of the treatment effect is based on Clinical Disease Diagnosis Criteria for Improvement[5], which is embodied by the one’s return of normal body temperature after one course of treatment, receded maculopapular rash, dried skin herpes and no exudate, and wound healing of oral herpes. Patient’s improvement is judged by: the body temperature returned to normal or significantly decreased, and the oral and skin rashes were significantly improved after 1 course of treatment. Likewise, if one suffers from repeated fever or high fever, his oral and skin rash does not reduce or increase after 1 course of treatment. Likewise, if one suffers from repeated fever or high fever, his oral and skin rash does not reduce or increase after 1 course of treatment, then it is invalid. Effective rate = (number of cured + number of improved)/total number.

### 2.6 Laboratory index

The first morning fasting venous blood 5 mL of the children is extracted before and after one course of treatment, Kit for ELISA to detect serum IL-4, IL-6, IL-10, bought in sangon biological engineering (Shanghai) co., LTD. is adopted. Kit to detect children’s IgA, IgG, IgM using immune turbidimetric method bought in Beijing Maiyusen biological technology co., LTD, is also utilized.

### 2.7 Statistical method

SPSS 18.0 software is used for all data entry and collation analysis. Measurement data is indicated by mean ± standard deviation. “t” test is used for comparison between the two groups, and the counting data is represented by composition ratio (%). Chi-square test is used for comparison between the two groups, and the test level was set at =0.05.

### 3. Results

#### 3.1 Comparison of efficacy between the two groups

The efficacy of the observation group is 92.1% (35/38), higher than that of the control group 83.3% (30/36), with statistically significant difference (P < 0.05).

#### 3.2 Comparison on the time required for the body temperature to return to normal and for the skin rash to subside between the two groups

The time required for the body temperature to return to normal is (2.64 ± 0.57) d for the observation group, which is lower than that of the control group: (3.12 ± 0.62) d. The time required for the skin rash to subside is (4.18 ± 0.69) d, which is lower than that of the control group: (5.25 ± 0.73) d. The difference is statistically significant (P < 0.01).
Comparison of immunoglobulin between the two groups (g/L).

Table 6.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Before the Treatment</th>
<th>After the Treatment</th>
<th>Before the Treatment</th>
<th>After the Treatment</th>
<th>Before the Treatment</th>
<th>After the Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>38</td>
<td>27.58±3.98</td>
<td>15.38±2.59</td>
<td>32.43±3.32</td>
<td>14.83±2.43</td>
<td>36.58±4.23</td>
<td>25.42±3.13</td>
</tr>
<tr>
<td>Control Group</td>
<td>36</td>
<td>26.85±4.21</td>
<td>19.54±3.41</td>
<td>31.87±3.89</td>
<td>18.42±2.74</td>
<td>37.12±3.89</td>
<td>26.39±3.53</td>
</tr>
</tbody>
</table>

\*P < 0.05 compared with the same group before treatment, and \*P < 0.05 compared with the control group.

Comparison of immunoglobulin between the two groups (g/L).

Table 6.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>IgA</th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>38</td>
<td>1.03±0.20</td>
<td>7.87±1.58</td>
<td>1.03±0.27</td>
</tr>
<tr>
<td>Control Group</td>
<td>36</td>
<td>1.08±0.18</td>
<td>8.05±1.42</td>
<td>1.01±0.20</td>
</tr>
</tbody>
</table>

\*P < 0.05 compared with the same group before treatment, and \*P < 0.05 compared with the control group.

3.3 Comparison of liver function between the two groups

ALT, AST, TBIL, BUN and Cr are comparable between the two groups before the treatment, with \( P > 0.05 \). ALT and AST levels in the observation group are lower than those in the control group after the treatment, and the difference is statistically significant, with \( P < 0.05 \).

3.4 Comparison of blood myocardial enzyme profiles between the two groups

The myocardial enzyme spectra (CK, CK-MB, LDH, -HBD) of the two groups are comparable (\( P > 0.05 \)) before the treatment. After the treatment, CK-MB is significantly lower than that of the control group, with statistically significant difference. \( P < 0.05 \).

3.5 Comparison of inflammatory cytokines between the two groups

There is no statistically significant difference in inflammatory cytokines (IL-4, IL-6, IL-10) between the two groups before the treatment (\( P > 0.05 \)). After the treatment, serum IL-4 and IL-6 levels of the observation group are lower than those of the control group, with statistically significant difference (\( P < 0.05 \)).

3.6 Comparison of immunoglobulin between the two groups

There is no significant difference in IgA, IgG and IgM between the two groups before the treatment (\( P > 0.05 \)). After the treatment, serum IgA and IgM levels in the observation group are higher than those in the control group, with statistically significant difference (\( P < 0.05 \)).

4. Discussion

Hand foot and mouth disease (HFMD) has been listed as a statutory infectious disease in China since 2008, and its number of cases and deaths has been at the top of category C infectious diseases for many years. Currently, there is no specific drug for HFMD, and the antiviral therapy is mainly used with the combination of traditional Chinese and western medicine clinically. From the view of traditional Chinese medicine, it is believed that hand foot and mouth disease belongs to the category of “temperature sickness” and “herpes”, and pathogenic toxin can easily enter one’s mouth and nose and collect in the lungs and spleen, while endogenous dampness and heat occur in the skin and mouth[6]. Lung and spleen dampness-heat syndrome, dampness-heat stagnation and steaming, and pathogenic factors causing lung health syndrome are the most common TCM syndromes of hand foot and mouth disease. Therefore, TCM often focuses on symptomatic treatment of clearing heat and changing dampness according to the syndromes[7].

The prescription of Modified Ganlu Xiaodu Dan for treating heat and humidity epidemic created by Ye Tianshi aims at reducing dampness, removing turbidity, clearing heat and detoxifying, which has a sound effect in treating the dampness and heat diseases[6]. Lung and spleen dampness-heat syndrome, dampness-heat stagnation and steaming, and pathogenic factors causing lung health syndrome are the most common TCM syndromes of hand foot and mouth disease.

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ALT and AST are reactions to one's liver function, and when liver cells are damaged, ALT and AST will increase correspondingly[12]. Chen Yongying[13] found that the levels of ALT, AST, TBIL, and DBIL which are liver function indicators are closely related to the severity of HFMD. This study has found that ALT, AST and TBIL in the two groups have decreased after the treatment, and ALT and AST levels in the observation group are lower than those in the control group after the treatment, with statistically significant differences (P < 0.05).

Myocardial enzyme profile reflects the degree of myocardial damage to a certain extent. Studies have shown that HFMD virus can affect myocardial cells, and myocarditis can be induced in severe cases[14]. The level of CK-MB in serum of ordinary people is low, but when myocardial cells are damaged, the serum CK-MB noticeably increases, so the level of CK-MB can reflect the degree of damage of centrifuge cells[15]. This study have found that the myocardial enzyme spectrum of the observation group and the control group are significantly decreased after the treatment, while the CK-MB level of the observation group is lower than that of the control group after the treatment, and the difference was statistically significant (P < 0.05).

IL is a cytoinflammatory cytokine produced by a variety of cells and involved in several immunoreactions. It is generally believed that IL can promote the maturation, activation, proliferation and immune regulation of immune cells[16]. Researches have shown that IL-6 and IL-10 levels are correlated with the severity of HFMD[17]. This study have found that cytoinflammatory cytokines are significantly reduced in the two groups after the treatment, while IL-4 and IL-6 of the observation group are lower than those in the control group (P < 0.05).

Serum immunoglobulin, a protein with antibody activity produced by lymphocytes B, is an important component of the human immune system[18]. Immunoglobulin can be divided into 5 categories: IgA, IgD, IgE, IgG and IgM. IgA accounts for 10%-20% of serum immune protein, which can effectively eliminate the free virus in the blood. IgG is an important immune protein in the body, which is a specific antibody with antiviral and antitoxin effects produced by the body after virus infection[19]. IgM is the first antibody to appear after infection, so IgM level can be used as an early diagnostic indicator of disease. This study have found that IgA, IgG and IgM levels of children in the observation group are higher than those in the control group after the treatment, P < 0.05.

To recap briefly, Modified Ganlu Xiaodu Dan and Kuhuang San combined with interferon for the treatment of HFMD of damp-heat accumulation toxin syndrome have a sound curative effect and it can improve liver function, protect cardiomyocytes, reduce inflammatory factors, and regulate immune function in children.

Reference