Clinical observation of effects of pidotimod combined with ribavirin on inflammatory factors, T lymphocyte subsets, immunoglobulin and blood biochemical markers in children with hand-foot-mouth disease

Shi-Chao Zhang, Sha-Sha Wang*, Jing-Feng Li, Na Ding, Jian-Hong Ren

Department of Pediatrics, Hubei Medical College Shiyan City Taihe Hospital, Hubei, Shiyan, 442000

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Objective: To observe the effects of pidotimod combined with ribavirin on inflammatory factors, T lymphocyte subsets, immunoglobulin, lactate, D-dimer and procalcitonin in children with hand-foot-mouth disease. Methods: A total of 108 children with foot-hand-and-mouth epidemic in our hospital from Jan. 2013-Dec. 2016 were divide into the observation group and the control group, each groups has 54 cases. Two groups of children were treated with isolation, the observation group was given pidotimod combined with ribavirin, and the control group was treated with ribavirin. 5 mL venous blood of two group patients were collected at admission and after 6 d treatment, respectively, to compare inflammatory factor, T lymphocyte subsets, immunoglobulin, lactate, D-dimer and procalcitonin in two groups. Results: Before treatment, the levels of inflammatory factor, T lymphocyte subsets, immunoglobulin, lactate, D-dimer and procalcitonin of two groups were not statistically significant. Compared with groups after treatment, the levels of CRP, IL-6, TNF-α were lower than that before treatment, CRP (2.23±0.37) mg/L, IL-6 (21.24±9.81) pg/mL and TNF-α (56.97±50.36) pg/mL levels in observation group after treatment were significantly lower than those in control group, the difference was statistically significant. After treatment, the levels of CD3, CD4, CD4/CD8, IgG, IgA and IgM in control group were significantly higher than that before treatment, the difference was statistically significant; After treatment, the levels of CD3 (51.26±10.27)%, CD4 (36.36±4.09)%, CD4/CD8 (1.60±0.30) mg/L and IgM (1.48±0.30) mg/L in observation group were significantly higher than in control group, the difference was statistically significant. After treatment, the levels of lactate, D-dimer and procalcitonin in two groups were significantly lower than that before treatment, the difference was statistically significant; After treatment, the levels of lactate (1.19±0.20) mmol/L, D-dimer (150.23±27.21) ng/mL, and procalcitonin (0.08±0.02) ng/mL in observation group were significantly higher than in control group, the difference was statistically significant. Conclusion: Pidotimod combined with ribavirin has a pronounced effect on children with hand-foot-mouth disease, which can effectively reduce the body’s inflammatory response, enhance immune function, improve clinical biochemical indicators, and should be widely recommended for clinical use.

1. Introduction

Hand, foot and mouth disease is a common, strong infectious diseases in clinical, with speed complex transmission, which can be induced by a variety of enterovirus, mainly EV71 and CoxA16[1-2]. This disease is more likely to occur at children under the age of 5, with a high incidence in the summer. Clinical manifestations of this disease are main fever as well as herpes at hand, foot, mouth and hip, accompanied by cough, antifeedant and other symptoms. This disease shows a long latent period. Delayed treatment may caused severe hand, foot and mouth disease, accompanied by meningitis, pulmonary edema, vomiting, myocarditis, lethargy, even coma and other complications, which is a serious threat to children’s life and health[3]. the principles of this disease are early detection, early
isolation, early treatment. Currently, our hospital is using pidotimod combined with ribavirin for the treatment of the disease, reported as follow.

2. Information and methods

2.1 Clinical Information

A total of 108 children with foot-hand-and-mouth epidemic in our hospital from Jan. 2013-Dec. 2016 were divide into the observation group and the control group, each groups has 54 cases. Two groups of children were treated with isolation, the observation group was given pidotimod combined with ribavirin, the control group was treated with ribavirin. In the control group, there were 30 males and 24 females; with ages of 1-5 years; temperature 38.0-39.4 °C, duration of 1-4 d; in the observation group, there were 28 males and 26 females; with ages of 7 months-4 years; temperature 38.2-39.2 °C, duration of 0.5-4 d. Inclusion criteria: (1) All children were in line with the 2013 "hand, foot and mouth disease diagnosis and treatment guidelines" diagnostic criteria[4]; (2) All children over the age of 6 months; (3) All children were voluntarily involved in the study with parental consent and signed informed consent. Exclusion criteria: (1) Use other antiviral drugs or (and) analgesic drugs after onset; (2) drug allergy; (3) combined with severe organic complications.

2.2 Therapeutic method

The patients in the observation group were treated with pidotimod combined with ribavirin. Ribavirin injection (Shandong Shenglu Pharmaceutical Co., Ltd., byua powerfulco H20043041), 10 mg per kg of body weight administration, adding 100 mL NaCl solution, 1 times/d, intravenous infusion. pidotimod (Jiangsu Wuzhong Pharmaceutical Group Co., Ltd., byua powerfulco H20043041). 10 mg per kg of weight administration, adding 100 mL NaCl solution, 1 times/d intravenous infusion and ribavirin. In the control group, there were 30 males and 24 females; with ages of 1-5 years; temperature 38.0-39.4 °C, duration of 1-4 d; in the observation group, there were 28 males and 26 females; with ages of 7 months-4 years; temperature 38.2-39.2 °C, duration of 0.5-4 d. Inclusion criteria: (1) All children were in line with the 2013 "hand, foot and mouth disease diagnosis and treatment guidelines" diagnostic criteria[4]; (2) All children over the age of 6 months; (3) All children were voluntarily involved in the study with parental consent and signed informed consent. Exclusion criteria: (1) Use other antiviral drugs or (and) analgesic drugs after onset; (2) drug allergy; (3) combined with severe organic complications.

2.3 Effect analysis

5 mL venous bloods of two group patients were collected by EDTA anticoagulant tubes at admission and after 6 d treatment, respectively, to compare inflammatory factor, including CRP, IL-6 and TNF-α. The blood was centrifuge by 15 min, and detected by enzyme-linked immunosorbent assay, the whole operation process must be strictly in accordance with the requirements of instruments and reagents[6]; T lymphocyte subsets, which including CD3, CD4 and CD4/CD8, were detected by FCM[6]. The whole operation process must be strictly in accordance with the requirements of instruments and reagents. Immunoglobulins, including IgG, IgA and IgM, were detected by Hitachi 7600 automatic biochemical analyzer[7]. Blood biochemical indicators include lactic acid, D-dimer and procalcitonin, the content of lactic acid was determined by enzyme colorimetric assay. D-dimer was determined by immunoturbidimetric assay. Calcitonin was determined by enzyme-linked immunosorbent assay kit[8], respectively.

2.4 Statistical analysis

SPSS 17.0 statistical package was conducted for statistical analysis. The level of each group was described as Mean ± SD, t test was conducted too, values of P<0.05 were considered to be statistically significant.

3. Result

3.1 Comparison of inflammatory factors before and after treatment

Before treatment, there was no significant difference in CRP, IL-6 and TNF-α between the two groups (P>0.05). After treatment, the levels of CRP, IL-6 and TNF-α were significantly lower than those before treatment (P<0.05). The levels of CRP, IL-6 and TNF-α in the observation group were (2.23 ± 0.37) mg/L, (21.24 ± 9.81) pg/mL and (56.97 ± 50.36) pg/mL, respectively, which were significantly lower than those in the control group, the difference was significant (P<0.05), as shown in Table 1.

3.2 Comparison of T lymphocyte subsets and immunoglobulin before and after

Before treatment, there was no significant difference in CRP, IL-6 and TNF-α between the two groups (P>0.05). After treatment, the levels of CRP, IL-6 and TNF-α were significantly lower than those before treatment (P<0.05). The levels of CRP, IL-6 and TNF-α in the observation group were (2.23 ± 0.37) mg/L, (21.24 ± 9.81) pg/mL and (56.97 ± 50.36) pg/mL, respectively, which were significantly lower than those in the control group, the difference was significant (P<0.05), as shown in Table 1.

5.06±3.18  53.18±27.04 110.47±50.66

Note: compared with group before treatment, P<0.05; compared with control group after treatment, *P<0.05.
Comparison of blood biochemical markers before and after treatment.

Table 3.
Comparison of blood biochemical markers before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>Lactic acid (mmol/L)</th>
<th>D-dimer (ng/mL)</th>
<th>Procalcitonin (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>54</td>
<td>Before treatment</td>
<td>9.47±2.09</td>
<td>284.56±50.12</td>
<td>0.69±0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>1.19±0.20*</td>
<td>150.23±27.21*</td>
<td>0.08±0.02*</td>
</tr>
<tr>
<td>Observation group</td>
<td>54</td>
<td>Before treatment</td>
<td>9.53±2.40</td>
<td>287.15±47.21</td>
<td>0.70±0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>2.03±0.31*</td>
<td>226.82±30.30*</td>
<td>0.17±0.05*</td>
</tr>
</tbody>
</table>

Note: compared with group before treatment, *P<0.05; compared with control group after treatment, #P<0.05.

were higher than that before treatment and after treatment in observation group. The difference was significant (P<0.05).

3.3. Comparison of blood biochemical markers before and after treatment

Before and after therapy, comparison of lactic acid, D-dimer and procalcitonin in two group was shown in Table 3. After treatment, there was no significant difference in lactic acid, D-dimer and procalcitonin between the two groups (P>0.05). After treatment, the lactic acid, D-dimer and procalcitonin were significantly lower than those before treatment (P<0.05), and the difference was significant (P<0.05). After treatment, the levels of lactic acid, D-dimer and procalcitonin in observation group were (1.19±0.20) mmol/L, (150.23±27.21) ng/mL and (0.08±0.02) ng/mL, respectively, which were significantly lower than that in control group (P<0.05).

4. Discussion

Hand, foot and mouth disease is mainly infected through the respiratory tract, gastrointestinal and physical contact, which is a more common acute infectious diseases in children, belonging to China's Category IV infectious diseases[9]. According to the statistics[10], in the past five years, the incidence and mortality rate of this disease showed a significant upward trend. This disease shows a long latent period. Children may suddenly infected when their immunity decreased. Although it is a self-healing disease, severe hand, foot and mouth disease may caused by the delayed treatment, which is a serious threat to children's life and health.

Ribavirin is a broad-spectrum antiviral drug which can efficiently inhibit monophosphate hypoxanthine dehydrogenase. It can occur phosphorylation after reaching the target cells, reduce the content of guanosine triphosphate, effectively inhibit a variety of enzymes' transformation and generation, block the synthesis of viral nucleic acids, prevent viral replication, and show significant inactivation and high safety[11,12]. In the past clinical experience[13], ribavirin was often used as the preferred treatment of this disease, but a single drug treatment effect is not ideal. After a long study summary, our hospital is currently used pidotimod combined with ribavirin for pediatric hand, foot and mouth disease treatment, and achieved good results. Pidotimod is a novel high-purity dipeptide drug and it is also a newly synthesized bioimmune response promoter[14]. It has a significant promotion on specific and non-specific immune responses by enhancing body fluid, cellular immunity function to eliminate bacteria, which can effectively promote phagocytic activity of macrophages and neutrophils, strengthen the chemotaxis and killing ability, speed up lymphocyte proliferation[15]; with the development of reaction, it can strengthen the cellular immune function, induce T lymphocyte maturation, accelerate the recovery of CD4/CD8 to normal levels; when the body into the slow response period, humoral immune function can be exerted, pidotimod is not a direct antiviral drugs, it can effectively improve the anti-viral effect of drugs, enhance immunity, and accelerate children's recovery through regulation of immune function[16]. The combination of these two drugs, complement each other, can not only play the role of dual immunization, improve the anti-viral effect, but also effectively avoid secondary bacterial infection during treatment, rapidly control the development of disease and promote recovery.

At the early stages, hand, foot and mouth disease may produce inflammatory response, which closely related to the severity of the disease. CRP, TNF-α and IL-6 are important inflammatory cytokines, all of them can be used to evaluate inflammatory response and stress status, which are the key response index of disease severity[17]. CRP, syntheised by hepatocyte, is an acute inflammatory response maker with high sensitivity, which plays an important role in natural immunity and keeps a good consistency with the degree of inflammatory response[18]. Besides, it has a high stability level, the administration is easy, not effect by the age of children, pain or mental factors and so on, which has been used as an important indicator of clinical diagnosis and prognosis of infectious diseases in children. Interleukin is a key regulator of inflammatory stress response, closely related to immune regulation function. IL-6, secreted by Th1 cells during the inflammatory response, is a proinflammatory mediator, which can promote the cascade amplification of inflammatory response. TNF-α is also one of the important inflammatory markers, which has a real-time effect on the inflammatory response, and its expression level is of great significance to the degree of infection[18]. From the above results can be seen, after treatment CRP, IL-6 and TNF-α indicators in the observation group were lower than that in the control group, the combination of pidotimod and ribavirin can reduce the degree of inflammatory response, improve the natural immunity, alleviate a series of adverse reactions caused by inflammation.
T lymphocytes maintain a dynamic balance in the normal body, and its common indicators, including CD3, CD4 and CD8, are important manifestations of the body's immune response to the immune system[9]. When the body is infected by the virus infection, T lymphocyte subsets and functional abnormalities, leading to changes in immune function[20]. From the above results can be seen, after treatment, CD3, CD4 and CD4/CD8 in the observation group were higher than in the control group, which indicated that pidotimod combined with ribavirin can effectively improve the immune function, enhance immunity, benefit to anti-viral infection, promote recovery. Immunoglobulin, secreted by plasma cells, is a kind of protein which has the function of preventing local infection, regulating immunity and antibody activity. It mainly includes IgG, IgA and IgM, etc. It can play a role in immune surveillance when the body is not infected by pathogenic microorganisms, as well as play a defensive role when the pathogenic microorganisms invade the body[21]. IgG, derived from the maternal body, is the most important specific antibody in humoral immunity, especially has a good protection for the lower respiratory tract. The proportion of it in serum immunoglobulin is as high as 75%. IgG also has the ability to neutralize free exotoxin and regulate phagocytic cells. IgA is an antibody, secreted by the mucosa of nose, lung and trachea, which can specifically prevent local infection. Microbes are likely to invade the body when IgG level declines and can combine with oral rash, clinical experience shows that it can effectively remove the free virus too. IgM, produced after the first immunoreaction, is an important immunoglobulin with the earliest emergence, shortest survival time in humoral immunity and half-life of 6 days only. The increase of IgM level always portends the occurrence and development of new infections. Hence, timely regulation of IgM, can effectively reduce the incidence of hand, foot and mouth disease severity. From the above results, the levels of IgG, IgA and IgM in the observation group were higher than those in the control group, which indicated that pidotimod combined with ribavirin could effectively prevent the virus from replicating, improve the level of immunoglobulin and alleviate the clinical symptoms. Lactic acid is a sensitive indicator of blood flow perfusion. Lactate levels will elevated if perfusion is insufficient; D-dimer is closely related to coagulation-fibrinolytic disorders; after acute infection, thyroid C cells synthesize a large number of calcitonin, the level of calcitonin can directly response to the degree of acute state. From the above results can be seen, after treatment, lactic acid, D-dimer and procalcitonin in the observation group were lower than that in the control group, which indicated that pidotimod combined with ribavirin can effectively improve the acute infection of children with hand, foot and mouth disease.

Pidotimod combined with ribavirin has a pronounced effect on children with hand-foot-mouth disease, which can effectively reduce the body’s inflammatory response, enhance immune function, improve clinical biochemical indicators, and should be widely recommended for clinical use.

References