Effect of adjuvant interferon aerosol inhalation on inflammatory response and stress response in neonatal viral pneumonia

Yong-Fang Zhang1, Hong-Yan Zhang2

1. Neonatology Department, the Central Hospital of Enshi Autonomous Prefecture Hubei Province, Enshi, Hubei Province, 445000
2. Health Management Center, the Central Hospital of Enshi Autonomous Prefecture Hubei Province, Enshi, Hubei Province, 445000

ARTICLE INFO

Article history:
Received 24 Apr 2018
Received in revised form 10 May 2018
Accepted 18 May 2018
Available online 28 May 2018

Keywords:
Viral pneumonia
Interferon
Inflammatory response
Stress response

ABSTRACT

Objective: To study the effect of adjuvant interferon aerosol inhalation on inflammatory response and stress response in neonatal viral pneumonia. Methods: The newborns with viral pneumonia who were treated in our hospital between May 2015 and October 2017 were selected as the research subjects and randomly divided into the IFN group who received interferon inhalation combined with routine symptomatic treatment and the control group who received routine symptomatic treatment. The contents of inflammatory cytokines and stress mediators in serum as well as the expression of inflammatory signaling molecules in peripheral blood were measured before treatment and 7 d after treatment. Results: Compared with those of same group before treatment, SP-A, sICAM1, suPAR, sTREM1, Copeptin, Ins, NE and 8-iso-PG levels in serum as well as Tim1, Tim3, TLR2, TLR4 and NF-κB mRNA expression in peripheral blood of both groups significantly decreased 7 d after treatment, and SP-A, sICAM1, suPAR, sTREM1, Copeptin, Ins, NE and 8-iso-PG levels in serum as well as Tim1, Tim3, TLR2, TLR4 and NF-κB mRNA expression in peripheral blood of IFN group 7 d after treatment were significantly lower than those of control group. Conclusion: Adjuvant interferon aerosol inhalation can reduce the activation of inflammatory response and stress response in neonatal viral pneumonia.

1. Introduction

Viral pneumonia is a common respiratory disease in infants, which is caused by respiratory syncytial virus, influenza virus, adenovirus and other pathogen infection, can cause significant interstitial inflammatory change in the course, and may lead to respiratory distress and high mortality in severe cases[1,2]. The treatment of neonatal viral pneumonia depends on symptomatic and supportive treatment, but the illness of some children is progressing during symptomatic and supportive treatment, and severe cases may develop into severe pneumonia and be life-threatening. Interferon α 1b is the genetic engineering drug independently researched and developed in our country, which has the immunoregulatory activity of interferon, and activates the specific receptors on the cell membrane to induce the expression of a variety of antiviral proteins and exert virus killing effect[3]. In the following studies, we specifically analyzed the effect of adjuvant interferon aerosol inhalation on inflammatory response and stress response in the course of neonatal viral pneumonia.

2. Case information and research methods

2.1 Case inclusion methods

The newborns with viral pneumonia who were treated in our hospital between May 2015 and October 2017 were selected as the research subjects, they were all diagnosed by serum virus nucleic acid or antigen detection, and those combined with congenital disease were eliminated. A total of 68 cases were included, and the random number table method was used to divide them into two groups, each with 34 cases. There were 18 males and 16 females in the IFN group, they were 13-20 d old, 11 cases were from spontaneous delivery and 23 cases were from cesarean section, and
15 cases were breast-feeding; there were 19 males and 15 females in the control group, they were 13-21 d old, 13 cases were from spontaneous delivery and 21 cases were from cesarean section, and 16 cases were breast-feeding. There was no significant difference in general information between the two groups (P>0.05).

2.2 Clinical therapy

Both groups of newborns received necessary nutrition support, oxygen uptake, electrolyte balance maintenance and other basic treatment; on the basis, IFN group were given aerosol inhalation of interferon 1b 1.5 μg/kg in saline 2 mL, 2 times a day. On the basis, control group were only given aerosol inhalation of saline 2 mL, 2 times a day.

2.3 Serum sample collection and index determination

Before treatment and 7 d after treatment, analysis of serum inflammatory cytokines SP-A, sICAM1, suPAR (ng/mL) and sTREM1 (pg/mL) levels between the two groups of children was as follows: serum SP-A, sICAM1, suPAR and sTREM1 levels were not significantly different between the two groups of children before treatment (P>0.05) whereas serum SP-A, sICAM1, suPAR and sTREM1 levels were significantly different after treatment (P<0.05), and serum SP-A, sICAM1, suPAR and sTREM1 levels of IFN group were lower than those of control group; compared with those of same group before treatment, serum SP-A, sICAM1, suPAR and sTREM1 levels of both groups were significantly lower 7 days after treatment (P<0.05).

2.4 Peripheral blood sample collection and index determination

Before treatment and 7 d after treatment, 0.5-1.0 mL of peripheral blood was collected from the two groups of neonates respectively, joined by Ficoll separating medium and purified to get peripheral blood mononuclear cells, and the steps in RNA extraction kit and fluorescence quantitative PCR kit instructions were referred to extract the RNA from peripheral blood mononuclear cells and determine Tim1, Tim3, TLR2, TLR4 and NF-κ B mRNA expression.

Table 1.

Comparison of serum inflammatory cytokines between the two groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>SP-A</th>
<th>sICAM1</th>
<th>suPAR</th>
<th>sTREM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN group</td>
<td>34</td>
<td>Before</td>
<td>28.52±3.37</td>
<td>273.6±33.8</td>
<td>10.85±1.37</td>
<td>79.31±9.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>15.2±1.83</td>
<td>140.2±17.6</td>
<td>5.72±0.83</td>
<td>44.6±6.84</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
<td>Before</td>
<td>29.1±3.19</td>
<td>279.1±31.9</td>
<td>11.0±1.44</td>
<td>80.1±8.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>20.35±2.89</td>
<td>194.5±22.6</td>
<td>7.57±0.94</td>
<td>59.6±7.24</td>
</tr>
</tbody>
</table>

*: comparison between before and after treatment within group, P<0.05; #: comparison between two groups after treatment, P<0.05.

Table 2.

Comparison of peripheral blood inflammatory signal molecules between the two groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>Tim1</th>
<th>Tim3</th>
<th>TLR2</th>
<th>TLR4</th>
<th>NF-κ B</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN group</td>
<td>34</td>
<td>Before</td>
<td>1.02±0.15</td>
<td>0.98±0.13</td>
<td>1.04±0.16</td>
<td>1.05±0.13</td>
<td>1.01±0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>0.67±0.08*</td>
<td>0.50±0.07*</td>
<td>0.66±0.09*</td>
<td>0.54±0.08*</td>
<td>0.58±0.07*</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
<td>Before</td>
<td>1.04±0.13</td>
<td>1.01±0.14</td>
<td>1.02±0.15</td>
<td>1.02±0.16</td>
<td>1.04±0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>0.83±0.12*</td>
<td>0.72±0.08*</td>
<td>0.79±0.11*</td>
<td>0.74±0.09*</td>
<td>0.77±0.09*</td>
</tr>
</tbody>
</table>

*: comparison between before and after treatment within group, P<0.05; #: comparison between two groups after treatment, P<0.05.

2.5 Statistical methods

Software SPSS 19.0 was used to input data, the differences in data between groups were analyzed by t test and P<0.05 indicated statistical significance in differences.

3. Results

3.1 Changes in serum inflammatory cytokines before and after treatment

Before treatment and 7 d after treatment, analysis of serum inflammatory cytokines SP-A, sICAM1, suPAR (ng/mL) and sTREM1 (pg/mL) levels between the two groups of children was as follows: serum SP-A, sICAM1, suPAR and sTREM1 levels were not significantly different between the two groups of children before treatment (P>0.05) whereas serum SP-A, sICAM1, suPAR and sTREM1 levels were significantly different after treatment (P<0.05), and serum SP-A, sICAM1, suPAR and sTREM1 levels of IFN group were lower than those of control group; compared with those of same group before treatment, serum SP-A, sICAM1, suPAR and sTREM1 levels of both groups were significantly lower 7 days after treatment (P<0.05).

3.2 Changes in peripheral blood inflammatory signal molecules before and after treatment

Before treatment and 7 d after treatment, analysis of peripheral blood inflammatory signal molecules Tim1, Tim3, TLR2, TLR4 and NF-κ B expression between the two groups of children was as follows: peripheral blood Tim1, Tim3, TLR2, TLR4 and NF-κ B mRNA expression were not significantly different between the two groups of children before treatment (P>0.05) whereas peripheral blood Tim1, Tim3, TLR2, TLR4 and NF-κ B mRNA expression were significantly different after treatment (P<0.05), and peripheral
blood Tim1, Tim3, TLR2, TLR4 and NF-κB mRNA expression of IFN group were lower than those of control group; compared with those of same group before treatment, peripheral blood Tim1, Tim3, TLR2, TLR4 and NF-κB mRNA expression of both groups were significantly lower 7 d after treatment (P<0.05).

3.3 Changes in serum stress mediators before and after treatment

Before treatment and 7 d after treatment, analysis of serum stress mediators Copeptin, Ins, NE and 8-iso-PG (pg/mL) levels between the two groups of children was as follows: serum Copeptin, Ins, NE and 8-iso-PG levels were not significantly different between the two groups of children before treatment (P>0.05) whereas serum Copeptin, Ins, NE and 8-iso-PG levels were significantly different after treatment (P<0.05), and serum Copeptin, Ins, NE and 8-iso-PG levels of IFN group were lower than those of control group; compared with those of same group before treatment, serum Copeptin, Ins, NE and 8-iso-PG levels of both groups were significantly lower 7 d after treatment (P<0.05).

4. Discussion

Viral pneumonia is a common disease in the neonatal period, which can lead to pulmonary interstitial inflammatory disease and increase the risk of respiratory distress. Severe cases can cause neonatal death. At present, the main method to treat neonatal viral pneumonia is symptomatic and supportive treatment, but the overall efficacy is not ideal[4,5]. Interferon 1b is the interferon preparation independently researched and developed in our country, which has the immunoregulatory activity of interferon, may be combined with the interferon receptors on the surface of a variety of immune cells to increase antiviral protein expression in cells, and then can on the one hand, directly inhibit viral replication, and on the other hand, enhance the killing activity of a variety of immune cells on the virus through the activity of antiviral proteins. It has been reported that on the basis of conventional symptomatic and supportive treatment, interferon 1b aerosol inhalation for neonatal viral pneumonia can shorten the course of disease and improve the curative effect[3]. In the process of persistent virus infection, the inflammation and stress in the body are excessively activated, but there is no report about the influence of interferon 1b aerosol inhalation on the inflammatory and stress response in the course of neonatal viral pneumonia.

The activation of inflammatory response in viral pneumonia is accompanied by the mass release of a large number of inflammatory cytokines. SP-A is an active protein produced by alveolar type 2 cells. The destruction of the alveoli by inflammatory cytokines in the inflammatory response process may cause a large amount of SP-A to be released into the blood circulation[6,7]; sICAM1 is a soluble intercellular adhesion molecule that mediates the adhesion between cells and between cells and extracellular matrix, and can promote the mass infiltration of inflammatory cells in the interstitium[8]; suPAR is a product when uPAR is detached from the surface of the cells, and it can mediate the activation of plasmin and promote the occurrence of pulmonary interstitial lesions[9]; sTREM1 is a cytokine produced by activated macrophages, which can trigger the activation of inflammation[10]. Analysis of the change trend of above serum inflammatory cytokines before and after treatment as well as the differences between groups showed that serum SP-A, sICAM1, suPAR and sTREM1 levels of both groups after treatment were significantly lower than those before treatment, and serum SP-A, sICAM1, suPAR and sTREM1 levels of IFN group after treatment were lower than those of control group. It means that both regular symptomatic and supportive treatment and interferon combined with regular symptomatic and supportive treatment can inhibit the inflammatory reaction and reduce the secretion of inflammatory cytokines in the course of neonatal viral pneumonia, and adjuvant interferon therapy is better than conventional treatment to inhibit the inflammatory response.

The activation of the inflammatory response after virus infection depends on the mediating of multiple signaling pathways in the body. Tim1 and Tim3 are co-stimulatory molecules on the surface of immune cells, which can regulate the differentiation and maturation of immune cells to influence the secretion of corresponding cytokines and cause the change of inflammatory response in the course of disease. Tim1 is mainly expressed on the surface of Th2 cells, it can promote the differentiation of Th2 and the secretion of corresponding anti-inflammatory cytokines, and its high expression is not conducive to the eradication of virus in the course of disease; Tim3 is mainly expressed on the surface of Th1 cells, it can inhibit the differentiation of Th1 and the secretion of corresponding pro-inflammatory cytokines, and its high expression is also not conducive to the elimination of virus in the course of disease[11]. TLR2 and TLR4 are important TLR family members that are able to identify a variety of viruses, increase NF-κB transcriptional activity through the transduction of downstream signal molecules, and promote the expression and secretion of a variety of inflammatory

Table 3.
Comparison of serum stress mediators between the two groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>Copeptin</th>
<th>Ins</th>
<th>NE</th>
<th>8-iso-PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN group</td>
<td>34</td>
<td>Before treatment</td>
<td>63.8±8.23</td>
<td>7.95±0.92</td>
<td>69.58±8.71</td>
<td>33.85±5.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>40.24±5.72</td>
<td>4.75±0.55</td>
<td>42.31±5.85</td>
<td>15.23±1.88</td>
</tr>
<tr>
<td>Control group</td>
<td>34</td>
<td>Before treatment</td>
<td>63.38±7.59</td>
<td>8.01±0.98</td>
<td>70.11±8.38</td>
<td>34.12±4.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>54.41±6.96</td>
<td>6.13±0.78</td>
<td>56.84±7.23</td>
<td>22.37±3.15</td>
</tr>
</tbody>
</table>

*: comparison between before and after treatment within group, P<0.05; #: comparison between two groups after treatment, P<0.05.
mediators(2,13). Analysis of the changing trends of above peripheral blood inflammatory signaling molecules before and after treatment as well as the differences between group showed that peripheral blood Tim1, Tim3, TLR2, TLR4 and NF-κB mRNA expression of both groups after treatment were significantly lower than those before treatment, and peripheral blood Tim1, Tim3, TLR2, TLR4 and NF-κB mRNA expression of IFN group after treatment were lower than those of control group. It means that both regular symptomatic and supportive treatment and interferon combined with regular symptomatic and supportive treatment can inhibit the inflammatory reaction and prevent the activation of inflammatory signaling pathways in the course of neonatal viral pneumonia, and adjuvant interferon treatment is better than conventional treatment to inhibit the activation of inflammatory signaling pathways.

Both persistent viral infection and excessive inflammation activation in newborns with viral pneumonia are strong stressors that can cause internal environment disturbance and increase the secretion of various stress mediators(14). AVP is an endocrine hormone synthesized by hypothalamus and released by neurohypophysis. Copeptin is its homologous hormone, and external stress can increase their secretion, and then cause transient hyperglycemia by promoting the secretion of glucagon, cortisol and so on(15,16); hyperglycemia can increase the compensatory secretion of Ins by islet β cells and produce a certain degree of insulin resistance. NE is a hormone secreted by the adrenal medulla, which is consistent with the activation of the stress response, and mainly mediates the contraction of peripheral blood vessels. 8-iso-PG is the peroxidation product of arachidonic acid, which can reflect the degree of local tissue damage in the stress process(17). Analysis of the change trend of above stress mediators before and after treatment as well as the differences between groups showed that serum Copeptin, Ins, NE and 8-iso-PG levels of both groups after treatment were significantly lower than those before treatment, and serum Copeptin, Ins, NE and 8-iso-PG levels of IFN group after treatment were lower than those of control group. It means that both regular symptomatic and supportive treatment and interferon combined with regular symptomatic and supportive treatment can suppress the stress reaction and reduce the secretion of stress mediators in the course of neonatal viral pneumonia, and auxiliary interferon treatment is better than conventional treatment to inhibit the stress reaction.

Based on above analysis and discussion about inflammatory and stress response indexes, it can be preliminarily concluded that adjuvant interferon aerosol inhalation can more significantly reduce the activation inflammatory and stress response in the course of neonatal viral pneumonia than regular treatment.

References