Effects of quadruple antituberculous drugs in combination with linezolid and moxifloxacin on CSF cytology, NSE, NGF and its receptors in patients with refractory tuberculous meningitis

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ABSTRACT

Objective: To investigate the effects of linezolid and moxifloxacin combined with quadruple antituberculosis drugs on CSF cytology, NSE (neuronal specific enolase), NGF (nerve growth factor) and its receptors, endothelin and its receptors and CRP (C reaction protein) in patients with refractory tuberculous meningitis. Method: A total of 56 patients were selected with tuberculous meningitis in our hospital from February 2014 to December 2017, randomly divided them into 2 groups, each group was 28 cases, set as the observation group and the control group, both groups were treated with quadruple antituberculosis drugs, the observation group was given linezolid on this basis, and the control group was combined with moxifloxacin, The course of treatment was 4 weeks, compared the levels of CSF cytology, NSE, NGF and NGF receptors, endothelin and endothelin receptors, and CRP after treatment in the two groups. Result: The CSF cytology, NSE, NGF and NGF receptors, endothelin and endothelin receptor, and CRP levels remained unchanged before treatment, the difference was not statistically significant. After treatment, the chloride and glucose levels in the observation group were higher than those before treatment and that of the control group, the protein, white blood cell count, and cerebrospinal fluid pressure levels were lower than before treatment and that of the control group, the difference was statistically significant; The NSE level in the observation group after treatment was lower than before treatment and that of the control group, the difference was statistically significant; After treatment, the levels of NGF and its receptors in the observation group were higher than those before treatment and that of the control group, and the levels of endothelin, and its receptor, CRP were lower than those before treatment and that of the control group, the difference was statistically significant. Conclusion: The use of linezolid in combination with quadruple antituberculosis drugs to treat refractory tuberculous meningitis has better clinical effect, effectively improve cerebrospinal fluid cytology, regulate cerebrospinal fluid NSE levels, restore NGF, endothelin and its receptor function, reduce inflammatory response, recommended for clinical promotion and application.

1. Introduction

Tuberculous meningitis is an infection of the subarachnoid space caused by Mycobacterium tuberculosis. It is the most serious chronic inflammatory response disease of the meninges and meningitis nonsuppurative central nervous system injury. The incidence rate is as high as 12% of the total number of tuberculosis[1]. Hidden onset, often misdiagnosed or delaying the early diagnosis and treatment, the majority of patients in the middle and late stages are severe, manifestation as low fever, headache, apathy, night sweats, nausea and vomiting, vision loss, whole body fatigue, neck stiffness, disturbance of consciousness, and loss of appetite. Decrease and other major manifestations[2], severely affect the nervous system function, extremely high prognosis morbidity, mortality rate. Most of the disease is not ideal after treatment with anti-tuberculosis drugs. The linezolid can across blood-brain barrier, and it has been found to have a strong inhibitory effect on Mycobacterium tuberculosis. Our hospital currently achieve better results using linezolid on the basis of quadruple anti-tuberculosis drugs. The report is as follows.
2. Materials and methods

2.1. Clinical data

From February 2014 to December 2017, 56 patients with tuberculosis meningitis admitted in our hospital were randomly divided into 2 groups, 28 in each group, which were set as observation group and control group. The observation group patients were 15 males and 13 females, age 39-60 years old, duration 4 months to 1 year, according to the international general MRC classification criteria: grade II 19 cases, grade III 9 cases; control group patients 17 males and 11 females, age 42-63 years old, The disease duration ranged from 3 months to 1 year, according to the MRC classification criteria: 20 cases in grade II and 8 cases in grade III. Inclusion criteria: a. All patients met the British Medical Research Council's criteria for diagnosis and grading of tuberculous meningitis[3]. All patients underwent head CT or MRI examinations, cerebrospinal fluid tests, and clinical symptoms. b. CSF positive culture; c. Clear consciousness, proper communication, and strong compliance; d. All patients and their families were voluntarily involved in the study and signed informed consent. Exclusion criteria: a. combined with intracranial tumors, severe heart, kidney, liver and other organ diseases; b. cerebrospinal fluid bacterial/fungal culture positive; c. HIV (human immunodeficiency virus) positive; d. combined with infection; e. with history of drug allergy.

2.2 Treatment method

After admission, all patients were treated according to their condition to reduce cerebral edema, improve cerebrospinal fluid circulation, nourish cranial nerve and other symptomatic treatment, and given quadruple antituberculosis drug treatment, isoniazid (Guangzhou Baiyunshan Pharmaceutical Co., Ltd. Guangzhou Baiyunshan Chemical Pharmaceutical Factory, Approval number H44025337) 0.6 g/time, 1 time/d, oral, rifampicin (Shenyang antibiotics factory, Approval number H21020837) 0.45 g/time, 1 time/d, oral, pyrazinamide (Liaoning Dr. Kang Pharmaceutical Co., Ltd., Approval number H44025337) 0.6 g/time, 1 time/d, oral, ethambutol (Xi'an Bikang Xinrong Pharmaceutical Co., Ltd., Approval number H21022391) 1.5 g/time, 1 time/d, oral, ethambutol (Xi'an Bikang Xinrong Pharmaceutical Co., Ltd., national medicine Zhunzi H61023098) 0.75 g/time, 1 time/d, oral; On this basis, observation group was given linezolid (Lianyangong Hongchuan Pharmaceutical Co., Ltd., Approval number H20150035) 600 mg/time, once a day, intravenous drip; the control group was given moxifloxacin hydrochloride on the basis of quadruple anti-tuberculosis drugs (Nanjing Youke Pharmaceutical Co., Ltd., Approval number H20130042) 400 mg/time, 1 time/d, intravenous drip, treatment period of both groups are 4 weeks. The CSF cytology, NSE, NGF and its receptor, endothelin, its receptor and CRP were detected in the cerebrospinal fluid of the lumbar puncture before and after the treatment for 4 weeks.

2.3 Efficacy analysis

CSF cytology (cerebrospinal fluid cytology), NSE (neuronal specific enolase), NGF (cerebrospinal fluid nerve growth factor) and its receptor, endothelin were measured by 3 mL of cerebrospinal fluid before and 4 weeks after treatment. And its receptor, CSF cytology was detected by enzyme-linked immunosorbent assay (ELISA). The number of white blood cells, glucose and chloride in cerebrospinal fluid were detected by optical microscopy. Protein was detected by automatic biochemical analyzer, and cerebrospinal fluid pressure is measured by cerebrospinal fluid pressure gauge. The NSE level was measured using an automated microplate reader. The kit was provided by the German labtech company. NGF and its receptor levels were measured by flow cytometry. The NGF protein kit was supplied by Ab-cam and the NGF receptor protein kit was supplied by Omega. The CRP level was detected by 3 ml of venous blood before and after 4 weeks, and was detected by fully automatic protein analyzer. The kit was provided by the German labtech company(4-6). The above test procedures are strictly followed by professionals who followed the instrument operating instructions.

2.4 Statistical methods

The statistical data were processed by SPSS 20.0. The results of measurement data between groups were expressed by Mean ± SD. The t test was used, and the difference was statistically significant at P<0.05.

3. Results

3.1. Comparison of CSF cytology after treatment in both groups

Before treatment of two groups, the level of CSF cytology was flat, the difference was not statistically significant (P>0.05); after treatment, the levels of chloride and glucose in the observation group were (135.42±13.40) mmol/L, (2.97±0.83) mmol/L, higher than before treatment and control group, the protein, leucocyte

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>Chloride(mmol/L)</th>
<th>Protein(g/L)</th>
<th>Glucose (mmol/L)</th>
<th>White blood cell count(×10⁶/L)</th>
<th>Cerebrospinal fluid pressure(mH2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>28</td>
<td>Before treatment</td>
<td>95.72±4.06</td>
<td>2.84±0.27</td>
<td>1.27±0.30</td>
<td>285.5±63.52</td>
<td>275.6±30.17</td>
</tr>
<tr>
<td>Observation group</td>
<td>28</td>
<td>After treatment</td>
<td>135.42±13.40</td>
<td>0.36±0.27</td>
<td>2.97±0.83</td>
<td>12.37±3.90</td>
<td>140.4±9.07</td>
</tr>
<tr>
<td>Control group</td>
<td>28</td>
<td>Before treatment</td>
<td>95.68±3.97</td>
<td>2.85±0.30</td>
<td>1.29±0.29</td>
<td>284.6±62.47</td>
<td>276.3±27.27</td>
</tr>
<tr>
<td>Control group</td>
<td>28</td>
<td>After treatment</td>
<td>102.50±17.56</td>
<td>1.64±0.69</td>
<td>1.79±0.44</td>
<td>129.56±42.37</td>
<td>190.5±14.86</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>NSE (pg/mL)</th>
<th>NGF (pg/mL)</th>
<th>NGF receptor(pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>28</td>
<td>Before treatment</td>
<td>0.19±0.01</td>
<td>0.25±0.03</td>
<td>0.25±0.03</td>
</tr>
<tr>
<td>Observation group</td>
<td>28</td>
<td>After treatment</td>
<td>0.39±0.07</td>
<td>0.50±0.08</td>
<td>0.50±0.08</td>
</tr>
<tr>
<td>Control group</td>
<td>28</td>
<td>Before treatment</td>
<td>0.20±0.02</td>
<td>0.24±0.02</td>
<td>0.24±0.02</td>
</tr>
<tr>
<td>Control group</td>
<td>28</td>
<td>After treatment</td>
<td>0.27±0.04</td>
<td>0.33±0.08</td>
<td>0.33±0.08</td>
</tr>
</tbody>
</table>

Note: Compared with the group before treatment, "P<0.05; compared with the control group after treatment, "#P<0.05.
Table 2.
Comparison of NSE and CRP levels after treatment in both groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>NSE (mg/L)</th>
<th>CRP (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>28</td>
<td>Before treatment</td>
<td>29.27±10.06</td>
<td>8.10±2.27</td>
</tr>
<tr>
<td>Control</td>
<td>28</td>
<td>Before treatment</td>
<td>14.15±2.98*</td>
<td>3.06±1.11*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>28.99±2.98</td>
<td>8.08±2.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.24±3.16*</td>
<td>4.60±2.37*</td>
</tr>
</tbody>
</table>

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

Table 3.
Comparison of endothelin and its receptor levels after treatment in both groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Time</th>
<th>ET (pg/mL)</th>
<th>EDNRB (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>28</td>
<td>Before</td>
<td>0.40±0.13</td>
<td>0.39±0.10</td>
</tr>
<tr>
<td>Control</td>
<td>28</td>
<td>Before</td>
<td>0.25±0.10</td>
<td>0.25±0.06*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>0.38±0.11</td>
<td>0.40±0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.31±0.08*</td>
<td>0.34±0.09*</td>
</tr>
</tbody>
</table>

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

4. Discussion

In recent years, China’s economy has developed rapidly, and the technology in the medical field has been continuously improved and innovated. However, there are still many diseases with early onset of illness that are easily misdiagnosed or not valued, therefore delaying the optimal treatment time, leading to aggravation of the disease, or even threatening life safety. One of the more common disease is tuberculous meningitis. Tuberculous meningitis is an inflammatory reaction of the central nervous system induced by infection with Mycobacterium tuberculosis. It can occur at any age, early symptoms are not obvious, brain parenchymal damage is caused in the middle and late stages, prognosis is poor, disability rate and the fatality rate are high. Immunodeficiency diseases are currently known to be the main cause of the increased incidence of this disease. The treatment of this disease only by anti-tuberculosis drugs was not very effective. At present, anti-infective drugs are used in combination with anti-tuberculosis drugs. However, most of the drugs cannot reach the lesions due to the blood-brain barrier, and the blood levels are low, with little effect. In our hospital, linezolid and moxifloxacin were respectively combined with quadruple anti-tuberculosis drugs for treatment. Both drugs can exert their efficacy through the blood-brain barrier, and linezolid has a more pronounced clinical effect and is unanimously approved.

Moxifloxacin is a novel fluoroquinolone antibiotic. Besides its strong passing blood-brain barrier capacity, it also has better antituberculous activity and better tolerance[7,8]; linezolid is easier to pass blood-brain barrier than moxifloxacin, that is a new type of artificially synthesized anti-gram-positive bacillus drug. It is effective against drug-resistant gram-negative bacilli. This drug is the first clinically used oxazolidinone antibiotic for the treatment of Mycobacterium tuberculosis, which can effectively inhibit the synthesis of Mycobacterium tuberculosis protein, in vitro experiments also proved that it has obvious in vitro bactericidal activity for Mycobacterium tuberculosis, and can play a good bactericidal activity in early stage of Mycobacterium tuberculosis, can rapid control of infection[9,10]; Some data showed that compared with other antibacterial drugs, its clinical effects on XDR-TB and MDR patients are obvious, and there is no cross-resistance reaction with other drugs, and can be applied to most patients with liver and kidney insufficiency, with higher safety, especially for the treatment of refractory TB infection[11].

The results of the study showed that after treatment, the chloride and glucose levels in the observation group were higher than before treatment in this group and control group. Protein, white blood cell count, and cerebrospinal fluid pressure were lower than before treatment in this group and control group. When the patient developed to tuberculous meningitis. The amount of white blood cells in the cerebrospinal fluid increases, the chloride content in the cerebrospinal fluid decreases due to the decrease of plasma chloride, and the glucose content in the cerebrospinal fluid was significantly reduced after the central nervous system infected by the pathogenic microorganism. When the blood-brain barrier is destroyed, most of the protein in the cerebrospinal fluid is an increasing trend, so it can be seen that both drugs combined with anti-tuberculosis drugs can improve cerebrospinal fluid cytology, while linezolid has more...
obvious clinical effects, effectively increasing chloride and glucose levels, reducing protein and white blood cell count, and relieving cerebrospinal fluid pressure. The NGF and its receptors levels in the observation group were higher than those in this group before treatment and control group. The levels of endothelin, its receptor and CRP were lower than those in the group before treatment and control group. NGF and its receptors were critical proteins for the development and maintenance of the nervous system, when brain tissue is damaged, its expression level can be abnormally changed, and it is also an important target for neurological repair of brain tissue after drug treatment. Endothelin and its receptors are the most potent identified vasoconstrictors currently, and they play an important role in the development, progression and prognosis of neurological diseases. Therefore, it can be seen that both drugs combined with anti-tuberculosis drugs can improve the degree of nerve damage, but the level of NGF and its receptors increase is more obvious after treatment with linezolid group, and it can effectively regulate the levels of endothelin and its receptors, suggesting that the drug as a lipophilic molecule, it can quickly exert its medicinal effect in the early stage of Mycobacterium tuberculosis, and has a better clinical effect on refractory tuberculous meningitis.

In addition, in this study, the NSE and CRP levels in the observation group were lower than those in this group before treatment and control groups, and NSE and CRP were currently used as important evaluation indicators for the severity and prognosis of tuberculous meningitis. NSE is an important factor in the glycolytic pathway, is a marker of sensitive neuronal damage and an unique component of nerve tissue. When neurons are destroyed, their levels are significantly increased in body fluids. CRP is a rapid and sensitive stress response protein, which is a non-specific marker of the acute phase of the inflammatory response. When the brain is infected with M. tuberculosis, CRP levels in the cerebrospinal fluid rise sharply. Therefore, the results showed that both drugs combined with anti-TB drugs can reduce the level of NSE and CRP, the linezolid group decreased more significantly, indicating that linezolid can better repair neuronal function and relieve inflammatory reactions.

In summary, the combined use of linezolid in the treatment of refractory tuberculous meningitis on the basis of quadruple anti-tuberculosis drugs has a better clinical effect, effectively improve the cytological indicators of cerebrospinal fluid, regulate the level of NSE in cerebrospinal fluid, and restore NGF, endothelin and receptor function, reduce inflammatory response, recommended clinical application.

References


