Original Article
The effects of reduning injection as an adjuvant of azithromycin-based therapy for mycoplasma pneumoniae and asthma in children

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Abstract: Objective: To explore the efficacy of reduning injection (RDN) combined with azithromycin for the treatment of mycoplasma pneumoniae infection and asthma in children, and its effects on pulmonary function and inflammatory cytokine expression. Methods: Eighty-four children with mycoplasma pneumoniae infection and asthma were randomly divided into an observation and a control group, with 42 cases in each group. The patients in the control group were given azithromycin enteric-coated tablets (10 mg PO QD) plus routine treatment, while the patients in the observation group were treated with an adjunctive RDN injection (10 mL of RDN in 100 mL of 5% dextrose injection, intravenous infusion) besides azithromycin and routine treatment. The main outcome measures, including the time to defervescence, the time to the disappearance of shortness of breath, cough and lung rales, the length of the hospital stay, the overall response rate, the incidence of adverse events, as well as the eosinophil count (EOS), eosinophil cationic protein (ECP), and interleukin-8 (IL-8) in the peripheral blood were compared. Pulmonary function, parameters including forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF), were also compared between the groups. Results: The patients in the observation group had significantly shorter times for the disappearance of symptoms such as fever, shortness of breath, cough, and lung rales, and shorter hospital stays than those in the control group (all P<0.05). The observation group also had a significantly higher rate of effective treatment than the control group (P<0.05). The levels of EOS, ECP, and serum IL-8 were significantly lower than they were before treatment for both groups (all P<0.05), and the decrease was more noticeable in the observation group (P<0.05). Both groups showed increases in FVC, FEV1, and PEF after treatment (all P<0.05), and the observation group had significantly higher FVC, FEV1, and PEF than the control group (all P<0.05). There was no statistically significant difference in the incidence of adverse events between the two groups (P>0.05). Conclusion: RDN combined with azithromycin is effective in treating children with mycoplasma pneumoniae infection and asthma, which can significantly improve their clinical symptoms and pulmonary function, and shorten their hospital stays. The combination also has a lower incidence of adverse events and a favorable safety profile. Therefore, it is worthy of popularization in clinical practice.

Keywords: Pediatric patients, reduning injection, azithromycin, mycoplasma pneumoniae infection and asthma, pulmonary function, inflammatory cytokines

Introduction

Mycoplasma pneumoniae is one of the most common types of community-acquired pneumonia in children. Children are prone to mycoplasma pneumoniae infection due to their immature and weak immune systems. Recent studies have shown that 20%-60% of hospitalized children are infected with mycoplasma pneumoniae in China [1]. In fact, mycoplasma pneumoniae in children under the age of 5 accounts for about 7% of community-acquired pneumonia in children, and its incidence is rising [2, 3]. Mycoplasma pneumoniae can cause shortness of breath, fever, cough, and lung rales, and it can result in reduced lung and airway function. It can also induce chronic allergic airway inflammation, enhance eosinophil accumulation and activation, and contribute to elevated levels of airway inflammatory mediators such as the eosinophil count (EOS) and eosinophil cationic protein (ECP). In addition, it can
stimulate monocytes to release large amounts of inflammatory cytokines like interleukin-8 (IL-8), further damaging lung tissues, leading to airway hyperresponsiveness, and accelerating the progression of disease [4]. The above pathological changes are similar to the basic pathological characteristics of typical asthma [5]. Therefore, scholars at home and abroad believe that mycoplasma pneumoniae can trigger acute asthma attacks and exacerbate asthma symptoms [6, 7]. Research shows that asthma caused by mycoplasma pneumoniae accounts for about 47% of asthma in children [8]. Active treatment is essential to relieve symptoms and improve prognosis for children with mycoplasma pneumoniae and asthma. At present, medications are used to fight bacterial infections, relieve cough and reduce sputum, ease muscle spasms, and prevent asthma attacks. Macrolide antibiotics, such as azithromycin injection for intravenous infusion, are mostly used to treat mycoplasma pneumoniae infection, which can achieve a desirable efficacy. However, newly found azithromycin-resistant bacterial strains and a high incidence of adverse events associated with azithromycin therapy makes it necessary to find a new treatment.

Reduning injection (RDN) is a traditional Chinese medicine (TCM) formula extracted from three Chinese herbal medicines, namely *Artemisia annua*, *Gardenia jasminoides*, and *Lonicera japonica*. It can inhibit bacterial and viral replication, and is effective in treating respiratory diseases such as pneumonia and acute upper respiratory tract infection [9]. Research by Ou Yanjuan et al. showed that RDN can significantly alleviate the clinical symptoms of elderly patients with acute lung injuries, improve the results of blood gas analysis, and reduce inflammation [10]. Research by Huang Hui et al. revealed that RDN combined with cefoperazone sodium and sulbactam sodium injection are effective and safe in treating chronic obstructive pulmonary disease and pulmonary infection [11].

Our study aimed to explore the efficacy and safety of RDN plus azithromycin for the treatment of mycoplasma pneumonia and asthma in children.

**Materials and methods**

**Patients**

A total of 84 pediatric patients with mycoplasma pneumoniae and asthma treated in the Department of Pediatrics at Haiyang People's Hospital from June 2017 to January 2018 were selected as subjects. They were divided into two groups (the observation group and the control group, 42 patients in each group) according to random number tables. There were 50 males and 34 females. All patients were between 2.0 and 6.6 years old (weight range, 17.84-40.88 kg) and received 6.18 to 8.83 days of treatment. This study was approved by the Ethics Committee of Haiyang People's Hospital, and the caregivers of all the patients signed an informed consent.

**Inclusion criteria**

Patients who met the diagnostic criteria for mycoplasma pneumoniae and asthma formulated by the Chinese Medical Association (CMA) Society of Pediatrics in 2008 [12] and patients who tested positive for mycoplasma pneumoniae IgM antibodies, or throat swab polymerase chain reaction for mycoplasma pneumoniae.

**Exclusion criteria**

Patients with severe asthma and systemic organic diseases; patients with infectious diseases, asthma complications, immune system diseases and congenital cardiopulmonary dysplasia or patients who were given macrolide antibiotics before admission.

**Medications**

Both groups were given routine treatment. The patients in the control group were given azithromycin enteric-coated tablets (CSPC Pharmaceutical Group Limited, 10 mg PO QD) plus routine treatment, while the patients in the observation group were treated with 10 mL of RDN (Jiangsu Kanion Pharmaceutical Co., Ltd.) and 100 mL of 5% Dextrose injection via IV drip once a day, plus azithromycin and routine treatment. All the patients received 7 days of treatment.

**Outcome measures**

**Time for symptoms to disappear and length of hospital stays:** The time for the recovery of body temperature and the disappearance of symptoms including shortness of breath, cough, and lung rales, as well as the length of stay in the hospital, were recorded and compared between the two groups.
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Clinical efficacy: The efficacy of the treatments was assessed after 7 days of treatment according to the “Routine prevention and treatment of bronchial asthma in children (trial version)” established by the Subspecialty Group of Respiratory Diseases in the Chinese Medical Association (CMA) Society of Pediatrics in 2003, and divided into 3 categories. Marked effect: clinical symptoms disappeared or abated significantly with only occasional mild attacks which relieved on their own and required no medications; effective: clinical symptoms improved, but medications were still needed; ineffective: symptoms remained basically unchanged, or even worsened. Overall response rate = the number of patients who had effective treatment or for whom treatment effect was marked/total number of patients * 100%.

Cytokines detection: Venous blood (5 mL) was drawn from patients on an empty stomach in the morning before and after treatment. The EOS in the peripheral blood was measured by the wi101600 automatic blood cell analyzer (Beijing Winstrument Science and Technology Co., Ltd.). The ECP levels were determined using an immunofluorescence assay kit (Pharmacia Biotech, Sweden), and the IL-8 levels were detected using an enzyme linked immunosorbent assay kit (R&D Systems, USA).

Pulmonary function parameters: The pulmonary function parameters, including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow (PEF), were measured. The JAEGER® MasterScreen pediatric (PAED) respiratory system was used to test patients’ pulmonary functions before and after treatment.

Safety of treatments: The incidence of adverse events was recorded to evaluate the safety profile of the treatments.

Statistical methods

SPSS 23.0 statistical software was used to analyze the data. The measurement data were expressed as the mean ± standard deviation (x ± sd). A paired t-test was used for comparisons within groups before and after treatment. An independent t-test was used for comparisons between groups after treatment. The enumeration data were expresses as n (%). The incidence of adverse events was compared with Yates’ correction and Fisher’s exact probability test. P<0.05 means the difference is statistically significant.

Results

Baseline clinical data

There were no statistically significant differences in sex, age, course of the disease, or weight between the two groups (all P>0.05). See Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation group (n=42)</th>
<th>Control group (n=42)</th>
<th>x²/t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>26/16</td>
<td>24/18</td>
<td>0.198</td>
<td>0.657</td>
</tr>
<tr>
<td>Age (years)</td>
<td>4.3 ± 2.3</td>
<td>4.5 ± 2.1</td>
<td>0.416</td>
<td>0.678</td>
</tr>
<tr>
<td>Course of disease (days)</td>
<td>7.51 ± 1.32</td>
<td>7.32 ± 1.14</td>
<td>0.706</td>
<td>0.482</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>29.36 ± 11.52</td>
<td>28.51 ± 10.14</td>
<td>0.359</td>
<td>0.721</td>
</tr>
</tbody>
</table>

Table 2. Comparison of the clinical symptoms and lengths of hospital stays between the two groups (x ± sd)

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation Group (n=42)</th>
<th>Control group (n=42)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time for recovery of body temperature</td>
<td>1.85 ± 0.77</td>
<td>2.79 ± 0.92</td>
<td>5.078</td>
<td>0.000</td>
</tr>
<tr>
<td>Time for disappearance of shortness of breath</td>
<td>3.08 ± 1.32</td>
<td>4.25 ± 1.26</td>
<td>4.155</td>
<td>0.000</td>
</tr>
<tr>
<td>Time for disappearance of cough</td>
<td>2.64 ± 1.02</td>
<td>3.58 ± 1.14</td>
<td>3.982</td>
<td>0.000</td>
</tr>
<tr>
<td>Time for disappearance of rales</td>
<td>2.46 ± 1.13</td>
<td>3.95 ± 1.26</td>
<td>5.705</td>
<td>0.000</td>
</tr>
<tr>
<td>Length of hospital stays</td>
<td>7.46 ± 0.37</td>
<td>8.58 ± 0.45</td>
<td>12.459</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 1. Comparison of the clinical data between the two groups (x ± sd)
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The time to disappearance of clinical symptoms and the length of hospital stays

The observation group had a significantly shorter time for the disappearance of symptoms including fever, shortness of breath, cough, and lung rales, and shorter hospital stays than the control group (all \( P < 0.05 \)). See Table 2 and Figure 1.

**Efficacy of treatment**

The observation group had a significantly higher rate of effec-
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The incidence of adverse events

There was no statistically significant difference in the incidence of adverse events between the two groups (P>0.05). See Table 6.

Discussion

Macrolides are commonly used to treat mycoplasma pneumoniae infection and asthma. Azithromycin is a broad-spectrum second-generation macrolide antibiotic with a long half-life, desirable stability, and excellent tissue penetration. It is widely used for the treatment of mycoplasma pneumonia and tonsillitis in children due to its favorable efficacy [13]. RDN is a TCM formula, which contains the effective components extracted from three herbs Artemisia annua, and Lonicera japonica. Its components have been proven to have multiple functions such as clearing heat, dispelling wind, and detoxification.

In recent years, RDN has been widely used for its outstanding and long-lasting therapeutic effects on fever, cough and headache. Research by Panbo et al. found that RDN combined with
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Ceftazidime sodium can significantly improve the clinical symptoms and vital signs of adult patients with mycoplasma pneumonia, and it was superior to ceftazidime sodium monotherapy in terms of efficacy and safety [14]. Studies by Tian Lili et al. showed that RDN combined with vidarabine in the treatment of children with herpes stomatitis had a total rate of effective treatment of 96.55%, much higher than that of vidarabine alone, suggesting that RDN was a potent anti-infective and anti-viral agent [15]. However, there are few studies on its use in the treatment of mycoplasma pneumoniae in children. Our study showed that the addition of RDN to azithromycin therapy could improve efficacy and promote the recovery of children with mycoplasma pneumoniae and asthma. Children treated with RDN and azithromycin are more likely to experience a faster disappearance of symptoms including fever, shortness of breath, cough and lung rales, and have significantly increased FVC, FEV1, and PEF.

Studies also showed elevated expression levels of inflammatory cytokines in children with mycoplasma pneumoniae and asthma, which can cause disease to progress [16, 17]. Therefore, inhibiting inflammatory responses is of great importance to their recovery. Research by Wan Yajuan et al. showed that RDN can significantly improve symptoms such as cough, shortness of breath, and wheezing in patients with bronchiolitis, and shorten their course of disease [18]. The mechanism of RDN may be that it can reduce the levels of inflammatory cytokines, and inhibit inflammatory responses in lung tissues [19].

The results of our study showed that the levels of EOS, ECP and IL-8 in the peripheral blood of patients in the observation group decreased significantly after treatment. These results were similar to the findings of other studies, proving that RDN combined with azithromycin is effective in inhibiting the production of pro-inflammatory mediators and alleviating inflammatory responses in children with mycoplasma pneumoniae and asthma [20, 21].

In addition, our study found that there was no statistically significant difference in the incidence of adverse events between the two groups, demonstrating the favorable safety profile of the combination therapy of RDN and azithromycin.

Table 6. Comparison of the incidence of adverse events between the two groups (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation Group (n=42)</th>
<th>Control group (n=42)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>4 (9.52)</td>
<td>1 (2.38)</td>
<td>0.851</td>
<td>0.356</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2 (4.76)</td>
<td>3 (7.14)</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Local pain from IV drip</td>
<td>2 (4.76)</td>
<td>0 (0.00)</td>
<td>0.494</td>
<td></td>
</tr>
<tr>
<td>Total incidence rate</td>
<td>19.05 (8/42)</td>
<td>9.52 (4/42)</td>
<td>1.556</td>
<td>0.212</td>
</tr>
</tbody>
</table>

Figure 3. Comparison of the pulmonary function parameters between the two groups. A. FVC; B. FEV1; C. PEF. Compared with before treatment, *P<0.05, **P<0.01, ***P<0.001; compared with the observation group, ▲P<0.05, ▲▲P<0.01. FVC, forced vital capacity; FEV1, forced expiratory volume in one second; PEF, peak expiratory flow.

Figure 3.

Table 6.

Table 6. Comparison of the incidence of adverse events between the two groups (n, %)
Reduning injection and azithromycin. This result was consistent with the findings of previous studies [22].

In conclusion, RDN combined with azithromycin is effective in treating children with mycoplasma pneumoniae infection and asthma, and it can significantly improve their clinical symptoms and pulmonary function, shorten their hospital stays, and have a lower incidence of adverse events. It also has a favorable safety profile and is worth being popularized in clinical practice.

However, only three inflammatory cytokines (EOS, ECP, and IL-8) were studied in our attempt to explain the mechanism of RDN on inflammation-related pulmonary injuries. So, further research is needed to elucidate the specific inflammatory response pathways for the management of mycoplasma pneumoniae infection and asthma.

Disclosure of conflict of interest

None.

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