Effects of short-term intensive insulin therapy on systemic inflammatory response and stress response in patients with severe pneumonia

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ABSTRACT

Objective: To study the effects of short-term intensive insulin therapy on systemic inflammatory response and stress response in patients with severe pneumonia.

Methods: Patients with severe pneumonia who were treated in our hospital between March 2015 and October 2017 were chosen as the research subjects and randomly divided into the INS group who received short-term intensive insulin combined with routine therapy and the control group who received short-acting insulin combined with routine therapy. The levels of inflammatory factors and stress mediators in serum as well as the expression intensity of inflammatory molecules in peripheral blood were determined before treatment as well as 3 d and 7 d after treatment.

Results: Compared with same group before treatment, serum IL-1β, IL-13, suPAR, sTREM1, sP-selectin, SF, 8-iso-PGF2α, AQP1 and AQP5 levels as well as peripheral blood NF-κB, COX2, RANTES, CD28 and CD80 expression intensity of both groups significantly decreased 3 days and 7 days after treatment, and serum IL-1β, IL-13, suPAR, sTREM1, sP-selectin, SF, 8-iso-PGF2α, AQP1 and AQP5 levels as well as peripheral blood NF-κB, COX2, RANTES, CD28 and CD80 expression intensity of INS group 3 d and 7 d after treatment were significantly lower than those of control group.

Conclusion: Short-term intensive insulin therapy has inhibitory effect on the systemic inflammatory response and stress response in patients with severe pneumonia.

1. Introduction

Severe pneumonia is a common severe respiratory disease, the inflammation shows the trend of cascade activation amplification after pathogen infection and can lead to the occurrence of systemic inflammatory response syndrome, and severe cases may progress to multiple organ dysfunction and increase the risk of death from disease[1,2]. In the clinical course of severe pneumonia, persistent inflammation will on the one hand, cause the insulin resistance of peripheral tissue, and on the other hand, also cause local tissue hypoxia, acidosis, microcirculation and so on, and lead to islet β cell secretion dysfunction, and the two factors work together to cause the occurrence of stress hyperglycemia and increase the level of systemic inflammatory response[3]. In recent years, intensive insulin therapy has been increasingly used in clinical treatment of critical illness, and the intensive insulin hypoglycemic therapy for critically ill patients combined with stress hyperglycemia can reduce blood glucose and relieve the aggravating and promoting effect of high glucose on the course[4]. The excessive activation of systemic inflammatory and stress response is the most prominent pathological feature in the course of severe pneumonia, and we specifically analyzed the effects of short-term intensive insulin therapy on systemic inflammatory response and stress response in patients with severe pneumonia in the following study.

2. Case inclusion and research methods

2.1 Case inclusion and information

Patients with severe pneumonia who were treated in our hospital between March 2015 and October 2017 were selected as the research subjects, and all the patients were in accordance with the diagnostic criteria for severe pneumonia and were with stress hyperglycemia, fasting blood glucose > 7.0 mmol/L or random blood glucose > 11.1 mmol/L in the course of disease. Patients who had history of diabetes, and those who had used hormones before the admission were excluded.
inclusion were excluded. A total of 116 patients were enrolled and divided into two groups by random number table method, each with 58 cases. There were 33 males and 25 females in the INS group, and they were 29-55 years old; there were 31 males and 27 females in the control group, and they were 27-52 years old. There was no significant difference in the general data between the two groups (P>0.05).

2.2 Clinical therapy

Both groups of patients received routine therapy for severe pneumonia, including choosing antibiotics for anti-infection according to the drug susceptibility results, maintaining water and electrolyte balance, protecting heart, liver, stomach and other viscera. INS group received intensive insulin therapy on the basis of routine treatment, which was as follows: they were given 4-7.8 mmol/L; control group received routine insulin treatment on the basis of electrolyte balance, protecting heart, liver, stomach and other viscera according to the drug susceptibility results, maintaining water and electrolyte balance, protecting heart, liver, stomach and other viscera.

2.3 Laboratory detection methods

Before treatment as well as 3 d and 7 d after treatment, 8-10 mL of peripheral venous blood was collected and divided into two parts. One part was used to separate the serum and then detect the contents of IL-1β, IL-13, suPAR, sTREM1, sP-selectin, SF, 8-iso-PGF2, AQP1 and AQP5 according to the operation steps in Elisa kit. The other part was used for laboratory testing according to the flow cytometry detection kit steps, the NF-κB, COX2, RANTES, CD28 and CD80 fluorescent antibody were incubated, and then flow cytometer was used to determine the expression intensity of corresponding molecules.

2.4 Statistical methods

Software SPSS 21.0 was adopted to input data, the differences in measurement data between two groups were analyzed by t test and P<0.05 indicated that the difference was statistically significant.

3. Results

3.1 Serum inflammatory factor levels

Before treatment as well as 3 d and 7 d after treatment, analysis of serum inflammatory factors IL-1β (ng/L), IL-13 (ng/L), suPAR (μg/L), sTREM1 (ng/L) and sP-selectin (μg/L) levels between the two groups of patients was as follows: serum IL-1β, IL-13, suPAR, sTREM1 and sP-selectin levels were not different between the two groups of patients before treatment (P>0.05) whereas serum IL-1β, IL-13, suPAR, sTREM1 and sP-selectin levels were different after treatment (P<0.05), and serum IL-1β, IL-13, suPAR, sTREM1 and sP-selectin levels of INS group were lower than those of control group; compared with same group before treatment, serum IL-1β, IL-13, suPAR, sTREM1 and sP-selectin levels of both groups significantly decreased after treatment (P<0.05).

3.2 Peripheral blood inflammatory molecule expression

Before treatment as well as 3 d and 7 d after treatment, analysis of peripheral blood inflammatory molecules NF-κ B, COX2, RANTES, CD28 and CD80 expression intensity between the two groups of patients was as follows: peripheral blood NF-κ B, COX2, RANTES, CD28 and CD80 expression intensity were not different between the two groups of patients before treatment (P>0.05) whereas peripheral blood NF-κ B, COX2, RANTES, CD28 and CD80 expression intensity were different after treatment (P<0.05), and peripheral blood NF-κ B, COX2, RANTES, CD28 and CD80 expression intensity of INS group were lower than those of control group; compared with same group before treatment, peripheral blood NF-κ B, COX2, RANTES, CD28 and CD80 expression intensity of both groups significantly decreased after treatment (P<0.05).

Table 1.

Comparison of serum IL-1β, IL-13, suPAR, sTREM1 and sP-selectin before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>IL-1β (ng/L)</th>
<th>IL-13 (ng/L)</th>
<th>suPAR (μg/L)</th>
<th>sTREM1 (ng/L)</th>
<th>sP-selectin (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS group</td>
<td>58</td>
<td>Before</td>
<td>5.29±0.77</td>
<td>28.33±4.28</td>
<td>7.94±0.93</td>
<td>63.2±8.2</td>
<td>89.3±11.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after</td>
<td>3.01±0.42*</td>
<td>16.34±2.03*</td>
<td>4.12±0.53*</td>
<td>40.1±6.8*</td>
<td>52.3±7.5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 d after</td>
<td>2.35±0.32*</td>
<td>11.32±1.84*</td>
<td>2.89±0.35*</td>
<td>28.6±0.4*</td>
<td>36.5±5.5*</td>
</tr>
<tr>
<td>Control group</td>
<td>58</td>
<td>Before</td>
<td>5.41±0.81</td>
<td>28.13±3.29</td>
<td>8.05±1.08</td>
<td>62.7±8.1</td>
<td>90.1±10.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after</td>
<td>3.95±0.52*</td>
<td>23.58±3.58*</td>
<td>6.88±0.78*</td>
<td>53.6±7.5*</td>
<td>68.4±8.2*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 d after</td>
<td>3.12±0.36*</td>
<td>17.59±2.2*</td>
<td>5.12±0.55*</td>
<td>42.3±5.8*</td>
<td>59.2±7.7*</td>
</tr>
</tbody>
</table>

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

Table 2.

Comparison of peripheral blood NF-κ B, COX2, RANTES, CD28 and CD80 before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>NF-κ B</th>
<th>COX2</th>
<th>RANTES</th>
<th>CD28</th>
<th>CD80</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS group</td>
<td>58</td>
<td>Before</td>
<td>1.03±0.15</td>
<td>1.02±0.11</td>
<td>0.97±0.14</td>
<td>1.01±0.15</td>
<td>0.98±0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after</td>
<td>0.57±0.08*</td>
<td>0.51±0.06*</td>
<td>0.60±0.08*</td>
<td>0.62±0.09*</td>
<td>0.48±0.06*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 d after</td>
<td>0.38±0.05*</td>
<td>0.31±0.04*</td>
<td>0.47±0.06*</td>
<td>0.43±0.07*</td>
<td>0.30±0.05*</td>
</tr>
<tr>
<td>Control group</td>
<td>58</td>
<td>Before</td>
<td>0.99±0.11</td>
<td>1.01±0.13</td>
<td>0.96±0.13</td>
<td>1.03±0.15</td>
<td>1.02±0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after</td>
<td>0.78±0.09*</td>
<td>0.72±0.08*</td>
<td>0.79±0.09*</td>
<td>0.83±0.11*</td>
<td>0.58±0.08*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 d after</td>
<td>0.61±0.07*</td>
<td>0.54±0.06*</td>
<td>0.68±0.06*</td>
<td>0.72±0.09*</td>
<td>0.51±0.06*</td>
</tr>
</tbody>
</table>

*: comparison between before and after treatment within the two groups, P<0.05; #: comparison between the two groups after treatment, P<0.05.
production of stress hyperglycemia has an aggravating effect on and increase blood glucose. In the course of severe pneumonia, the cause ventilation dysfunction, then lead to hypoxia and acidosis glucose; (3) the aggravation of inflammation in the local lung can leads to insufficiency of insulin secretion and increase of blood can directly cause damage to the islet cell secretion function, which the process of inflammation activation can affect the transduction irritability hyperglycemia, and the possible mechanisms might be stress response in the course of critical diseases have shown that the studies about the characteristics of inflammation and oxidative factors leading to poor prognosis of disease organ dysfunction caused by continuous inflammation and oxidative complication incidence rate and mortality rate, and the multiple Severe pneumonia is with difficult clinical treatment, and high therapy is needed to reduce blood glucose[9,10]. Intensive insulin therapy is a new means for critically ill treatment in recent years, and the insulin is applied via short-term intravenous micro pump to lower blood glucose and create favorable conditions for the relief of inflammation and oxidative stress[11,12].

The cascade release of inflammatory factors is the characteristic of continuous inflammation activation in the course of severe pneumonia, and the inflammatory factors associated with severe pneumonia include a variety of pro-inflammatory factors, anti-inflammatory factors, adhesion factors, etc. IL-1β and IL-13 are the interleukin family members with pro-inflammatory and anti-inflammatory activity; in the process of inflammatory response activation, the former is actively secreted by mononuclear macrophages, neutrophils and other inflammatory cells and participates in the amplification of inflammatory response, and the latter shows the trend of compensatory secretion and can inhibit the excessive activation of the inflammatory response[13,14]. suPAR and sTREM1 are newly discovered markers of inflammation, the former can promote the infiltration of inflammatory cells in the interstitial tissue, and the latter can participate in the triggering of inflammatory response[15]. P-selectin is a cytokine that mediates the adhesion between neutrophils and endothelial cells, and it will also fall off, become sP-selectin and enter the blood circulation when it participates in amplification and activation of inflammation. Analysis of the change of inflammatory cytokine levels in serum before and after treatment showed that serum IL-1β, IL-13, suPAR, sTREM1 and sP-selectin levels of both groups after treatment were lower than those before treatment, and serum IL-1β, IL-13, suPAR, sTREM1 and sP-selectin levels of INS group after treatment were lower than those of control group. This shows that both intensive insulin treatment and regular insulin treatment can relieve the inflammatory reaction and reduce the secretion of a variety of inflammatory factors in the course of severe pneumonia, and intensive insulin therapy is better than regular insulin therapy to reduce the inflammatory reaction in the course of severe pneumonia.

In the process of inflammatory response activation, the process of inflammatory cell synthesis and secretion by inflammatory factors is regulated by various signaling molecules. NF-κB is the nuclear transcription factor to regulate the inflammatory response, it can

### Table 3.
Comparison of serum SF, 8-iso-PGF2α, AQP1 and AQP5 before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>SF</th>
<th>8-iso-PGF2α</th>
<th>AQP1</th>
<th>AQP5</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS group</td>
<td>58</td>
<td>Before treatment</td>
<td>147.2±17.4</td>
<td>17.9±2.2</td>
<td>18.4±2.2</td>
<td>10.6±1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after treatment</td>
<td>93.4±11.3</td>
<td>10.3±1.4</td>
<td>11.7±1.5</td>
<td>6.4±0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 d after treatment</td>
<td>79.5±9.3</td>
<td>8.3±1.2</td>
<td>8.3±1.7</td>
<td>5.2±0.7</td>
</tr>
<tr>
<td>Control group</td>
<td>58</td>
<td>Before treatment</td>
<td>150.±15.8</td>
<td>18.3±2.4</td>
<td>18.8±2.5</td>
<td>10.3±1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 d after treatment</td>
<td>125.1±15.8</td>
<td>14.1±1.9</td>
<td>14.2±1.5</td>
<td>8.5±0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 d after treatment</td>
<td>107.3±15.8</td>
<td>11.9±1.4</td>
<td>10.9±1.5</td>
<td>6.7±0.9</td>
</tr>
</tbody>
</table>

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

#### 3.3 Serum stress mediator levels

Before treatment as well as 3 d and 7 d after treatment, analysis of serum stress mediators SF (μg/L), 8-iso-PGF2α (ng/L), AQP1 (μg/L) and AQP5 (μg/L) levels between the two groups of patients was as follows: serum SF, 8-iso-PGF2α, AQP1 and AQP5 levels were not different between the two groups of patients before treatment (*P*>0.05) whereas serum SF, 8-iso-PGF2α, AQP1 and AQP5 levels were different after treatment (*P*<0.05), and serum SF, 8-iso-PGF2α, AQP1 and AQP5 levels of INS group were lower than those of control group; compared with same group before treatment, serum SF, 8-iso-PGF2α, AQP1 and AQP5 levels of both groups significantly decreased after treatment (*P*<0.05).

### 4. Discussion

Severe pneumonia is with difficult clinical treatment, and high complication incidence rate and mortality rate, and the multiple organ dysfunction caused by continuous inflammation and oxidative stress activation in the course of the disease is one of the important factors leading to poor prognosis of disease[5,6]. In recent years, the studies about the characteristics of inflammation and oxidative stress response in the course of critical diseases have shown that the inflammatory mediators and oxidative stress mediators can cause irritability hyperglycemia, and the possible mechanisms might be as follows[7,8]: (1) the mass secretion of inflammatory mediators in the process of inflammation activation can affect the transduction of biological insulin signals, reduce the peripheral tissue sensitivity to insulin and decrease the glucose uptake and utilization to result in elevated blood glucose; (2) inflammatory and stress mediators can directly cause damage to the islet cell secretion function, which leads to insufficiency of insulin secretion and increase of blood glucose; (3) the aggravation of inflammation in the local lung can cause ventilation dysfunction, then lead to hypoxia and acidosis and increase blood glucose. In the course of severe pneumonia, the production of stress hyperglycemia has an aggravating effect on inflammatory response and oxidative stress response, and insulin

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*Note: The table and text are formatted as provided, with some adjustments for clarity and coherence. The content is a scientific discussion on the effects of critical diseases on blood glucose levels and the role of inflammatory and oxidative stress mediators. The table compares serum levels of specific markers before and after treatment in two groups of patients with severe pneumonia.*
be recognized by corresponding pattern receptors after pathogen infection, then the signal transduction of receptor downstream makes the NF-κB disassociated with inhibitor I-κB, and the free NF-κB has extremely strong transcriptional activity, and can start the expression of a variety of inflammatory molecules[16]. COX2 and RANTES are two kinds of inflammatory molecules regulated by NF-κB, the former can mediate the prostaglandin anabolism, increase the permeability of local microcirculation and enhance the local infiltration of inflammatory mediators, and the latter belongs to the chemokine CC family, and can promote eosinophil infiltration in local inflammatory response[17,18]. CD28 and CD80 are the co-stimulatory signal molecules on the surface of the immune cells, the former is expressed in T cells, and the latter is expressed in dendritic cells, which identify pathogen and present antigen signals to cause immune cell activation and participate in the excessive activation process of inflammatory and immune responses[19-20]. Analysis of the changes of inflammatory molecule expression in peripheral blood before and after treatment showed that peripheral blood NF-κB, COX2, RANTES, CD28 and CD80 expression intensity of both groups after treatment were lower than those before treatment, and peripheral blood NF-κB, COX2, RANTES, CD28 and CD80 expression intensity of INS group after treatment were lower than those of control group. This indicates that both intensive insulin treatment and regular insulin treatment can inhibit the inflammation mediated by a variety of signaling molecules in the course of severe pneumonia, and intensive insulin therapy is better than regular insulin therapy to inhibit the inflammatory signaling molecule expression in the course of severe pneumonia.

Oxidative stress response is another important pathological change in the course of severe pneumonia in addition to inflammation. Local tissue hypoxia and mitochondrial oxidation respiratory chain coupling disorder will increase the production of oxygen free radicals, the high expression of myeloperoxidase in neutrophils in the process of inflammation can also increase the production of oxygen free radicals, and the constantly generated oxygen free radicals have strong oxidation on the lipids in biological cell membranes and organelle outer membrane, and cause lipid peroxidation to result in the membrane structure damage and the corresponding cell dysfunction[21,22]. SF is the main form of iron storage, and the damage of oxygen free radicals to cells will cause the increase of SF release; 8-iso-PGF2α is the peroxidation reaction product of lipid arachidonic acid in the membrane structure, which is directly related to the production of oxygen free radicals. AQP1 and AQP5 are the AQP family members that are highly expressed in the lung tissue and participate in the transport of water molecules in local tissue; these two AQP molecules are released into the blood circulation when oxygen free radicals cause alveolar epithelial damage[23]. Analysis of the change of oxidative stress mediator contents in serum before and after treatment showed that serum SF, 8-iso-PGF2α, AQP1 and AQP5 levels of both groups after treatment were lower than those before treatment, and serum SF, 8-iso-PGF2α, AQP1 and AQP5 levels of INS group after treatment were lower than those of control group. This shows that both intensive insulin treatment and regular insulin treatment can relieve the oxidative stress and reduce the secretion of a variety of oxidative stress mediators in the course of severe pneumonia, and intensive insulin therapy is better than regular insulin therapy to relieve the oxidative stress in the course of severe pneumonia.

Based on the analysis of above laboratory indicators before and after intensive insulin treatment, it may be concluded that the short-term intensive insulin therapy for severe pneumonia can be more effective than regular insulin therapy to inhibit the activation of systemic inflammatory and stress response.

References

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